# *Meet The Professor*

# Optimizing the Management of HER2-Positive Breast Cancer

**Thursday, September 1, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

**Mark D Pegram, MD**

## Moderator

**Neil Love, MD**

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# Commercial Support

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

# Dr Love — Disclosures

**Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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# Dr Pegram — Disclosures

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| **Data and Safety Monitoring Board/Committee** | AstraZeneca Pharmaceuticals LP |
| **Nonrelevant Financial Relationship** | Spouse employed by Rain Therapeutics Inc |

Dr Mark Pegram's contribution to this activity was as a paid consultant and was not part of his Stanford University duties or responsibilities.

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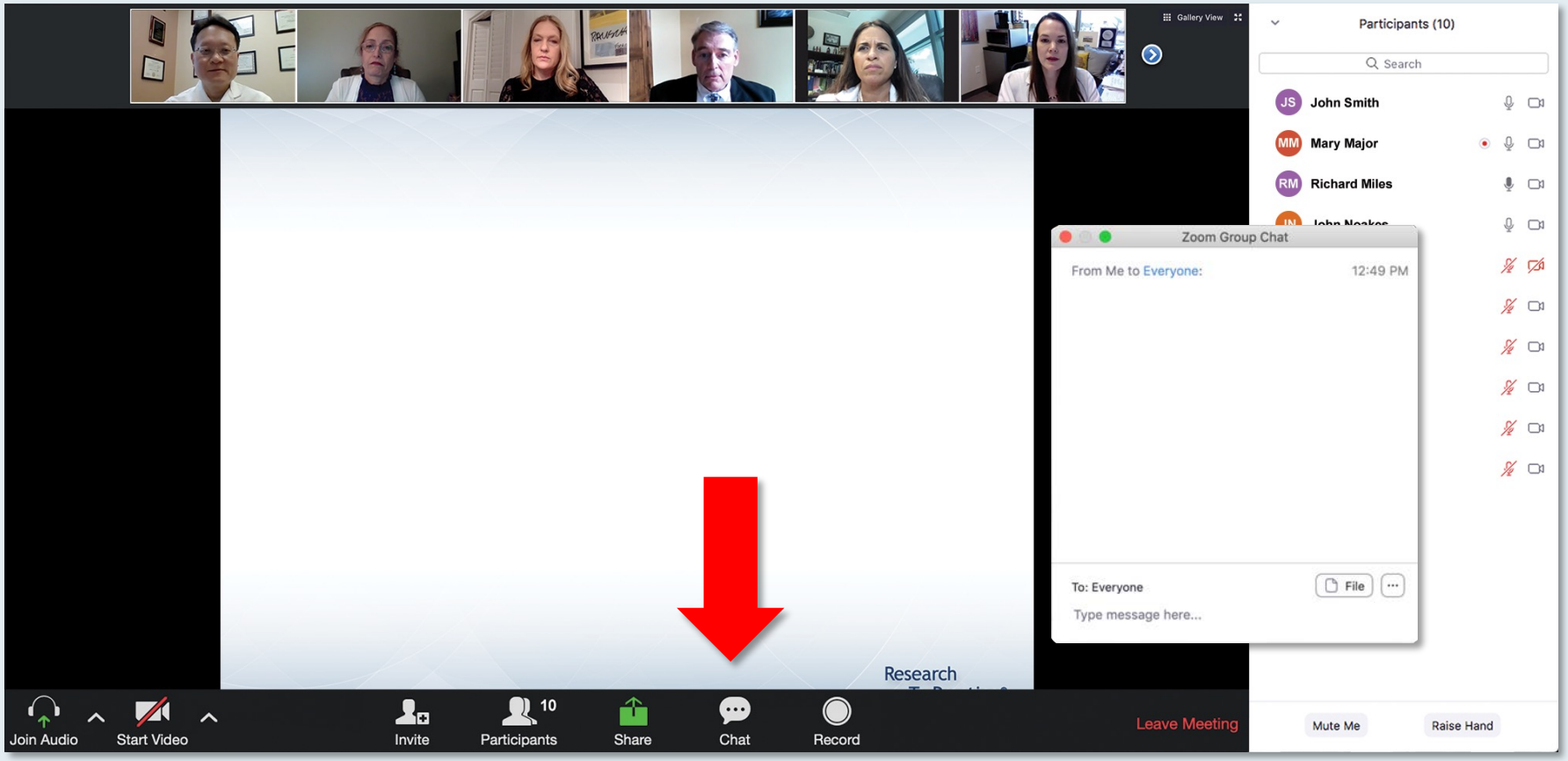
# We Encourage Clinicians in Practice to Submit Questions




**Feel free to submit questions now before the program begins and throughout the program.**

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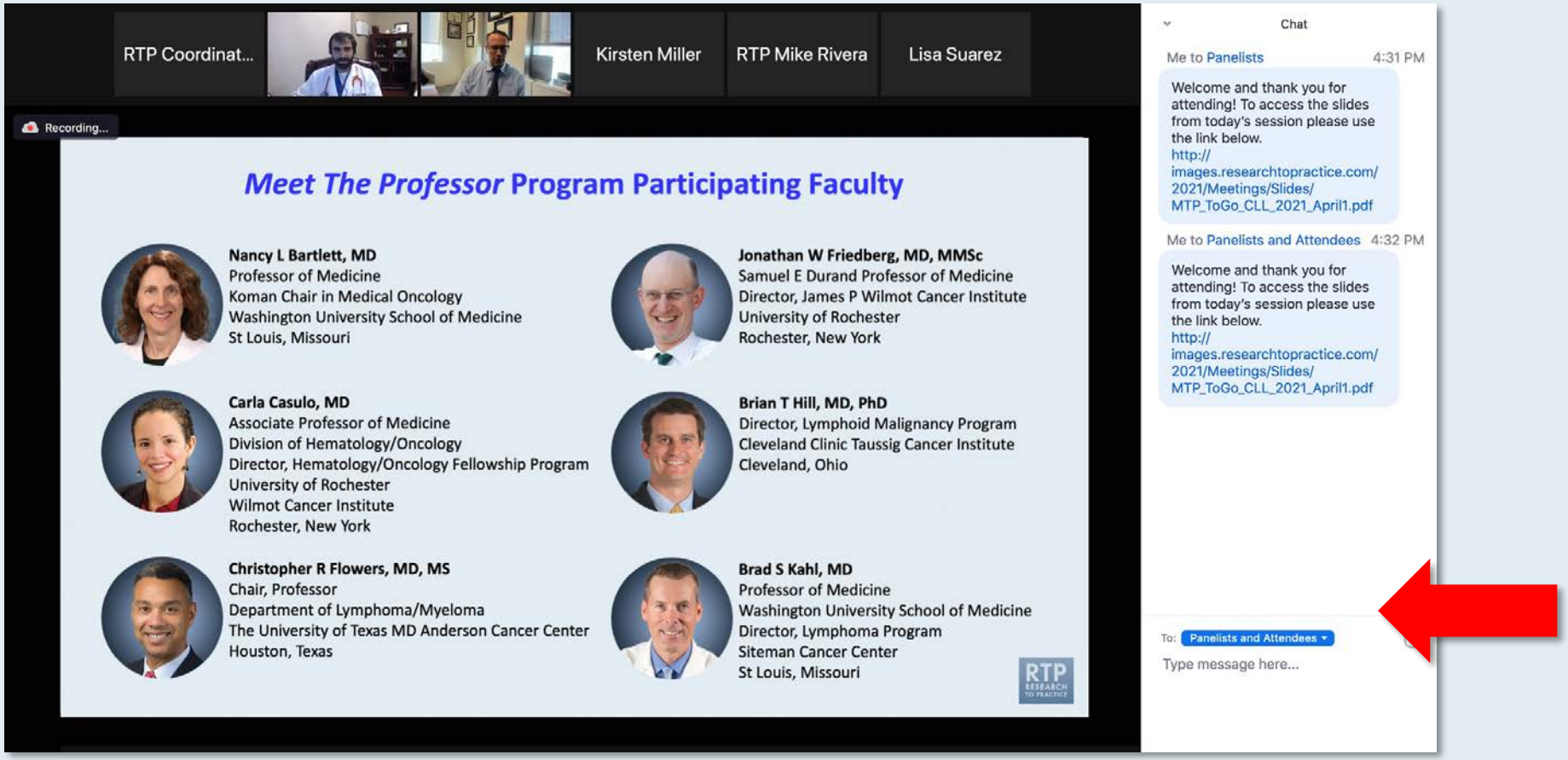
# Familiarizing Yourself with the Zoom Interface

## Expand chat submission box




**Drag the white line above the submission box up to create more space for your message.**

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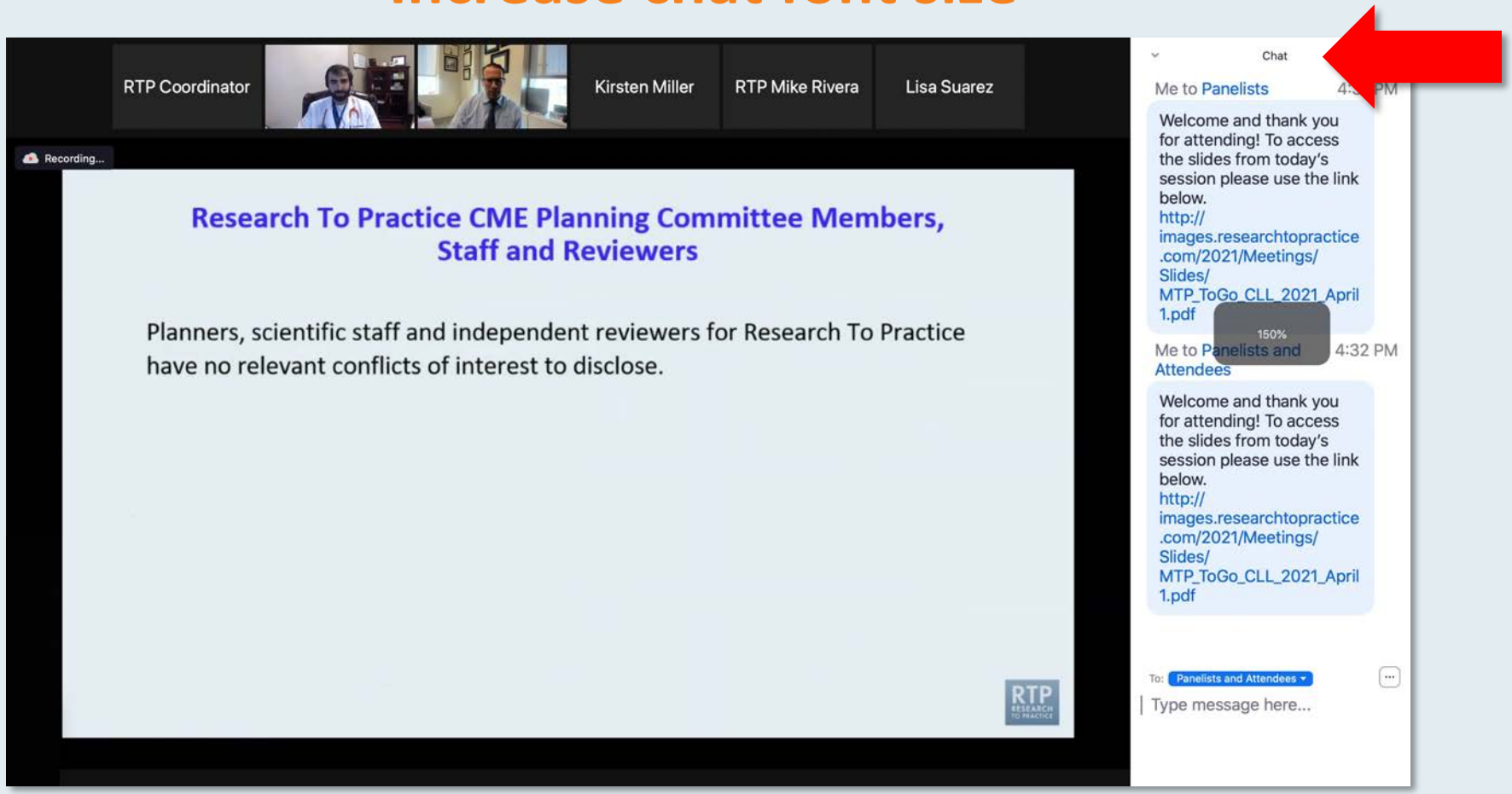
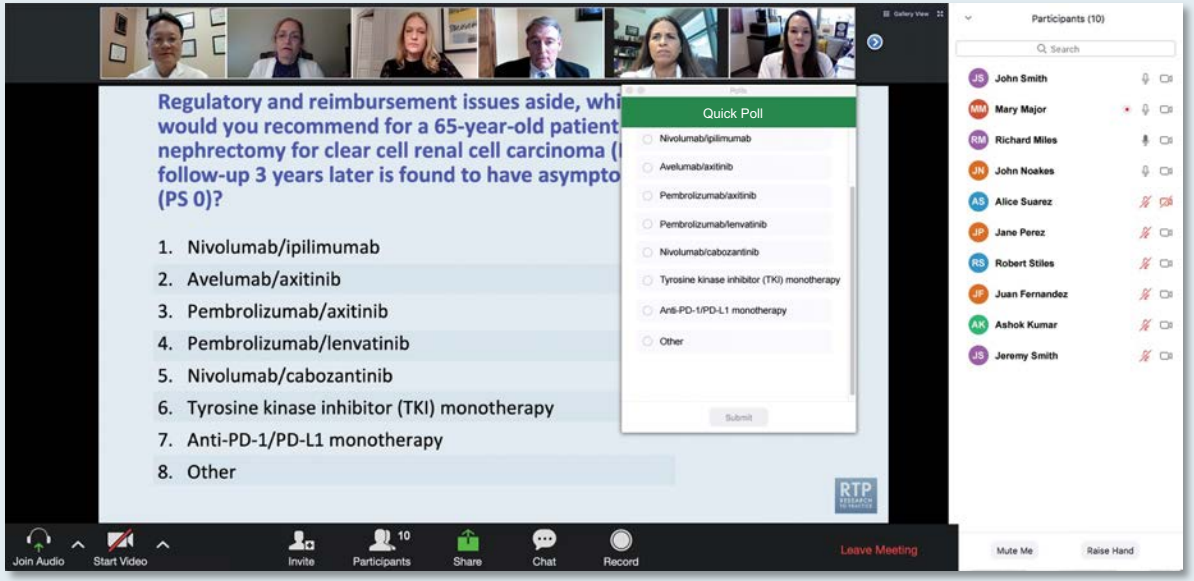
# Familiarizing Yourself with the Zoom Interface

## Increase chat font size




**Press Command (for Mac) or Control (for PC) and the + symbol.**
**You may do this as many times as you need for readability.**

# Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys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# ONCOLOGY TODAY

WITH DR NEIL LOVE

## Management of HER2-Low Breast Cancer

DR SHANU MODI
MEMORIAL SLOAN KETTERING CANCER CENTER

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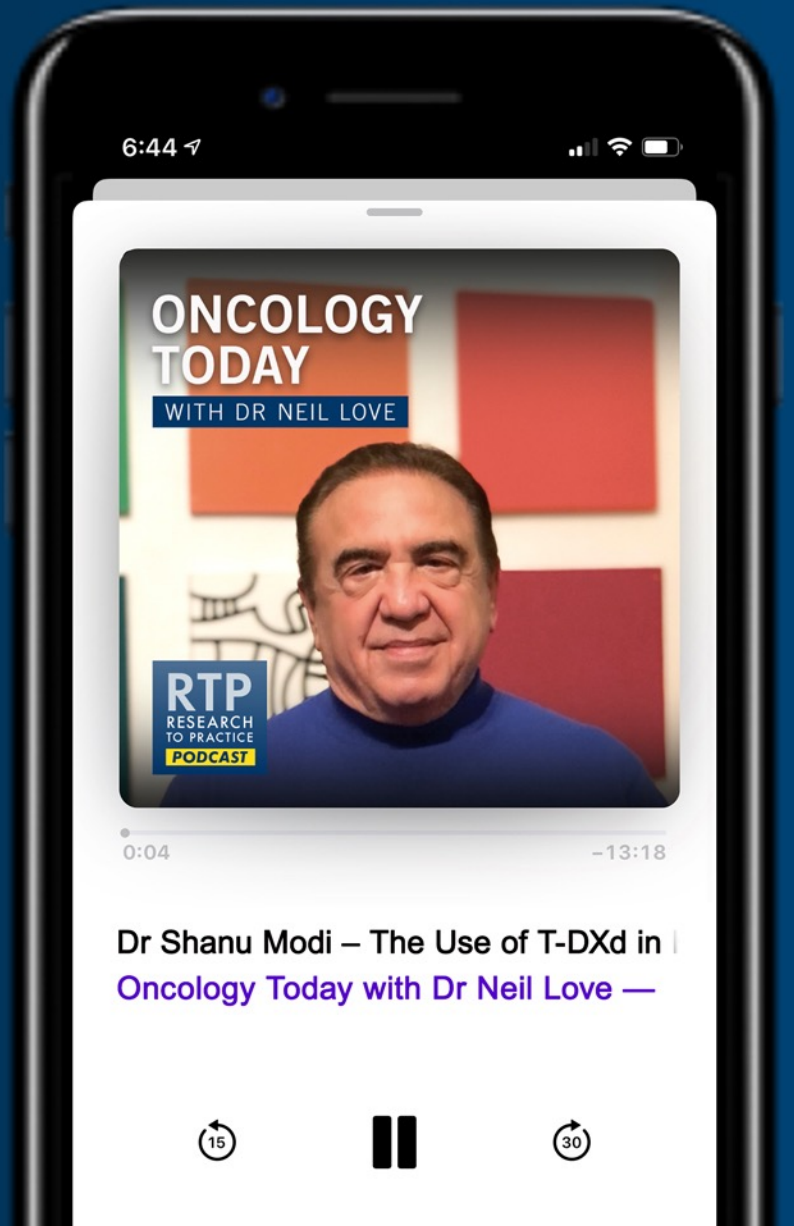

# Exploring Current Considerations and Promising Investigational Approaches for Patients with Myelodysplastic Syndromes

*A CME/MOC-Accredited Virtual Event*

**Thursday, September 8, 2022**

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## Faculty

**Guillermo Garcia-Manero, MD**
**Gail J Roboz, MD**
**David Sallman, MD**

## Moderator

**Neil Love, MD**

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# Challenging Cases from the Community: Investigators Provide Perspectives on the Optimal Management of Diffuse Large B-Cell Lymphoma

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## Faculty

**Jeremy Abramson, MD**
**Sonali M Smith, MD**
**Jason Westin, MD, MS**

## Moderator

**Neil Love, MD**

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# Oncology Today with Dr Neil Love — Management of Endometrial Cancer

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## Faculty

**Michael J Birrer, MD, PhD**

## Moderator

**Neil Love, MD**

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# Current Paradigm and Future Directions for Immunotherapy in the Treatment of Metastatic Non-Small Cell Lung Cancer

*A CME/MOC-Accredited Virtual Event*

**Tuesday, September 27, 2022**
**5:00 PM – 6:00 PM ET**

## Faculty

*Faculty to be announced*

## Moderator

**Neil Love, MD**

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*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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# *Meet The Professor*
# Optimizing the Management of HER2-Positive Breast Cancer

**Mark D Pegram, MD**
Susy Yuan-Huey Hung Endowed Professor of Oncology
Director, Clinical and Translational Research Unit
Associate Dean for Clinical Research Quality
Stanford University School of Medicine
Associate Director for Clinical Research
Stanford Comprehensive Cancer Institute
Stanford, California

# *Meet The Professor* Program Participating Faculty

**Adam M Brufsky, MD, PhD**
Professor of Medicine
Co-Director, Comprehensive Breast Cancer Center
UPMC Hillman Cancer Center
Department of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

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

**Lisa A Carey, MD, ScM**
L Richardson and Marilyn Jacobs Preyer Distinguished Professor for Breast Cancer Research
Deputy Director for Clinical Sciences
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, North Carolina

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

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# *Meet The Professor* Program Participating Faculty

**Joyce O'Shaughnessy, MD**
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

**MODERATOR**
**Neil Love, MD**
Research To Practice

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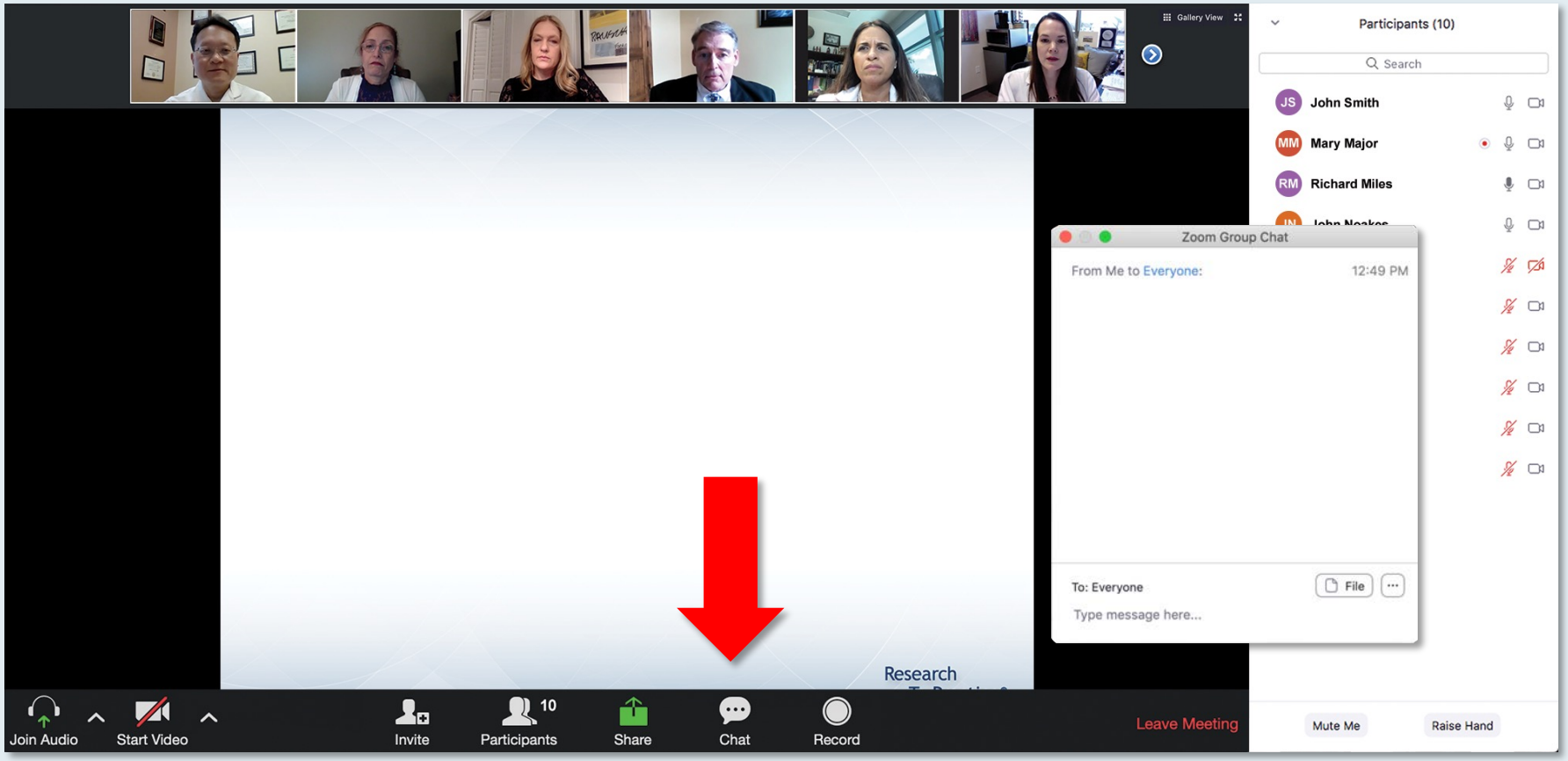


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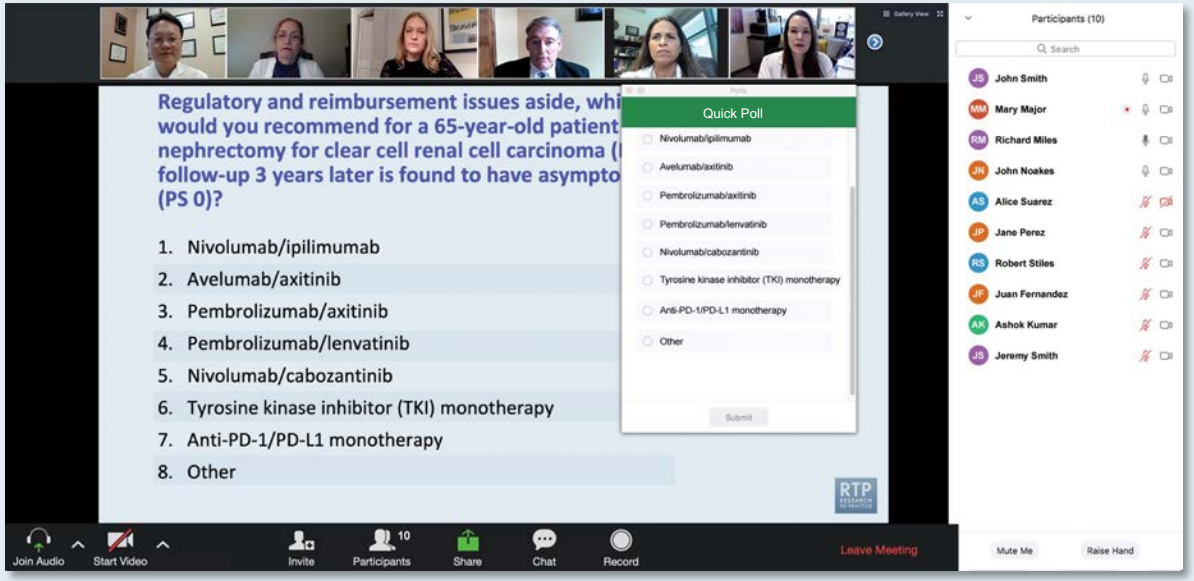


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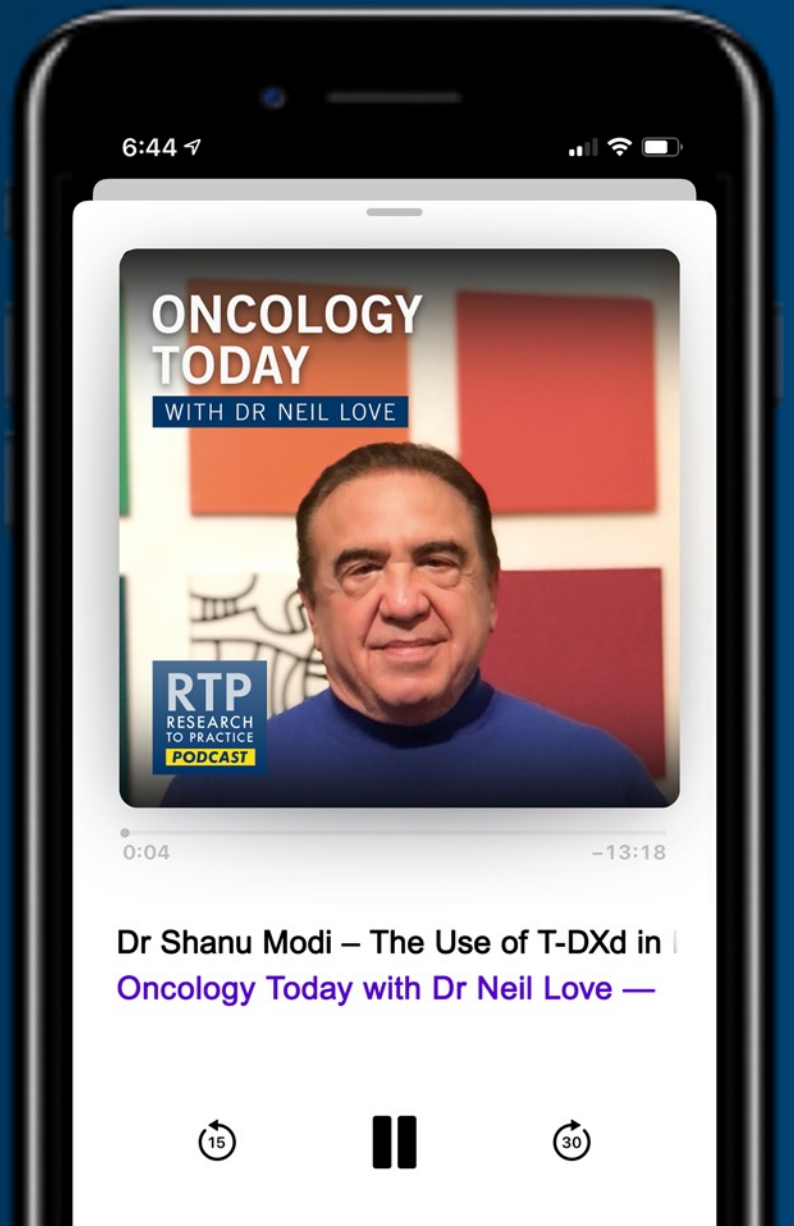

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# Dr Pegram — Disclosures

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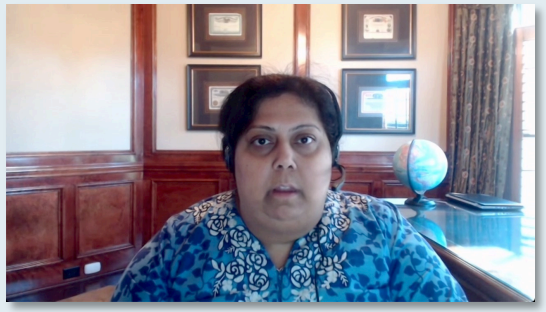
**Alan B Astrow, MD**
NewYork-Presbyterian Brooklyn Methodist Hospital
Brooklyn, New York

**Shaachi Gupta, MD, MPH**
Florida Cancer Specialists
Lake Worth, Florida

**Zanetta S Lamar, MD**
Florida Cancer Specialists
Naples, Florida

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



**Niyati A Nathwani, MD**
Carolina Blood and Cancer Care Associates
Charlotte, North Carolina

**Chris Prakash, MD**
US Oncology Research
Paris, Texas

**Raman Sood, MD**
Brooks Memorial Hospital
Dunkirk, New York

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# Meet The Professor with Dr Pegram

**Introduction: Journal Club with Dr Pegram – Part 1**

**MODULE 1: Case Presentations**

**MODULE 2: Faculty Survey**

**MODULE 3: Journal Club with Dr Pegram – Part 2**

**MODULE 4: Appendix**

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npj | Breast Cancer

*NPJ Breast Cancer* 2021 October 8;7(1):134. www.nature.com/npjbcancer

REVIEW ARTICLE OPEN

# A careful reassessment of anthracycline use in curable breast cancer

Sara Alsterlind Hurvitz[1]✉, Nicholas P. McAndrew[1], Aditya Bardia[2], Michael F. Press[3], Mark Pegram[4], John P. Crown[5], Peter A. Fasching[6], Bent Ejlertsen[7], Eric H. Yang[1], John A. Glaspy[1] and Dennis J. Slamon[1]

**"The following statements are true: as of this writing, there has been no prospective randomized trial that has demonstrated an OS benefit from the addition of anthracyclines to taxane-based chemotherapy in the curative setting … no randomized study has shown the addition of anthracycline to a taxane/trastuzumab-based regimen improves outcomes for HER2-amplified breast cancer … Thus, rather than asking which patients can be safely be treated *without* an anthracycline, we should be asking, does the data clearly exist to warrant the use of an anthracycline, keeping in mind that in many cases we are potentially harming patients more than helping them."**

Hurvitz SA et al. *NPJ Breast Cancer* 2021 October 8;7(1):134.

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*J Clin Oncol* 2021 August 20;39(24):2667-75.

original reports

# Pertuzumab Plus High-Dose Trastuzumab in Patients With Progressive Brain Metastases and HER2-Positive Metastatic Breast Cancer: Primary Analysis of a Phase II Study

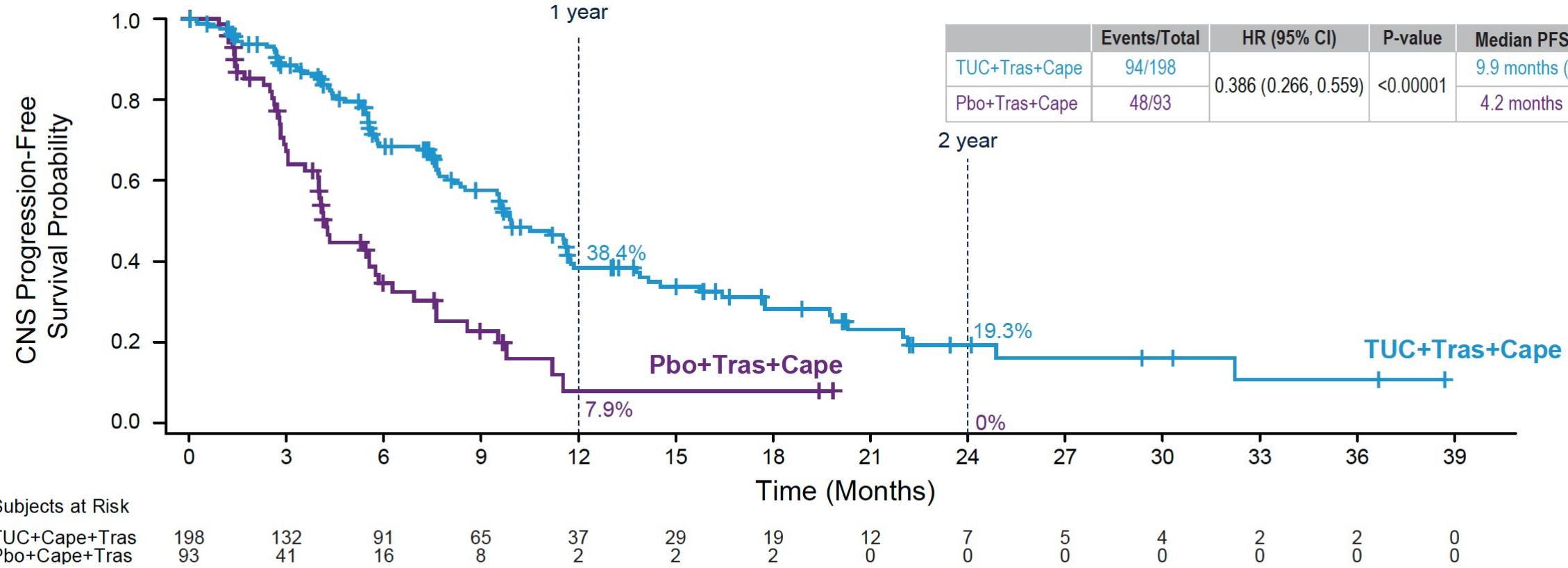
Nancy U. Lin, MD[1]; Mark Pegram, MD[2]; Solmaz Sahebjam, MD[3]; Nuhad Ibrahim, MD[4]; Anita Fung, PharmD[5]; Anna Cheng, PharmD[5]; Alan Nicholas, PhD[5]; Whitney Kirschbrown, PharmD, PhD[5]; and Priya Kumthekar, MD[6]

# Updated Results of Tucatinib vs Placebo Added to Trastuzumab and Capecitabine for Patients with Previously Treated HER2-Positive Metastatic Breast Cancer with Brain Metastases (HER2CLIMB)

Lin NU et al.

SABCS 2021;Abstract PD4-04.

# HER2CLIMB: CNS-PFS for All Patients with Brain Metastases




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

Subjects at Risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TUC+Cape+Tras | 198 | 132 | 91 | 65 | 37 | 29 | 19 | 12 | 7 | 5 | 4 | 2 | 2 | 0 |
| Pbo+Cape+Tras | 93 | 41 | 16 | 8 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- CNS-PFS benefit with tucatinib was maintained with longer follow-up in all patients with brain metastases.

CNS-PFS = central nervous system progression-free survival

Lin NU et al. SABCS 2021;Abstract PD4-04.

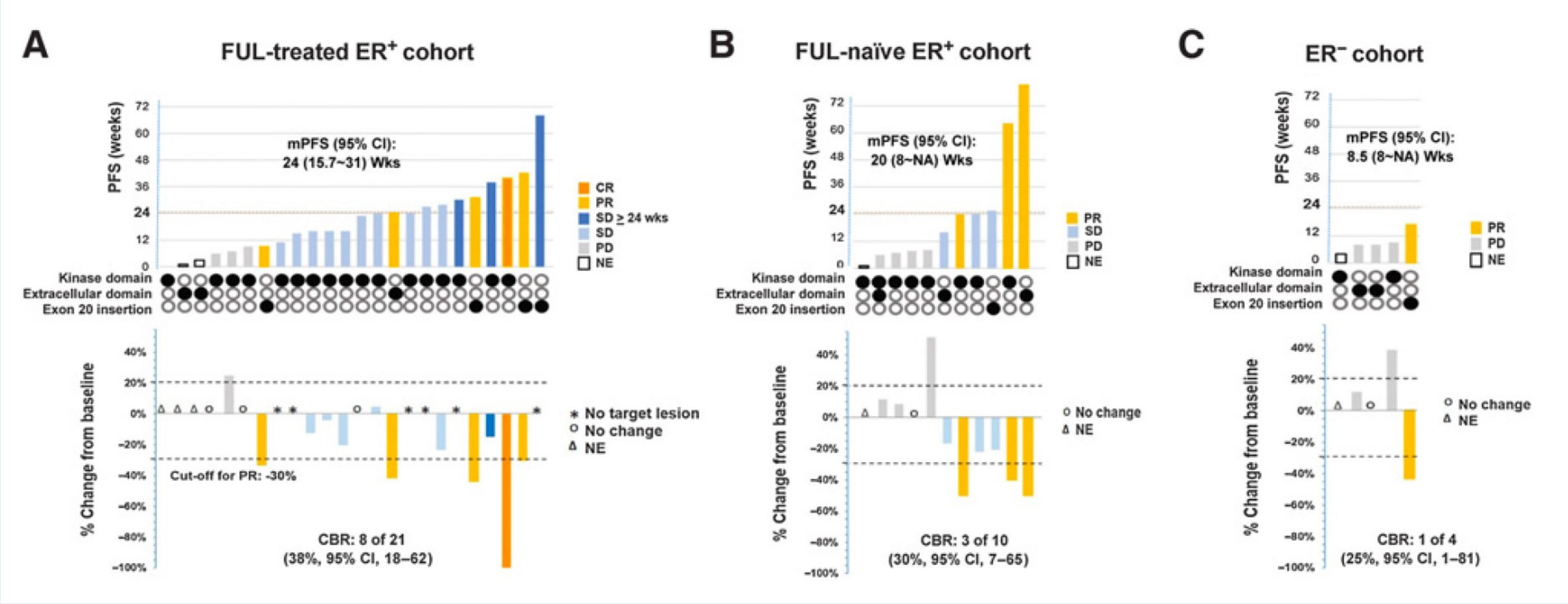
*Clin Cancer Res* 2022 April 1;28(7):1258-67.

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

# The Phase II MutHER Study of Neratinib Alone and in Combination with Fulvestrant in HER2-Mutated, Non-amplified Metastatic Breast Cancer

Cynthia X. Ma[1,2], Jingqin Luo[2,3], Rachel A. Freedman[4], Timothy J. Pluard[5], Julie R. Nangia[6], Janice Lu[7], Frances Valdez-Albini[8], Melody Cobleigh[9], Jason M. Jones[10], Nancy U. Lin[4], Eric P. Winer[4], P. Kelly Marcom[11], Shana Thomas[1], Jill Anderson[1], Brittney Haas[1], Leslie Bucheit[12], Richard Bryce[13], Alshad S. Lalani[13], Lisa A. Carey[14], Matthew P. Goetz[15], Feng Gao[2,3], Gretchen Kimmick[11], Mark D. Pegram[16], Matthew J. Ellis[17], and Ron Bose[1,2]

# Efficacy of Neratinib with Fulvestrant for ER-Positive Cohorts and Neratinib Monotherapy for ER-Negative Cohort




Ma CX et al. *Clin Cancer Res* 2022 April 1;28(7):1258-67.

# Meet The Professor with Dr Pegram

## MODULE 1: Case Presentations

- Dr Sood: 65-year-old woman with ER/PR-, HER2+ metastatic breast cancer, s/p multiple lines of HER2-directed therapy, now NED after 8 years of pertuzumab/trastuzumab
- Dr Gupta: 63-year-old woman with a 1.8-cm triple-positive IDC s/p partial mastectomy/ALND (9 N+) receives adjuvant TCHP x 6
- Dr Prakash: 70-year-old woman with de novo ER+, HER2+ breast cancer who develops asymptomatic, bilateral brain metastases on TCHP
- Dr Nathwani: 44-year-old woman with metastatic ER/PR-, HER2+ breast cancer completes THP with CR but 3 months later has multiple brain metastases
- Dr Lamar: 31-year-old woman with ER/PR+, HER2- breast cancer s/p neoadjuvant dd AC → paclitaxel and bilateral mastectomy, now with HER2+ disease on repeat testing
- Dr Astrow: 45-year-old woman with triple-negative breast cancer at biopsy declines neoadjuvant therapy and at surgery has a 3.2-cm node-negative, HER2+ tumor
- Dr Metzner-Sadurski: 62-year-old woman with ER/PR-, HER2+ breast cancer develops paralysis but recovers functioning after paclitaxel/trastuzumab, now with bone metastases responding to T-DXd

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# Case Presentation: 65-year-old woman with ER/PR-, HER2+ metastatic breast cancer, s/p multiple lines of HER2-directed therapy, now NED after 8 years of pertuzumab/trastuzumab


**Dr Raman Sood (Dunkirk, New York)**

RTP RESEARCH TO PRACTICE

# A 63-year-old woman with a 1.8-cm ER-positive, HER2-positive IDC goes directly to surgery and is found to have 9 positive nodes. What would be your likely postoperative systemic approach?

- Chemotherapy/trastuzumab/pertuzumab
- Chemotherapy/trastuzumab/pertuzumab → T-DM1
- Chemotherapy/trastuzumab/pertuzumab → T-DM1 → neratinib
- Chemotherapy/trastuzumab/pertuzumab → neratinib
- Other
- I'm not sure

# Case Presentation: 63-year-old woman with a 1.8-cm triple-positive IDC s/p partial mastectomy/ALND (9 N+) receives adjuvant TCHP x 6

Dr Shaachi Gupta (Lake Worth, Florida)

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**A 70-year-old woman with de novo ER-positive, HER2-positive metastatic breast cancer responds to TCHP but then has disease progression, including asymptomatic bilateral brain metastases. Generally, would you use systemic treatment and hold off on radiation therapy?**

- Yes
- No, I would likely use radiation therapy also
- I'm not sure

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# Which systemic treatment would you likely recommend for the patient in the previous scenario?

- T-DM1
- Tucatinib/trastuzumab/capecitabine
- Tucatinib
- Trastuzumab deruxtecan (T-DXd)
- Other
- I’m not sure

# Case Presentation: 70-year-old woman with de novo ER+, HER2+ breast cancer who develops asymptomatic, bilateral brain metastases on TCHP

Dr Chris Prakash (Paris, Texas)

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# Case Presentation: 44-year-old woman with metastatic ER/PR-, HER2+ breast cancer completes THP with CR but 3 months later has multiple brain metastases

**Dr Niyati Nathwani (Charlotte, North Carolina)**

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**A 31-year-old patient with T2N2 ER-positive, HER2-negative IDC receives neoadjuvant dose-dense AC-T with minor response at surgery, but the tumor is now HER2-positive and a BRCA2 mutation is found. Which of the following agents would likely be part of your adjuvant systemic strategy?**

- Trastuzumab, pertuzumab
- Trastuzumab, pertuzumab, neratinib
- Trastuzumab, pertuzumab, neratinib, olaparib
- Trastuzumab, pertuzumab, olaparib
- Paclitaxel, trastuzumab, pertuzumab
- Paclitaxel, trastuzumab, pertuzumab, neratinib
- Paclitaxel, trastuzumab, pertuzumab, neratinib, olaparib
- Paclitaxel, trastuzumab, pertuzumab, olaparib
- Other
- I’m not sure

RTP RESEARCH TO PRACTICE

# Case Presentation: 31-year-old woman with ER/PR+, HER2- breast cancer s/p neoadjuvant dd AC → paclitaxel and bilateral mastectomy, now with HER2+ disease on repeat testing

Dr Zanetta Lamar (Naples, Florida)

RTP RESEARCH TO PRACTICE

# A 45-year-old patient with a 3.2-cm ER-positive, HER2-positive IDC goes directly to surgery and is found to be node-negative. What would be your likely postoperative systemic approach?

- Chemotherapy/trastuzumab/pertuzumab
- Chemotherapy/trastuzumab/pertuzumab →neratinib
- Chemotherapy/trastuzumab
- Chemotherapy/trastuzumab → neratinib
- Other
- I'm not sure

RTP RESEARCH TO PRACTICE

# Case Presentation: 45-year-old woman with triple-negative breast cancer at biopsy declines neoadjuvant therapy and at surgery has a 3.2-cm node-negative, HER2+ tumor

Dr Alan Astrow (Brooklyn, New York)

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# Case Presentation: 62-year-old woman with ER/PR-, HER2+ breast cancer develops paralysis but recovers functioning after paclitaxel/trastuzumab, now with bone metastases responding to T-DXd

Dr Joanna Metzner-Sadurski (Greenwood, South Carolina)

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Introduction: Journal Club with Dr Pegram – Part 1

MODULE 1: Case Presentations

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MODULE 3: Journal Club with Dr Pegram – Part 2

MODULE 4: Appendix

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# Regulatory and reimbursement issues aside, would you offer trastuzumab deruxtecan to a patient with HER2 IHC 0 metastatic breast cancer (mBC) with a HER2 mutation?

| | | | |
|---|---|---|---|
|  Dr Brufsky | No |  Dr Lin | Yes |
|  Dr Carey | Yes |  Dr O'Shaughnessy | Yes |
|  Prof Curigliano | Yes |  Dr Pegram | No |

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# Regulatory and reimbursement issues aside, how are you most likely to approach the use of trastuzumab deruxtecan for HER2 IHC 1+ versus HER2 IHC 2+ mBC?

| | | | |
|---|---|---|---|
|  Dr Brufsky | Equally likely to use for IHC 2+ and IHC 1+ disease |  Dr Lin | Equally likely to use for IHC 2+ and IHC 1+ disease |
|  Dr Carey | Equally likely to use for IHC 2+ and IHC 1+ disease |  Dr O'Shaughnessy | Equally likely to use for IHC 2+ and IHC 1+ disease |
|  Prof Curigliano | Equally likely to use for IHC 2+ and IHC 1+ disease |  Dr Pegram | Equally likely to use for IHC 2+ and IHC 1+ disease |

# A woman who has completed 5 years of an adjuvant aromatase inhibitor for ER-positive, HER2 IHC 2+, FISH-negative breast cancer develops symptomatic liver metastases 3 years later. Regulatory and reimbursement issues aside, when would you most likely offer trastuzumab deruxtecan?


RTP RESEARCH TO PRACTICE

# A woman undergoes neoadjuvant chemotherapy and surgery for BRCA wild-type, ER-negative, HER2 IHC 2+, FISH-negative breast cancer and develops symptomatic liver metastases while receiving adjuvant capecitabine. Regulatory and reimbursement issues aside, when would you most likely offer trastuzumab deruxtecan?

| | | | |
|---|---|---|---|
|  Dr Brufsky | As first-line therapy |  Dr Lin | As second-line therapy |
|  Dr Carey | As second-line therapy |  Dr O'Shaughnessy | As third-line therapy |
|  Prof Curigliano | As first-line therapy |  Dr Pegram | As first-line if PD-L1(-), second-line if PD-L1(+) |

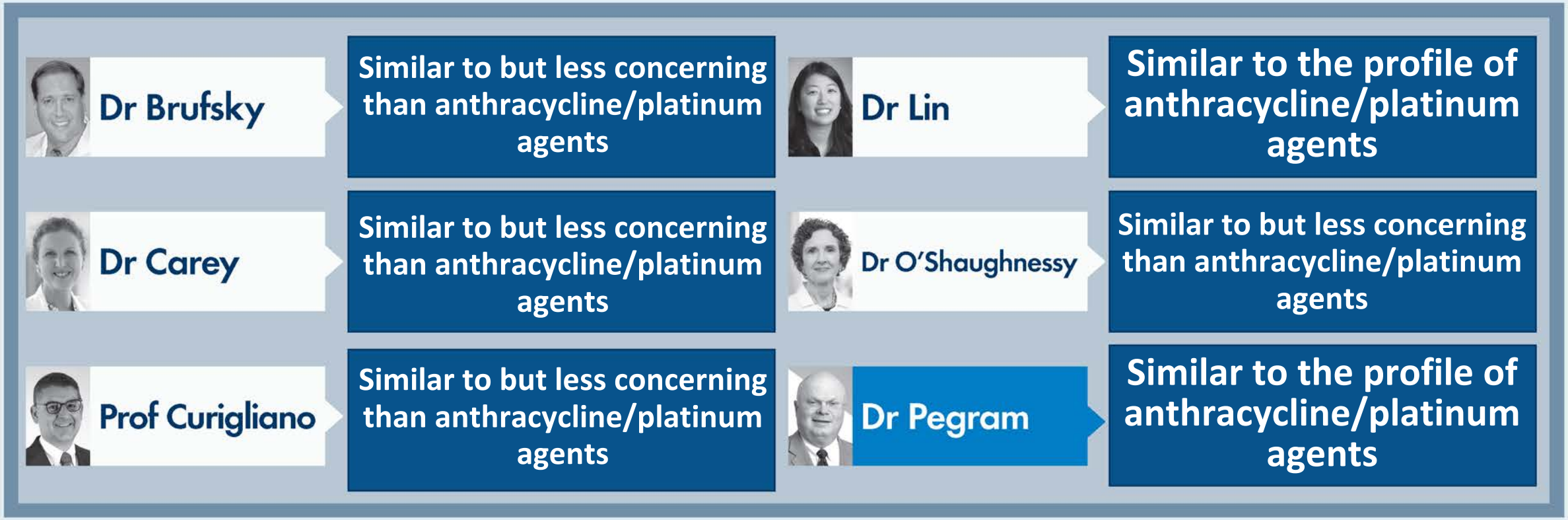
RTP RESEARCH TO PRACTICE

# On the basis of your personal experience and available clinical trial data, how would you characterize the degree of alopecia observed with trastuzumab deruxtecan?

| | | | |
|---|---|---|---|
|  Dr Brufsky | Less alopecia than that observed with platinum agents |  Dr Lin | Moderate alopecia as observed with platinum agents |
|  Dr Carey | Moderate alopecia as observed with platinum agents |  Dr O'Shaughnessy | Moderate alopecia as observed with platinum agents |
|  Prof Curigliano | Moderate alopecia as observed with platinum agents |  Dr Pegram | Moderate alopecia as observed with platinum agents |

RTP RESEARCH TO PRACTICE

# On the basis of your personal experience and available clinical trial data, how would you describe the “chemotherapy-like” side-effect profile (fatigue, GI symptoms) of trastuzumab deruxtecan?



# What grade of interstitial lung disease (ILD) would lead you to permanently discontinue treatment with trastuzumab deruxtecan?

| | | | |
|---|---|---|---|
|  Dr Brufsky | Grade 2 |  Dr Lin | Grade 2 |
|  Dr Carey | Grade 2 |  Dr O'Shaughnessy | Grade 2 |
|  Prof Curigliano | Grade 3 or 4 |  Dr Pegram | Grade 2, or Grade 1 if no resolution by day 49 |

RTP RESEARCH TO PRACTICE

# Have you re-administered trastuzumab deruxtecan to a patient who developed Grade 1 ILD and recovered from it?

| | | | |
|---|---|---|---|
|  Dr Brufsky | Yes |  Dr Lin | Yes |
|  Dr Carey | Yes |  Dr O'Shaughnessy | Yes |
|  Prof Curigliano | Yes |  Dr Pegram | Yes |

RTP RESEARCH TO PRACTICE

# Do you use chest imaging to monitor a patient receiving trastuzumab deruxtecan who otherwise does not require chest imaging? How often would you perform chest imaging if the patient remained asymptomatic?

| | | | |
|---|---|---|---|
|  Dr Brufsky | No |  Dr Lin | Yes, every 3 to 4 cycles |
|  Dr Carey | No if asymptomatic |  Dr O'Shaughnessy | No |
|  Prof Curigliano | No |  Dr Pegram | Yes, q6weeks |

NA = not applicable

# Do you evaluate pulmonary function, either clinically or by specific PFTs?

| | | | |
|---|---|---|---|
|  Dr Brufsky | No |  Dr Lin | Yes |
|  Dr Carey | Yes |  Dr O'Shaughnessy | No |
|  Prof Curigliano | No |  Dr Pegram | No |

RTP RESEARCH TO PRACTICE

# Regulatory and reimbursement issues aside, which next line of therapy would you recommend to a patient with hormone receptor-negative, HER2 IHC 1+ or 2+, BRCA wild-type breast cancer who receives neoadjuvant chemoimmunotherapy and develops metastatic disease while receiving adjuvant immunotherapy?

| | | | |
|---|---|---|---|
|  Dr Brufsky | Sacituzumab govitecan |  Dr Lin | Sacituzumab govitecan |
|  Dr Carey | T-DXd |  Dr O'Shaughnessy | Sacituzumab govitecan |
|  Prof Curigliano | Sacituzumab govitecan |  Dr Pegram | Sacituzumab govitecan or T-DXd |

RTP RESEARCH TO PRACTICE

# Meet The Professor with Dr Pegram

Introduction: Journal Club with Dr Pegram – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

**MODULE 3: Journal Club with Dr Pegram – Part 2**

MODULE 4: Appendix

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*Front Oncol* 2022 April 27;12:890810.

# Editorial: Metabolic Abnormalities and Breast Cancer: Challenges From Bench to Bedside

*Zheng Wang[1*], Pu Li[2*], Mark Daniel Pegram[3*] and Xiaosong Chen[1*]*

# *Frontiers in Oncology* July 2022

## Table of Contents

# *Frontiers in Oncology* July 2022

## Table of Contents (Continued)

# *Frontiers in Oncology* July 2022

## Table of Contents (Continued)

Original Study

*Clin Breast Cancer* 2021 August;21(4):e340-61.

# Real-world Evidence of Diagnostic Testing and Treatment Patterns in US Patients With Breast Cancer With Implications for Treatment Biomarkers From RNA Sequencing Data

Louis E. Fernandes,[1] Caroline G. Epstein,[1] Alexandria M. Bobe,[1] Joshua S.K. Bell,[1] Martin C. Stumpe,[1] Michael E. Salazar,[1] Ameen A. Salahudeen,[1] Ruth A. Pe Benito,[1] Calvin McCarter,[1] Benjamin D. Leibowitz,[1] Matthew Kase,[1] Catherine Igartua,[1] Robert Huether,[1] Ashraf Hafez,[1] Nike Beaubier,[1] Michael D. Axelson,[1] Mark D. Pegram,[2] Sarah L. Sammons,[3] Joyce A. O'Shaughnessy,[4] Gary A. Palmer[1]

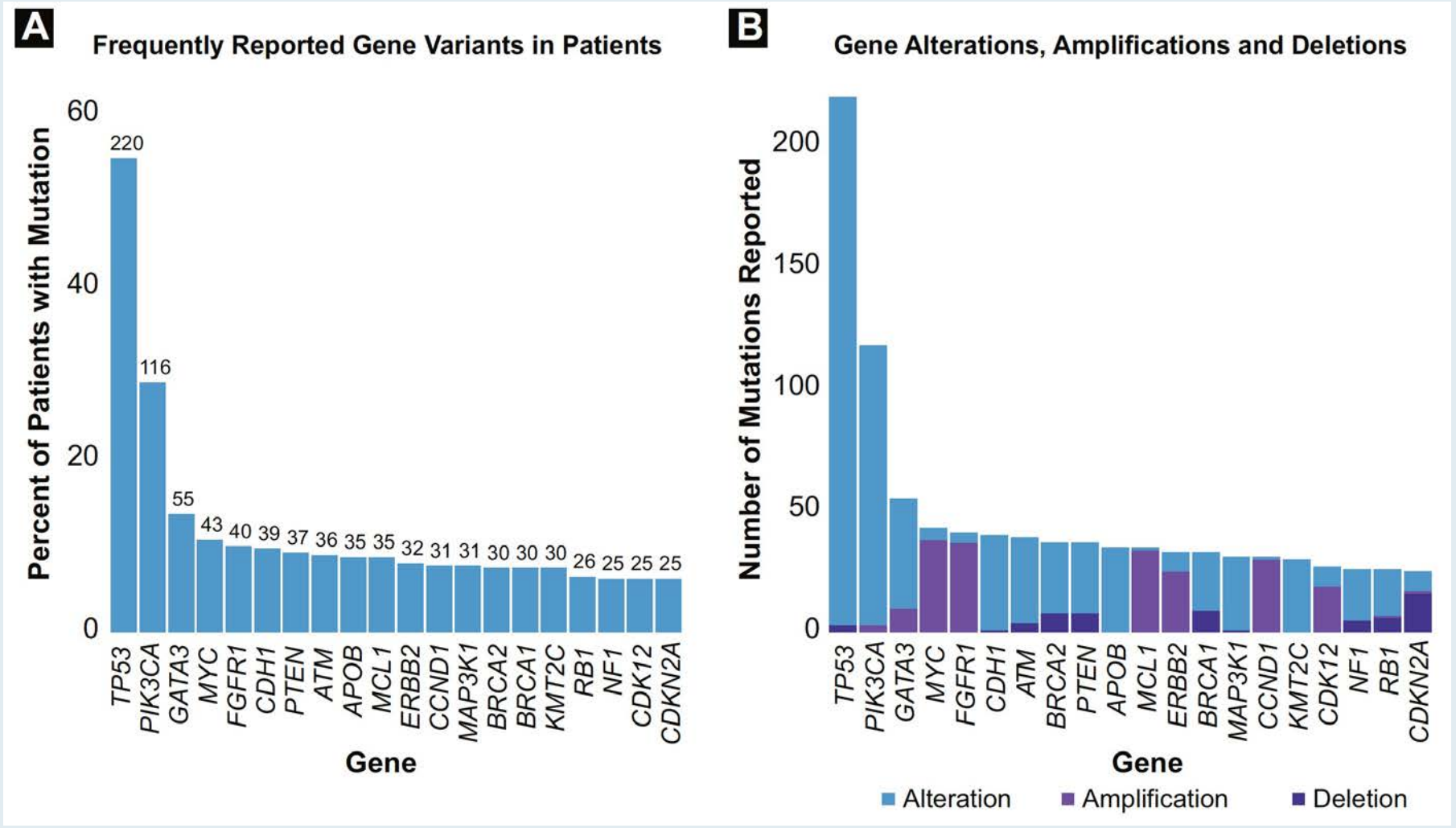
**Supplementary Table 2** Inter-test Comparison of HER2 Status From IHC and FISH Results Among Patients in the Clinical Abstraction Cohort With Both Tests Conducted at Initial Diagnosis (N = 709)

| HER2 Status | IHC Positive (n = 82), n (%) | IHC Equivocal (n = 445), n (%) | IHC Negative (n = 182), n (%) |
|---|---|---|---|
| FISH positive | 51 (62.2) | 51 (11.5) | 7 (3.9) |
| FISH equivocal | 5 (6.1) | 35 (7.9) | 9 (4.9) |
| FISH negative | 26 (31.7) | 359 (80.7) | 166 (91.2) |
| Total discordant | 31 (37.8) | 410 (92.1) | 16 (8.8) |

Abbreviations: FISH = Fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.

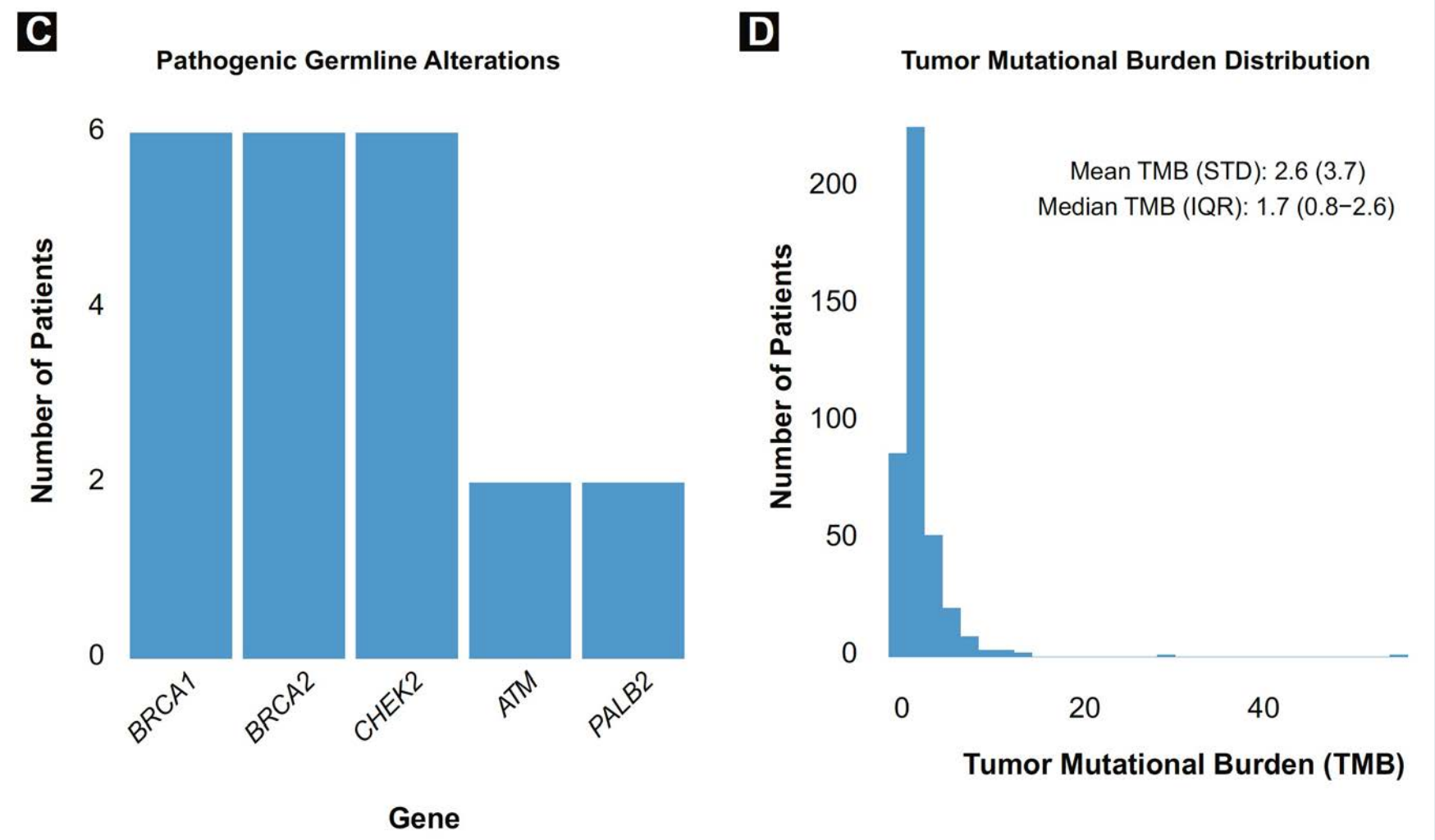
Fernandes LE et al. *Clin Breast Cancer* 2021 August;21(4):e340-61.

# Molecular Characteristics of the Tempus Molecular Sequenced Cohort




Fernandes LE et al. *Clin Breast Cancer* 2021 August;21(4):e340-61.

# Molecular Characteristics of the Tempus Molecular Sequenced Cohort (Continued)




Fernandes LE et al. *Clin Breast Cancer* 2021 August;21(4):e340-61.

Open access Review

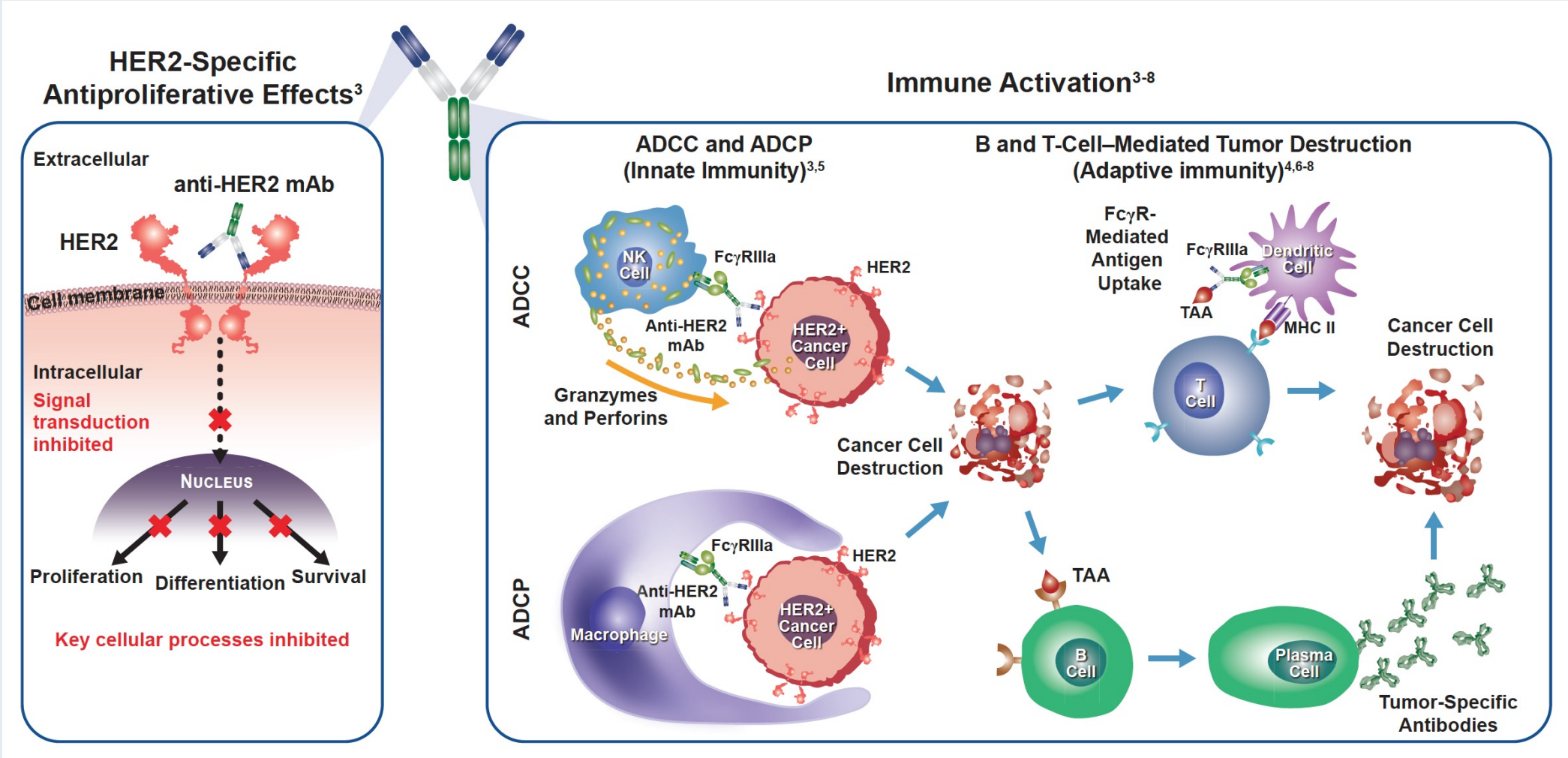
Journal for ImmunoTherapy of Cancer

# Role of Fcγ receptors in HER2-targeted breast cancer therapy

Antonino Musolino,[1] William J Gradishar,[2] Hope S Rugo ,[3] Jeffrey L Nordstrom,[4] Edwin P Rock,[4] Fernanda Arnaldez,[4] Mark D Pegram[5]

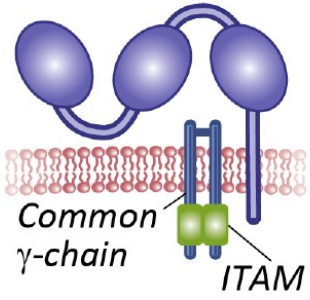
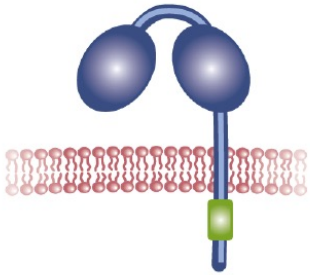
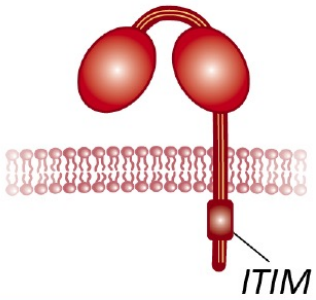
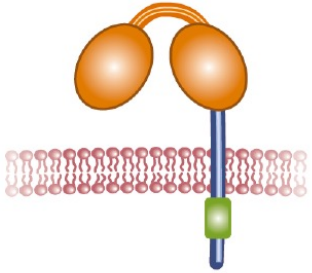
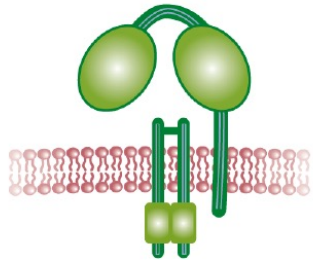
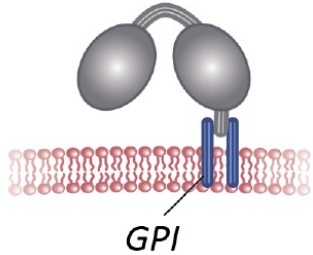
*J Immunother Cancer* 2022 January;10(1):e003171.

# Mechanism of Action of Anti-HER2 Monoclonal Antibodies: Antiproliferative Effects and Immune Activation



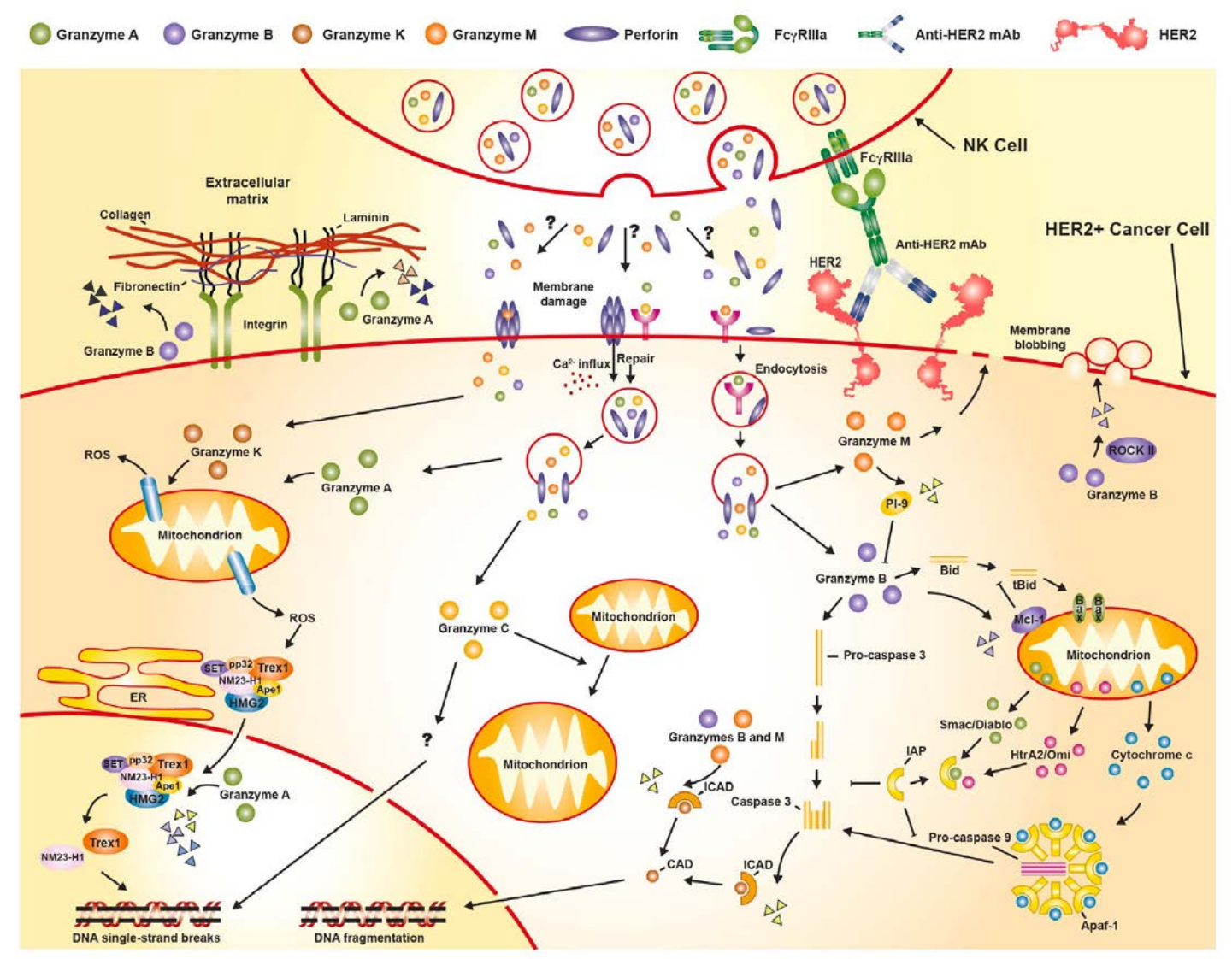

Musolino A et al. *J Immunother Cancer* 2022 January;10(1):e003171.

# Fcγ Receptors Differ in Function, Cell Distribution, Immune Response, Signaling Motifs and Affinity for IgG Molecules

| Name | FcγRI CD64 | FcγRIIa CD32A | FcγRIIb CD32B | FcγRIIc CD32C | FcγRIIIa CD16A | FcγRIIIb CD16B |
|---|---|---|---|---|---|---|
| Structure[11] |   |  |   |  |  |   |
| Function[11] | Activating | Activating | Inhibitory | Activating | Activating | Activating |
| Affinity[11] | High | Low | Low | Low | Low | Low |
| Cell Distribution[9,12-26] | Macrophages, monocytes, neutrophils, dendritic cells, mast cells | Macrophages, monocytes, neutrophils, eosinophils basophils, dendritic cells, mast cells | Macrophages, monocytes, eosinophils, basophils, B cells, mast cells, dendritic cells[b] | NK cells, monocytes, neutrophils, macrophages, B cells[c] | NK cells, NKT cells, γδ T cells, dendritic cells, macrophages, monocytes, neutrophils, eosinophils | Neutrophils, eosinophils, basophils |
| Effect of Antibody Binding[9,10,27-33] | ADCP, cytokine release | ADCC, ADCP, vaccinal effect[a] | Inhibits ADCC, ADCP, B cell activation | Enhances ADCC, ADCP, B cell activation | ADCC, ADCP | Decoy receptor that inhibits ADCP[d] |

Musolino A et al. *J Immunother Cancer* 2022 January;10(1):e003171.

# Classical Granzyme/Perforin-Mediated Apoptosis Pathway




Musolino A et al. *J Immunother Cancer* 2022 January;10(1):e003171.

(Adapted from Bots and Medema)

RTP RESEARCH TO PRACTICE

*Proc Natl Acad Sci U S A* 2021 July 20;118(29):e2026849118.

# Combining CD47 blockade with trastuzumab eliminates HER2-positive breast cancer cells and overcomes trastuzumab tolerance

Rosalynd Upton[a], Allison Banuelos[a], Dongdong Feng[a], Tanuka Biswas[a], Kevin Kao[a], Kelly McKenna[a], Stephen Willingham[a], Po Yi Ho[a], Benyamin Rosental[b], Michal Caspi Tal[a], Tal Raveh[a], Jens-Peter Volkmer[a], Mark D. Pegram[c,1,2], and Irving L. Weissman[a,1,2]

# Meet The Professor with Dr Pegram

**Introduction: Journal Club with Dr Pegram – Part 1**

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**MODULE 4: Appendix**

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# Optimal Management of Patients with HER2-Positive Localized Breast Cancer (BC)

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TO PRACTICE

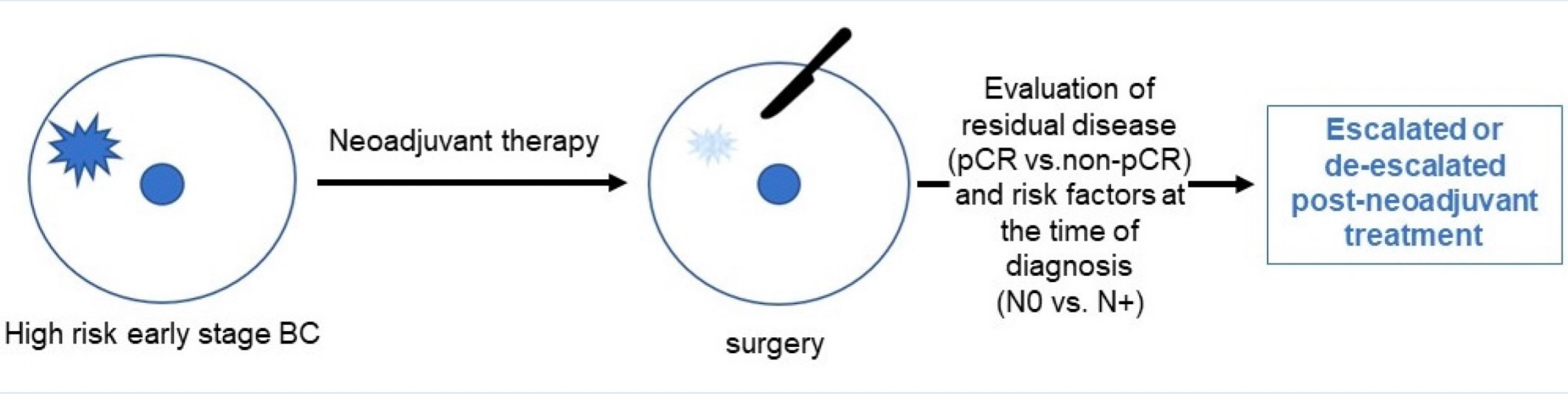
# FDA-Approved Agents for HER2-Positive Localized Breast Cancer

| Agent | Setting | Pivotal trial(s) | Regimens | Year approved |
|---|---|---|---|---|
| Trastuzumab | Adjuvant HER2+ LBC, first line | NSABP-31<br>N9831<br>BCIRG 006<br>HERA | AC-T-placebo vs AC-T-H<br>AC-T vs AC-H vs AC-T-H<br>AC-T vs ACT-H vs TC-H<br>Observation vs trastuzumab | 2006 |
| Pertuzumab | Neoadjuvant HER2+ LBC | NeoSphere | TD vs PTD vs PT vs PD | 2013 |
| Pertuzumab | Adjuvant HER2+ LBC | APHINITY | Chemotherapy + trastuzumab + pertuzumab vs placebo | 2017 |
| Neratinib | Extended adjuvant HER2+ LBC | ExteNET | Placebo vs neratinib | 2017 |
| T-DM1 | Adjuvant HER2+ LBC with residual disease after neoadjuvant taxane and trastuzumab-based treatment | KATHERINE | Trastuzumab vs T-DM1 | 2019 |

LBC = localized breast. cancer; AC = doxorubicin and cyclophosphamide; T = paclitaxel; H = trastuzumab; TC = docetaxel and cyclophosphamide; TD = trastuzumab and docetaxel; PTD = pertuzumab, trastuzumab and docetaxel; PT = pertuzumab and trastuzumab; PD = pertuzumab and docetaxel

Choong GM et al. *CA Cancer J Clin* 2020;70:355-74.

# Flow of Neoadjuvant and Adjuvant Therapy in Breast Cancer




Krawczyk N et al. Cancers 2022 Jun 18;14(12):3002.

ORIGINAL ARTICLE

*Ann Oncol* 2017;28:2768-72.

# De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR− phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel

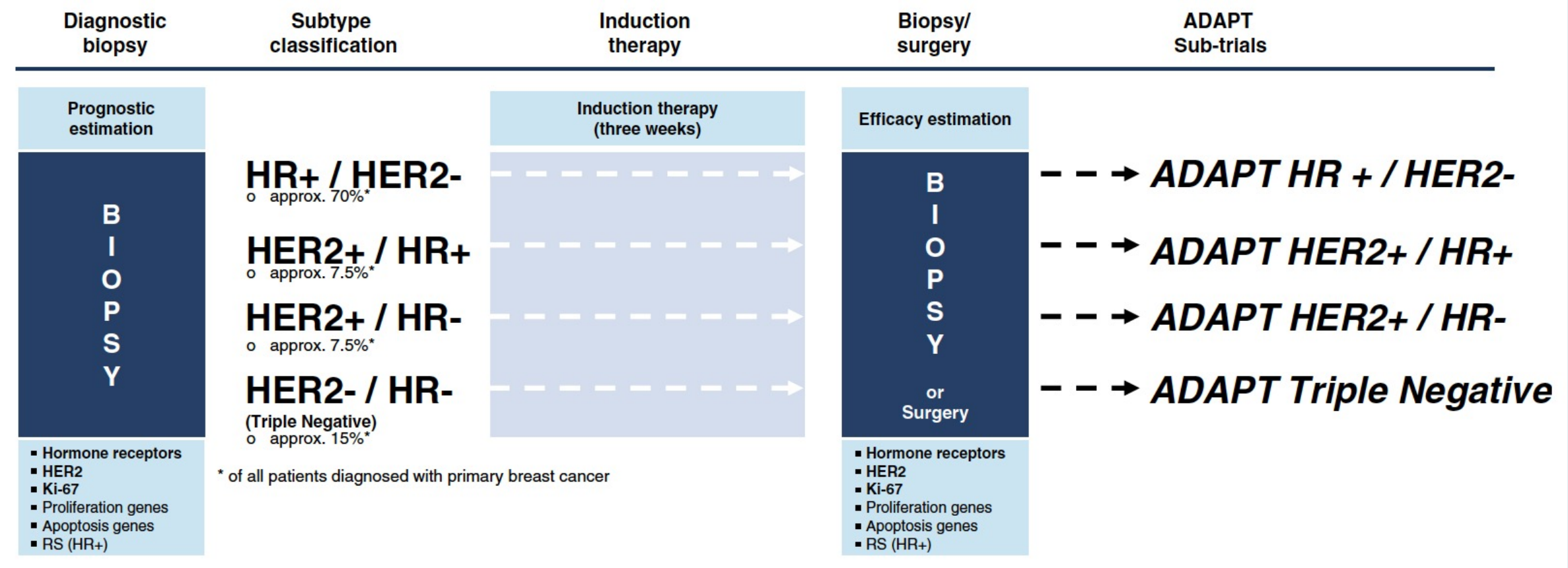
U. A. Nitz[1,2], O. Gluz[1,2,3*], M. Christgen[4], E.-M. Grischke[5], D. Augustin[6], S. Kuemmel[7], M. Braun[8], J. Potenberg[9], A. Kohls[10], K. Krauss[11], A. Stefek[12], C. Schumacher[13], H. Forstbauer[14], T. Reimer[15], H. Fischer[16], C. Liedtke[17,18], R. Wuerstlein[19], J. Schumacher[20], R. Kates[1], H. Kreipe[3] & N. Harbeck[1,19], on behalf of the West-German Study Group (WSG)-ADAPT Investigators

*Lancet Oncol* 2022;23:625-35.

# De-escalated neoadjuvant pertuzumab plus trastuzumab therapy with or without weekly paclitaxel in HER2-positive, hormone receptor-negative, early breast cancer (WSG-ADAPT-HER2+/HR–): survival outcomes from a multicentre, open-label, randomised, phase 2 trial

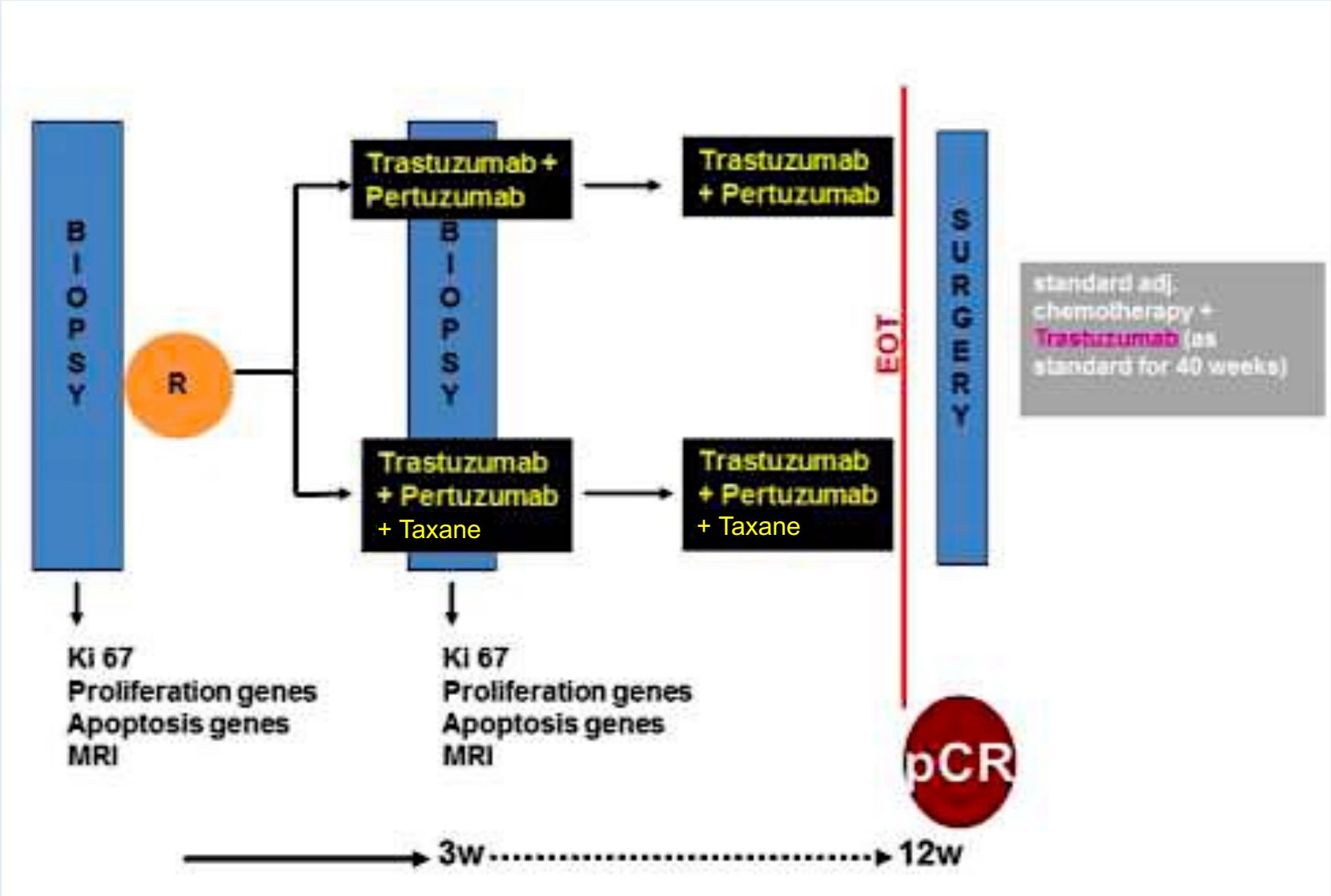
*Ulrike Nitz*, Oleg Gluz*, Monika Graeser, Matthias Christgen, Sherko Kuemmel, Eva-Maria Grischke, Michael Braun, Doris Augustin, Jochem Potenberg, Katja Krauss, Claudia Schumacher, Helmut Forstbauer, Toralf Reimer, Andrea Stefek, Hans Holger Fischer, Enrico Pelz, Christine zu Eulenburg, Ronald Kates, Rachel Wuerstlein, Hans Heinrich Kreipe, Nadia Harbeck, on behalf of the WSG-ADAPT investigators*

# Adjuvant Dynamic Marker-Adjusted Personalized Therapy (ADAPT) Trial: Umbrella Trial Design




Hofmann D et al. *Trials* 2013;14:261.

# ADAPT HER2-Positive Schema




Nitz U et al. *Lancet Oncol* 2022;23:625-35.

# WSG ADAPT Neoadjuvant Studies for HER2-Positive Disease

| Study | N and setting | Treatment arms | pCR rate* | Survival |
|---|---|---|---|---|
| **WSG-ADAPT HER2+/HR-** | 134<br>ER/PR-negative<br>cT1-4c | • Trastuzumab + pertuzumab<br>• Trastuzumab + pertuzumab + paclitaxel | 34.4% vs 90.5% | **5-year iDFS**<br>87% vs 98%<br>**5-year dDFS**<br>92% vs 98%<br>**5-year OS**<br>94% vs 98% |
| **WSG-ADAPT-TP HER2+/HR+** | 375<br>ER and/or PR-positive<br>cT1-4c | • T-DM1<br>• T-DM1 + ET<br>• Trastuzumab + ET | 41% vs 41.5% vs 15% | **5-year DFS**<br>88.9% vs 85.3% vs 84.6%<br>**5-year OS**<br>97.2% vs 96.4% vs 96.3 |

pCR = pathologic complete response; iDFS = invasive disease-free survival; dDFS = distant disease-free survival; OS = overall survival; ET = endocrine therapy

*Defined as ypT0/is ypN0

*Lancet Oncol* 2018;9(12):1630-40.

# Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial

*Mette S van Ramshorst, Anna van der Voort, Erik D van Werkhoven, Ingrid A Mandjes, Inge Kemper, Vincent O Dezentjé, Irma M Oving, Aafke H Honkoop, Lidwine W Tick, Agnes J van de Wouw, Caroline M Mandigers, Laurence J van Warmerdam, Jelle Wesseling, Marie-Jeanne T Vrancken Peeters, Sabine C Linn, Gabe S Sonke, on behalf of the Dutch Breast Cancer Research Group (BOOG)*

Research

*JAMA Oncol* 2021;7(7):978-84.

JAMA Oncology | Original Investigation

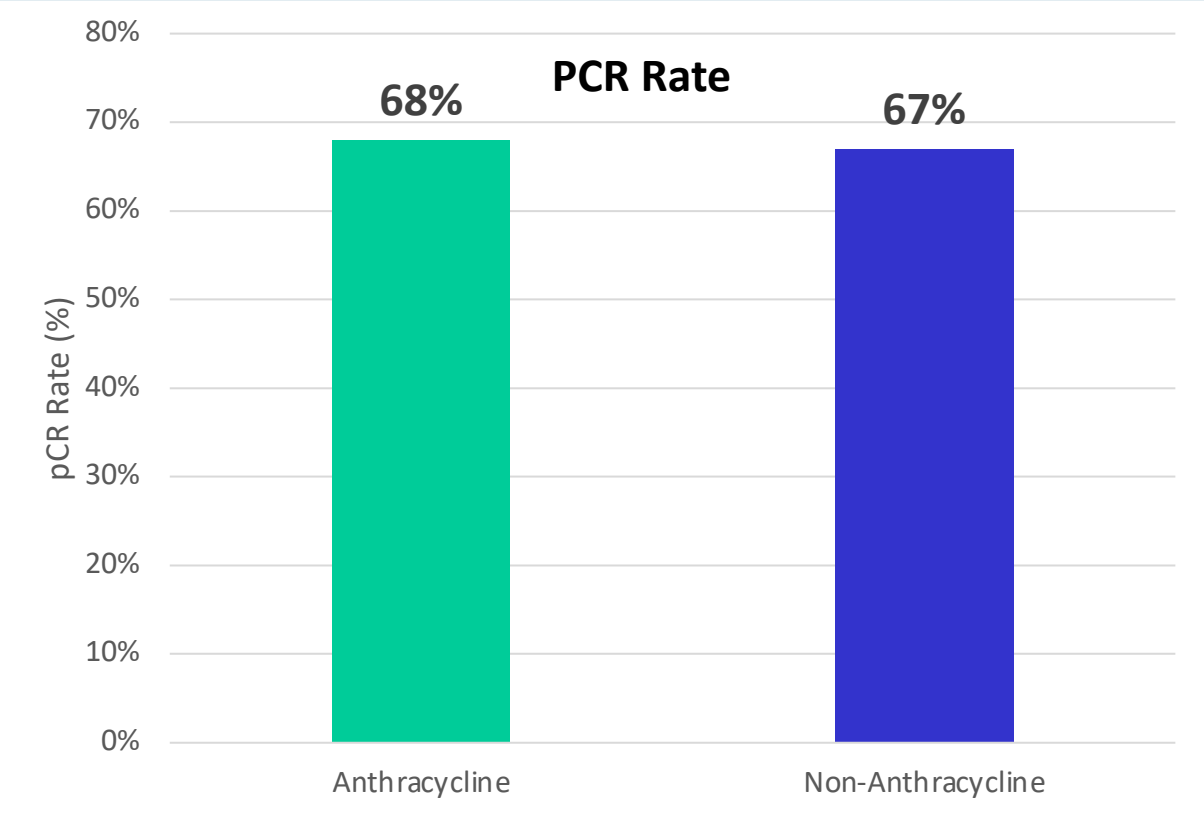
# Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual *ERBB2* Blockade in Patients With *ERBB2*-Positive Breast Cancer

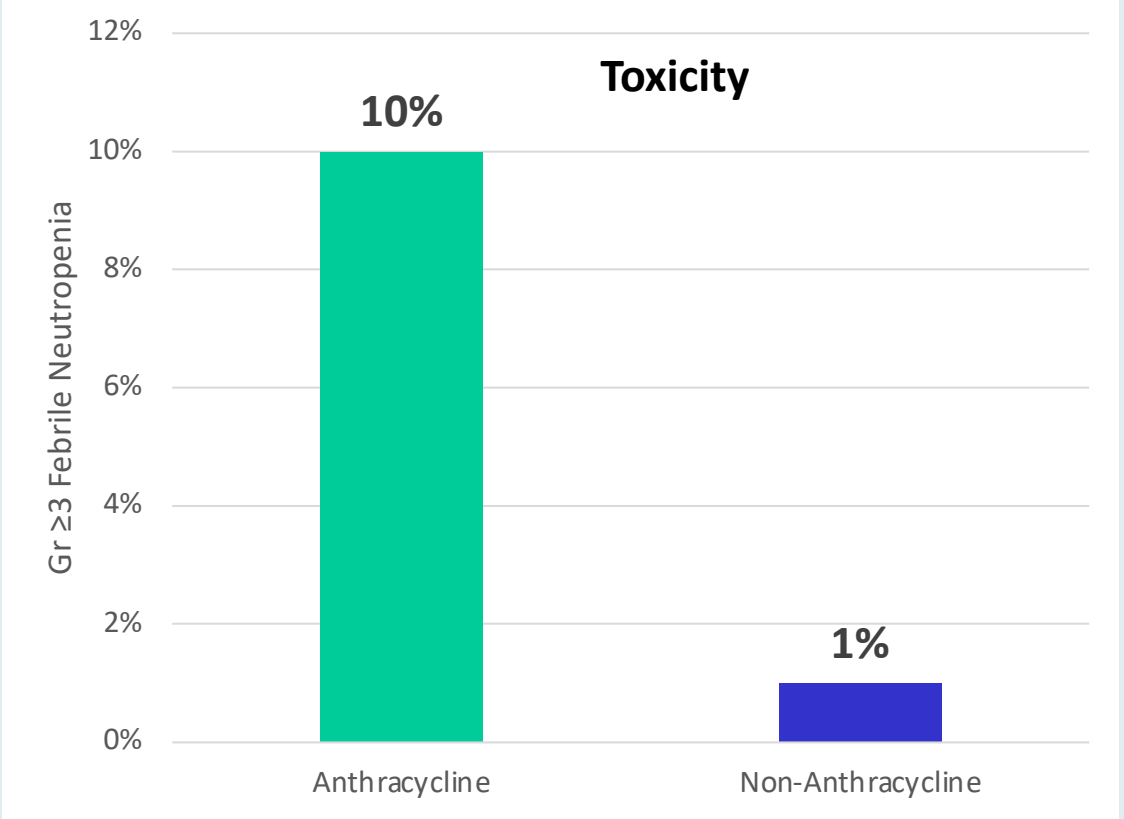
## A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial

Anna van der Voort, MD; Mette S. van Ramshorst, MD, PhD; Erik D. van Werkhoven, MSc; Ingrid A. Mandjes, MSc; Inge Kemper, MANP; Annelie J. Vulink, MD; Irma M. Oving, MD, PhD; Aafke H. Honkoop, MD, PhD; Lidwine W. Tick, MD, PhD; Agnes J. van de Wouw, MD, PhD; Caroline M. Mandigers, MD, PhD; Laurence J. van Warmerdam, MD, PhD; Jelle Wesseling, MD, PhD; Marie-Jeanne T. Vrancken Peeters, MD, PhD; Sabine C. Linn, MD, PhD; Gabe S. Sonke, MD, PhD

RTP RESEARCH TO PRACTICE

# TRAIN-2: pCR Rates and Key Toxicity Differences with Anthracycline- and Non-Anthracycline-Containing Regimens




van Ramshorst MS et al. *Lancet Oncol* 2018;9(12):1630-40.

RTP RESEARCH TO PRACTICE

# TRAIN-2: Three-Year Follow-Up Summary

- TRAIN-2 is not powered to detect differences for event-free survival (EFS) and OS secondary endpoints, and results are for descriptive purposes

| Endpoint | Anthracycline group (n = 219) | Nonanthracycline group (N = 219) | HR |
|---|---|---|---|
| 3-y EFS rate | 92.7% | 93.6% | 0.90 |
| 3-y OS rate | 97.7% | 98.2% | 0.91 |
| Results were irrespective of hormone receptor and nodal status | | | |

- pCR in the breast and axillary lymph nodes was associated with DFS (HR 0.42; $p = 0.006$)
- A decline in LVEF ≥10% from baseline to less than 50% was more common in patients who received anthracyclines than in those who did not (7.7% vs 3.2%; $p = 0$ .04)

van der Voort A et al. *JAMA Oncol* 2021;7(7):978-84.

original reports

# Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial

Sara M. Tolaney, MD, MPH[1,2]; Nabihah Tayob, PhD[1]; Chau Dang, MD[3]; Denise A. Yardley, MD[4]; Steven J. Isakoff, MD, PhD[5]; Vicente Valero, MD[6]; Meredith Faggen, MD[1]; Therese Mulvey, MD[5]; Ron Bose, MD, PhD[7]; Jiani Hu, MSc[1]; Douglas Weckstein, MD[1]; Antonio C. Wolff, MD[8]; Katherine Reeder-Hayes, MD, MBA, MSc[9]; Hope S. Rugo, MD[10]; Bhuvaneswari Ramaswamy, MD[11]; Dan Zuckerman, MD[12]; Lowell Hart, MD[13]; Vijayakrishna K. Gadi, MD, PhD[14]; Michael Constantine, MD[1]; Kit Cheng, MD[15]; Frederick Briccetti, MD[1]; Bryan Schneider, MD[16]; Audrey Merrill Garrett, MD[17]; Kelly Marcom, MD[18]; Kathy Albain, MD[19]; Patricia DeFusco, MD[20]; Nadine Tung, MD[2,21]; Blair Ardman, MD[22]; Rita Nanda, MD[23]; Rachel C. Jankowitz, MD[24]; Mothaffar Rimawi, MD[25]; Vandana Abramson, MD[26]; Paula R. Pohlmann, MD, PhD, MSc[27]; Catherine Van Poznak, MD[28]; Andres Forero-Torres, MD[29]; Minetta Liu, MD[30]; Kathryn Ruddy, MD[30]; Yue Zheng, MSc[1]; Shoshana M. Rosenberg, ScD, MPH[1,2]; Richard D. Gelber, PhD[1,2]; Lorenzo Trippa, PhD[1,2]; William Barry, PhD[1]; Michelle DeMeo, BS[1]; Harold Burstein, MD, PhD[1,2]; Ann Partridge, MD, MPH[1,2]; Eric P. Winer, MD[1,2]; and Ian Krop, MD, PhD[1,2]

*J Clin Oncol* 2021 July 20;39(21):2375-85.

# ATEMPT: Invasive Disease-Free Survival (iDFS) and Recurrence-Free Interval (RFI)

| Outcome | T-DM1 (n = 383) | Paclitaxel/trastuzumab (n = 114) |
|---|---|---|
| Three-year iDFS | 97.8% | 93.4% |
| Three-year RFI | 99.2% | 94.3% |

Tolaney SM et al. *J Clin Oncol* 2021;39(21):2375-85.

RTP RESEARCH TO PRACTICE

# ATEMPT: Clinically Relevant Toxicity

| Clinically Relevant Toxicity | T-DM1 (n = 383) | TH (n = 114) |
|---|---|---|
| Grade ≥3 nonhematologic toxicity | 9% | 11% |
| Grade ≥2 neurotoxicity | 11% | 23% |
| Grade ≥4 hematologic toxicity | 1% | 0% |
| Febrile neutropenia | 0% | 2% |
| Any toxicity requiring dose delay | 28% | 26% |
| Any toxicity requiring early discontinuation | 17% | 6% |
| Total | 46% | 47% |

Tolaney SM et al. *J Clin Oncol* 2021;39(21):2375-85.

RTP RESEARCH TO PRACTICE

# Select Ongoing Trials HER2-Positive Localized Breast Cancer

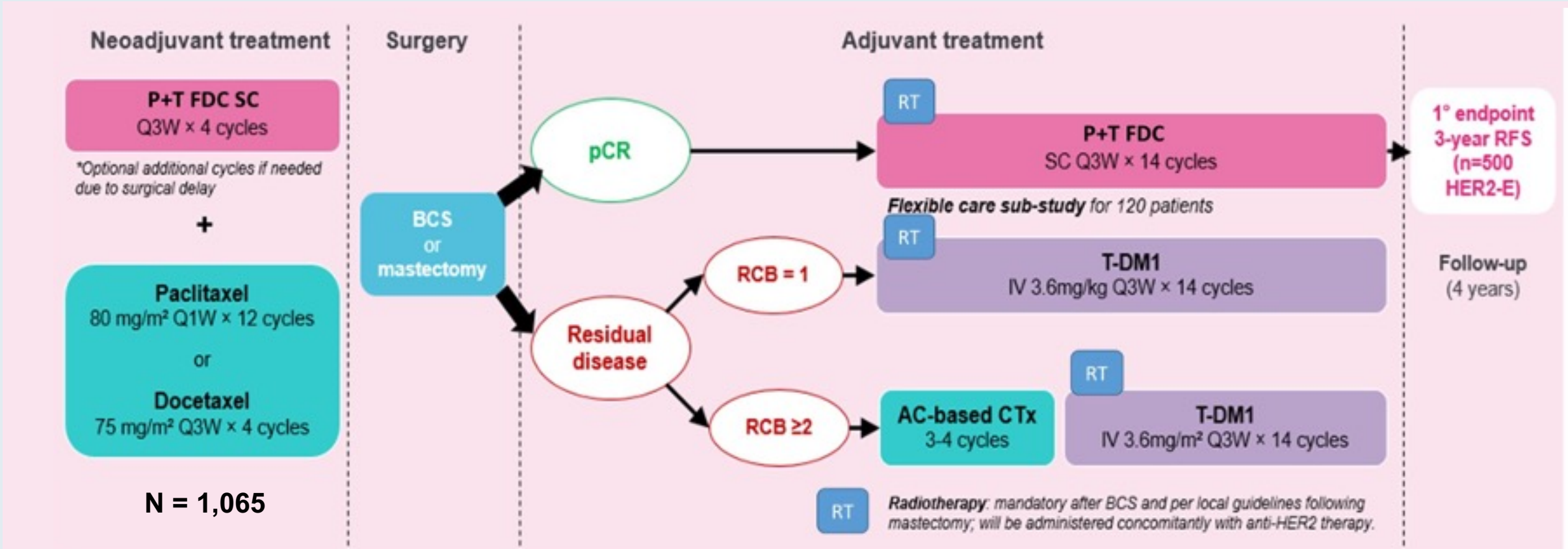
| Trial identifier | Phase (N) | Setting | Regimens | Estimated completion date |
|---|---|---|---|---|
| CompassHER2 pCR (NCT04266249) | II (N = 2,156) | Neoadjuvant and adjuvant | • Preoperative chemotherapy + trastuzumab/pertuzumab<br>• *If pCR* → postoperative trastuzumab/pertuzumab<br>• *If residual disease* → postoperative T-DM1 or T-DM1 + tucatinib | 2023 |
| DESTINY-Breast05 (NCT04622319) | III (N = 1,600) | High risk, residual disease after neoadjuvant chemotherapy | • Trastuzumab deruxtecan (T-DXd)<br>• T-DM1 | 2027 |
| DESTINY-Breast11 (NCT05113251) | III (N = 624) | Neoadjuvant, high risk | • T-DXd<br>• T-DXd → THP<br>• AC → THP | 2024 |

THP = paclitaxel, trastuzumab and pertuzumab

www.clinicaltrials.gov. Accessed August 2022.

RTP RESEARCH TO PRACTICE

# DECRESCENDO Phase II De-escalation Study Design




| Inclusion criteria |
|---|
| • Candidates for neoadjuvant treatment<br>• Early HER2+ (IHC 3+ or FISH), HR- (ER<1% and PR<1%) per local assessment<br>• Tumor size between 15 and 50mm<br>• Node 0 (micro metastasis not accepted) |

| | |
|---|---|
| **Primary endpoint** | **3-year recurrence-free survival (RFS) in patients with HER2-E tumors who achieve pCR (RCB=0) after neoadjuvant treatment** |
| **Key secondary endpoint** | • 3-year RFS in all patients with pCR (RCB=0). |
| **Secondary endpoints** | • pCR rates in the overall population and by primary tumor dimension.<br>• Short-and long-term safety of paclitaxel, docetaxel, P+T FDC SC, T-DM1. |

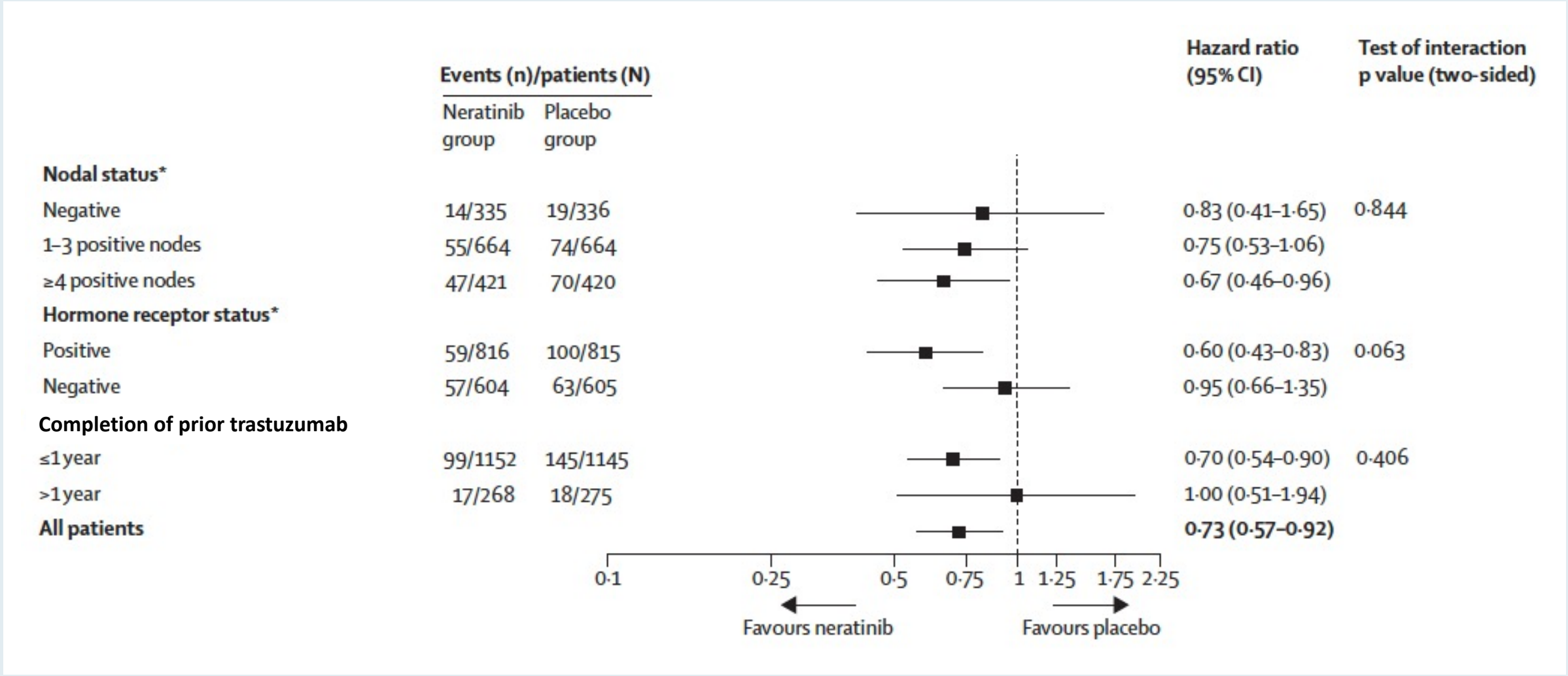
Debien V et al. ASCO 2022;Abstract TPS621.

*Lancet Oncol* 2017;18:1688-700.

# Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

*Miguel Martin, Frankie A Holmes, Bent Ejlertsen, Suzette Delaloge, Beverly Moy, Hiroji Iwata, Gunter von Minckwitz, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Zorica Tomašević, Neelima Denduluri, Robert Šeparović, Erhan Gokmen, Anna Bashford, Manuel Ruiz Borrego, Sung-Bae Kim, Erik Hugger Jakobsen, Audrone Ciceniene, Kenichi Inoue, Friedrich Overkamp, Joan B Heijns, Anne C Armstrong, John S Link, Anil Abraham Joy, Richard Bryce, Alvin Wong, Susan Moran, Bin Yao, Feng Xu, Alan Auerbach, Marc Buyse, Arlene Chan, for the ExteNET Study Group**

# ExteNET: 5-Year Analysis of Invasive Disease-Free Survival



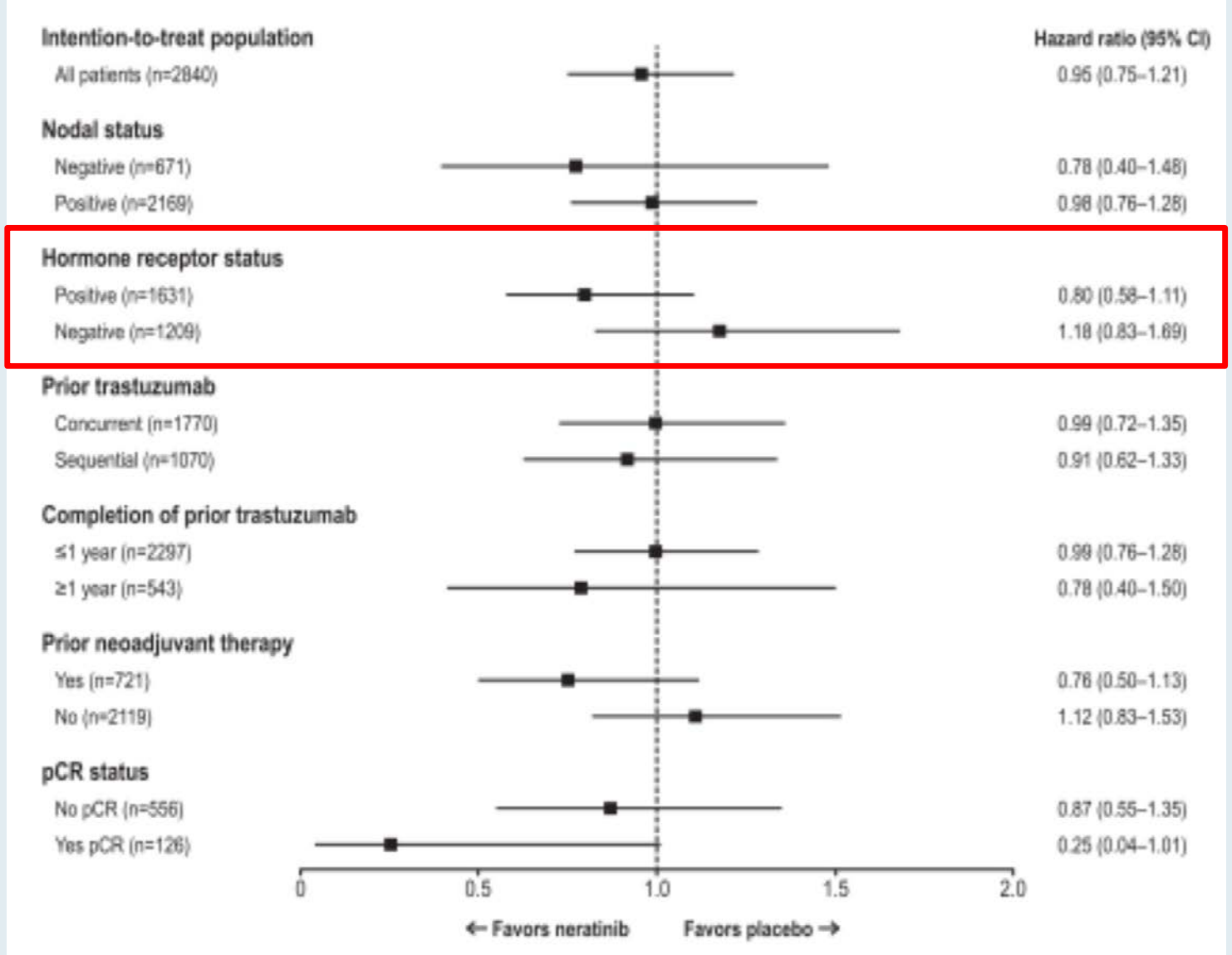

Martin M et al. *Lancet Oncol* 2017;18:1688-700.

# Continued Efficacy of Neratinib in Patients with HER2-Positive Early-Stage Breast Cancer: Final Overall Survival Analysis from the Randomized Phase 3 ExteNET Trial

Holmes FA et al.

SABCS 2020;Abstract PD3-03.

# ExteNET: Final Overall Survival Analysis (8-Year Follow-Up)




Holmes FA et al. SABCS 2020;Abstract PD3-03.

# ExteNET Final Overall Survival Analysis: Conclusions

- In the final protocol-defined analysis, there were fewer deaths in the neratinib arm, but no significant improvement in OS (HR 0.95; 95% CI 0.75–1.21) in the ExteNET ITT population after 8 years of follow-up:
  - The data suggest an association between neratinib and improved OS in patients with HR+ disease (HR 0.80; 95% CI 0.58–1.12) when compared with patients with HR– tumors (HR 1.18; 95% CI 0.83–1.69), which is consistent with the primary 2-year and 5-year analyses of iDFS and DDFS.
- Descriptive analyses also suggest that neratinib may be associated with longer OS in subgroups of clinical interest including the HR+/≤1-year population (HR 0.79; 95% CI 0.55–1.13), and in the high-risk patient subgroup with residual disease after neoadjuvant therapy (HR 0.47; 95% CI 0.23–0.92):
  - Clinically meaningful improvements were consistently observed across the endpoints (iDFS, DDFS, OS).
- Neratinib is the first HER2-directed agent to show a trend towards improved CNS outcomes in early-stage HER2+ breast cancer:
  - In all groups (ITT, HR+/≤1-year, and no pCR), consistently fewer CNS events were observed in the neratinib arm compared with placebo.

Holmes FA et al. SABCS 2020;Abstract PD3-03.

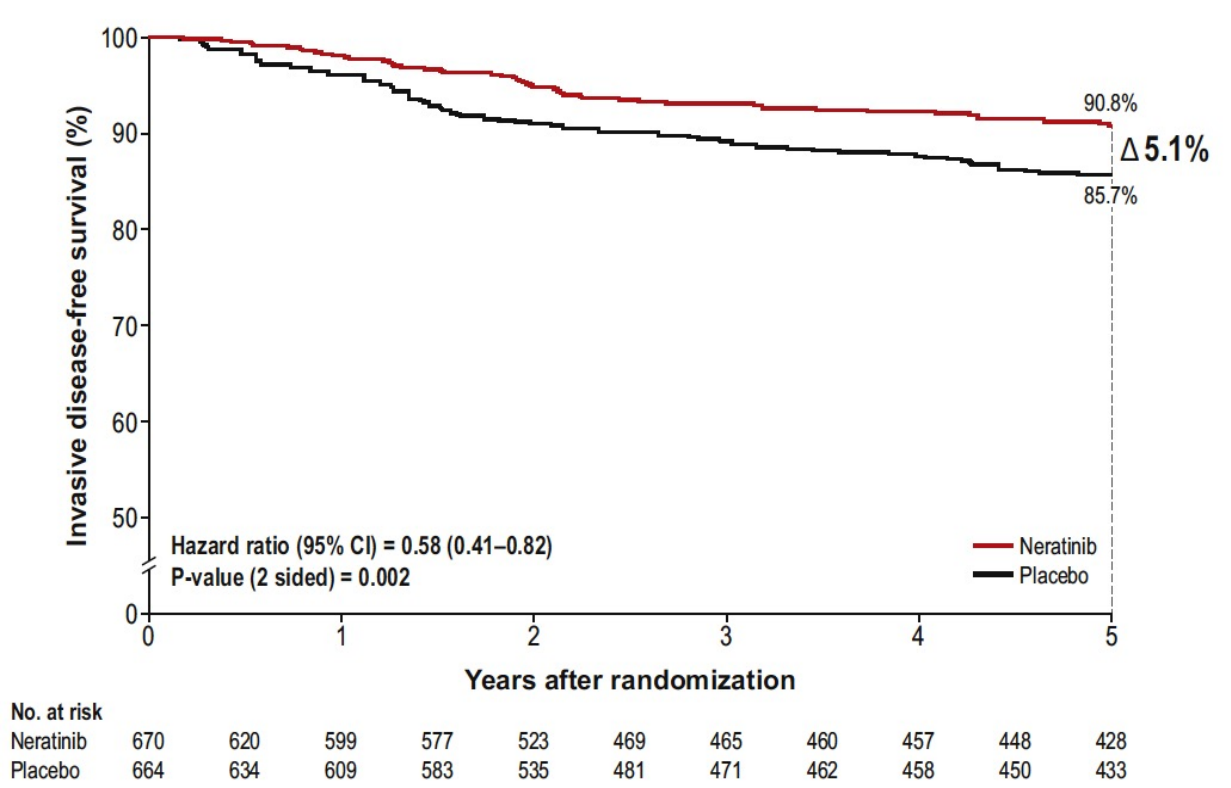
# Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

Arlene Chan,[1] Beverly Moy,[2] Janine Mansi,[3] Bent Ejlertsen,[4] Frankie Ann Holmes,[5] Stephen Chia,[6] Hiroji Iwata,[7] Michael Gnant,[8] Sibylle Loibl,[9] Carlos H. Barrios,[10] Isil Somali,[11] Snezhana Smichkoska,[12] Noelia Martinez,[13] Mirta Garcia Alonso,[14] John S. Link,[15] Ingrid A. Mayer,[16] Søren Cold,[17] Serafin Morales Murillo,[18] Francis Senecal,[19] Kenichi Inoue,[20] Manuel Ruiz-Borrego,[21] Rina Hui,[22] Neelima Denduluri,[23] Debra Patt,[24] Hope S. Rugo,[25] Stephen R.D. Johnston,[26] Richard Bryce,[27] Bo Zhang,[27] Feng Xu,[27] Alvin Wong,[27] Miguel Martin,[28] for the ExteNET Study Group

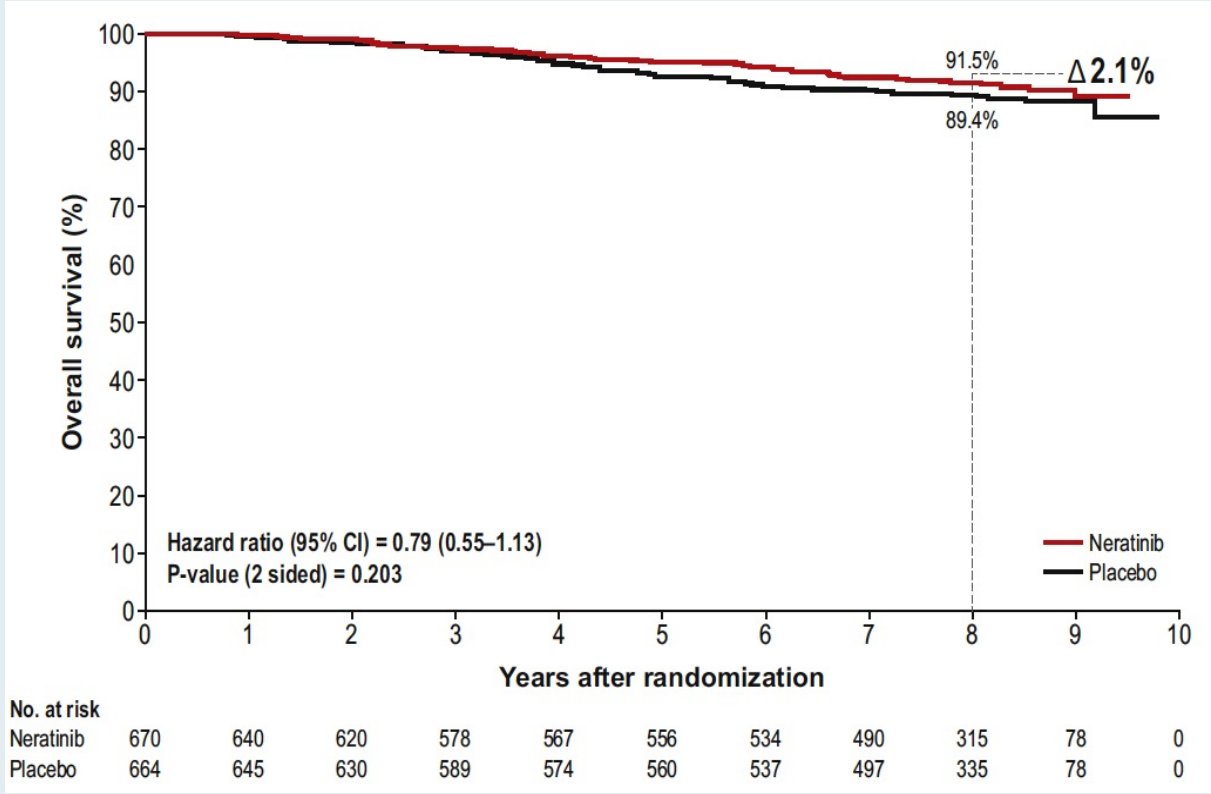
***Clin Breast Cancer* 2021;21(1):80-91.**

# ExteNET: Final Analysis with Neratinib for HER2-Positive Localized Breast Cancer (HR+/≤ 1-Year population)

## Invasive disease-free survival at 5 years



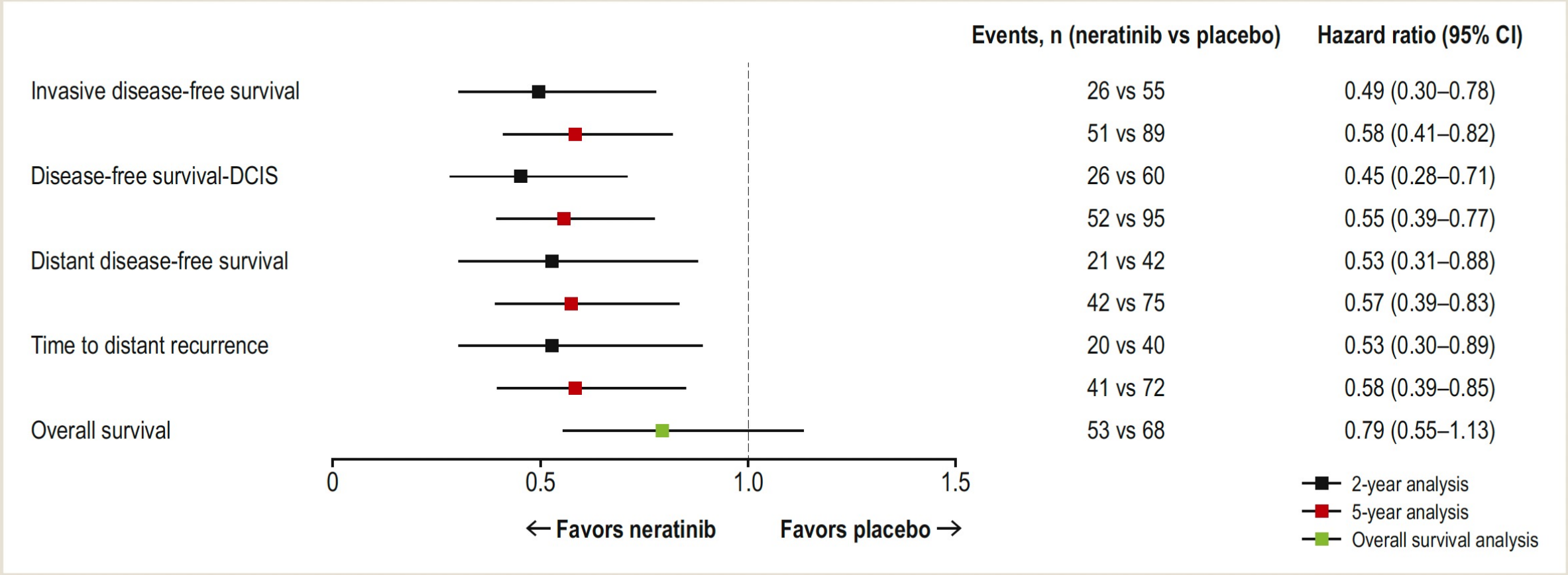

## Overall survival at 8 years




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

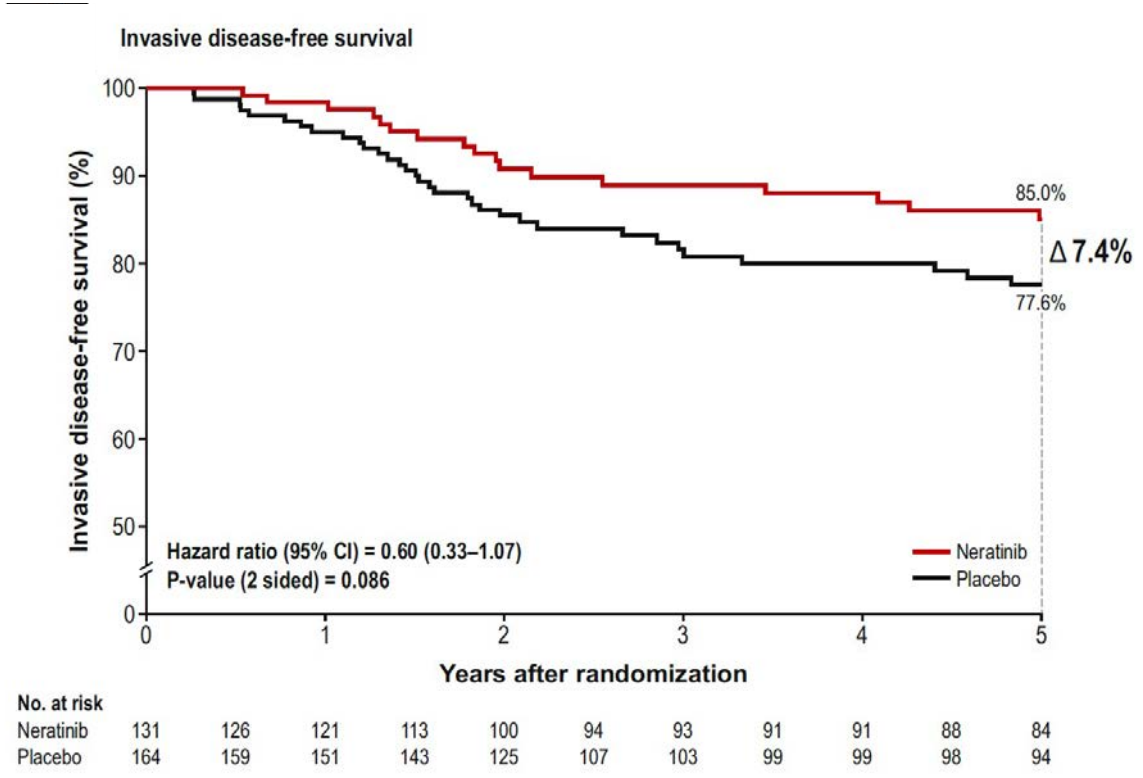
RTP RESEARCH TO PRACTICE

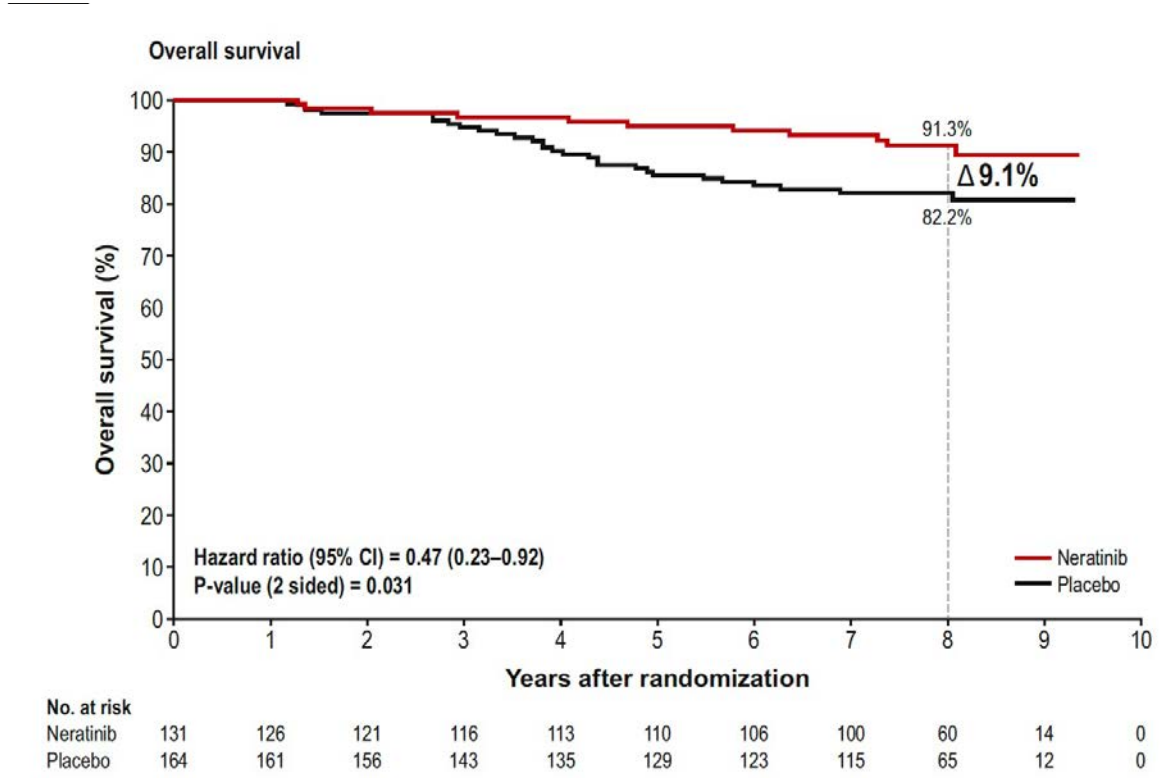
# ExteNET: 2-Year, 5-Year and Overall Survival in HR+/≤1-Year Population (N = 1,334)




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

# ExteNET: Invasive Disease-Free and Overall Survival at 5 Years in the HR+/≤1-Year Population with No pCR After Neoadjuvant Therapy (N = 295)




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

RTP RESEARCH TO PRACTICE

# ExteNET: Cumulative Incidence of CNS Recurrence

| Population or subgroup | Events, n | | Cumulative incidence of CNS recurrence | |
|---|---|---|---|---|
| | Neratinib | Placebo | Neratinib | Placebo |
| **Intention-to-treat population** (n = 2,840) | 16 | 23 | 1.3% | 1.8% |
| **HR-positive/≤1-year population (EU indication)** (n = 1,334) | 4 | 12 | 0.7% | 2.1% |
| **Adjuvant or neoadjuvant therapy (n = 1,334)** | | | | |
| Adjuvant (n = 980) | 3 | 6 | 0.7% | 1.5% |
| Neoadjuvant (n = 354) | 1 | 6 | 0.7% | 3.7% |
| **pCR status** (n = 354) | | | | |
| No (n = 295) | 1 | 5 | 0.8% | 3.6% |
| Yes (n = 38) | 0 | 1 | 0 | 5.0% |

Chan A et al. *Clin Breast Cancer* 2021;21(1):80-91; Holmes FA et al. San Antonio Breast Cancer Symposium 2020;Abstract PD3-03.

RTP RESEARCH TO PRACTICE

# ExteNET: Adverse Events (AEs)

## Summary of AEs

| | Neratinib (n = 662) | Placebo (n = 657) |
|---|---|---|
| Any TEAE | 649 (98) | 567 (86) |
| Grade 3 or 4 TEAE | 327 (49) | 76 (12) |
| Fatal TEAE | 1 (<1) | 0 (0) |
| Serious TEAE | 45 (7) | 36 (6) |
| Treatment-related TEAE | 630 (95) | 360 (55) |
| Serious treatment-related TEAE | 19 (3) | 5 (<1) |
| TEAE leading to | | |
| Treatment discontinuation | 178 (27) | 30 (5) |
| Study withdrawal | 11 (2) | 2 (<1) |
| Dose reduction | 203 (31) | 13 (2) |
| Hospitalization | 41 (6) | 35 (5) |
| Dose interruption | 280 (42) | 75 (11) |

## Frequent Treatment-Emergent AEs (TEAEs)

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

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

RTP RESEARCH TO PRACTICE

# Association Between Treatment Duration and Overall Survival in Early-Stage HER2+ Breast Cancer Patients Receiving Extended Adjuvant Therapy with Neratinib in the ExteNET Trial

Moy B et al.

ASCO 2021;Abstract 540.

# ExteNET: Survival Summary for Patients Who Completed Planned Neratinib Therapy

| Population or subgroup | N | | 5-year analysis | | | | OS analysis | |
|---|---|---|---|---|---|---|---|---|
| | | | iDFS rate | | DDFS rate | | OS rate[a] | |
| | Neratinib | Placebo | Difference, %[b] | HR (95% CI) | Difference, %[b,8,9] | HR (95% CI) | Difference, %[b] | HR (95% CI) |
| **ITT population** | 1420 | 1420 | +2.5 | 0.73 (0.57–0.92)[c] | +1.7 | 0.78 (0.60–1.01)[c] | –0.1 | 0.95 (0.75–1.21)[c] |
| Completed therapy[d] | 872 | 1420 | +3.3 | 0.68 (0.52–0.90) | +2.0 | 0.76 (0.56–1.02) | +2.0 | 0.78 (0.58–1.04) |
| **HR+/≤1 year[e] (EU indication)** | 670 | 664 | +5.1 | 0.58 (0.41–0.82) | +4.7 | 0.57 (0.39–0.83) | +2.1 | 0.79 (0.55–1.13) |
| Completed therapy[d] | 402 | 664 | +7.4 | 0.44 (0.28–0.68) | +5.9 | 0.49 (0.30–0.76) | +5.8 | 0.49 (0.29–0.78) |
| **HR+/≤1 year no pCR[f]** | 131 | 164 | +7.4 | 0.60 (0.33–1.07) | +7.0[g] | 0.61 (0.32–1.11) | +9.1 | 0.47 (0.23–0.92) |
| Completed therapy[d] | 92 | 164 | +11.9 | 0.42 (0.19–0.83) | +10.9[h] | 0.42 (0.18–0.88) | +13.2 | 0.29 (0.10–0.68) |

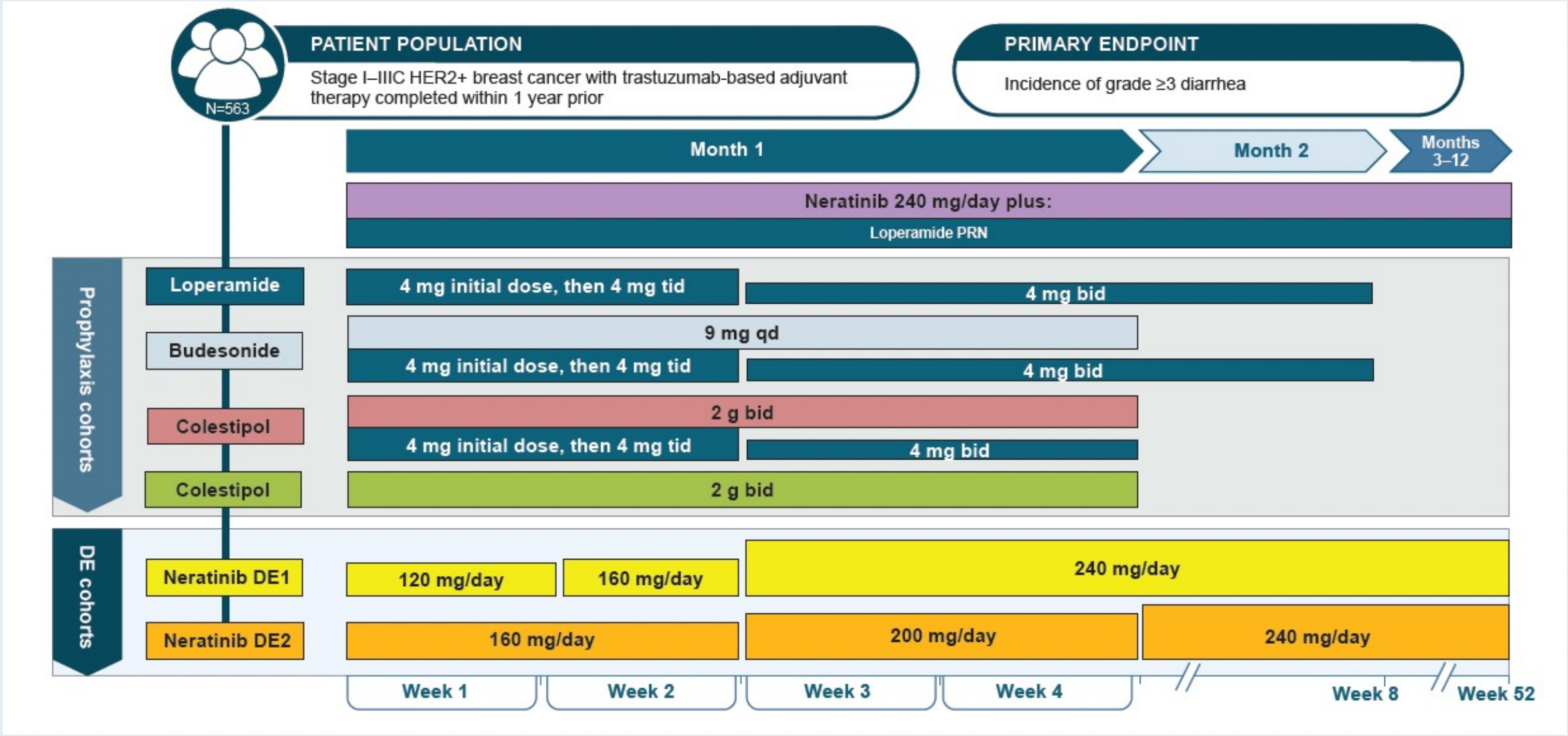
Moy B et al. ASCO 2021;Abstract 540.

# Effects of Diarrheal Prophylaxis or Dose Escalation on Neratinib-Associated Diarrhea and Tolerability in Patients with HER2+ Early-Stage Breast Cancer: Final Findings from the CONTROL Trial

Chan A et al.

ESMO Breast 2022;Abstract P73.

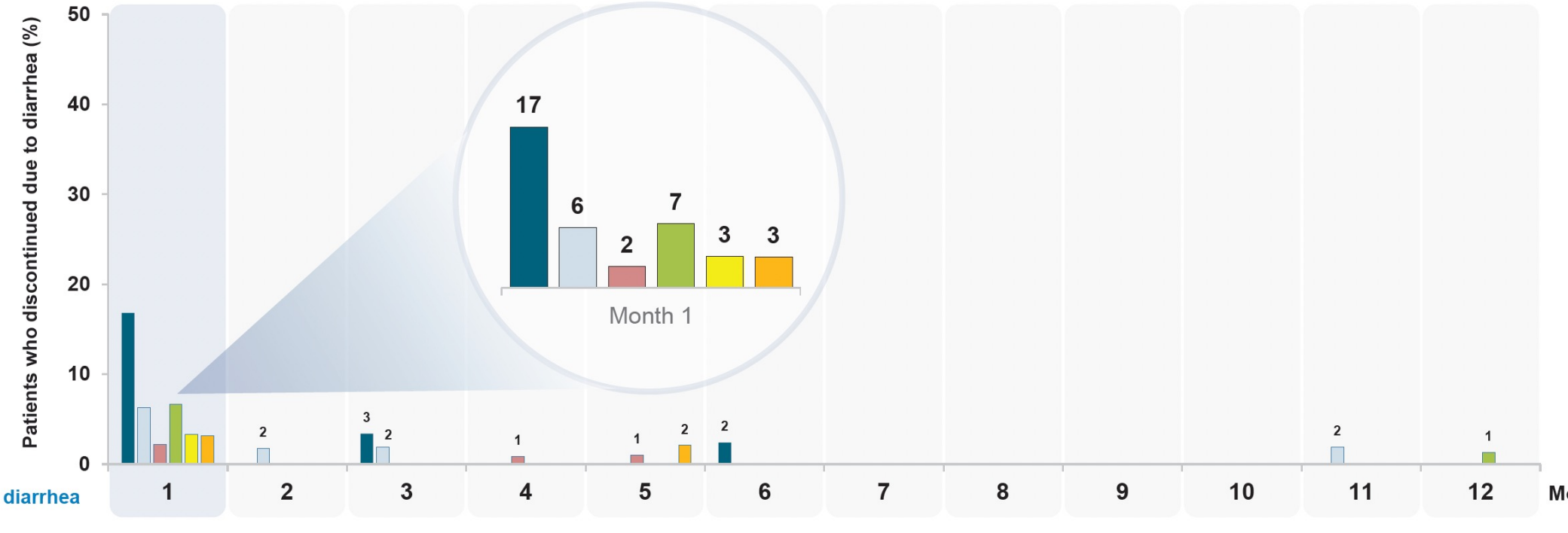
# CONTROL Trial Cohorts: Study Schema




Chan A et al. ESMO Breast 2022;Abstract P73.

RTP RESEARCH TO PRACTICE

# CONTROL: All Strategies Reduced the Rate of Discontinuation Due to Diarrhea




| No. of patients who discontinued due to diarrhea / No. at risk | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Loperamide | 23/137 | 0/93 | 3/89 | 0/84 | 0/83 | 2/83 | 0/81 | 0/80 | 0/78 | 0/77 | 0/76 | 0/75 |
| Budesonide + loperamide | 4/64 | 1/57 | 1/54 | 0/53 | 0/53 | 0/53 | 0/53 | 0/53 | 0/53 | 0/53 | 1/53 | 0/51 |
| Colestipol + loperamide | 3/136 | 0/115 | 0/112 | 1/107 | 1/105 | 0/104 | 0/103 | 0/103 | 0/102 | 0/102 | 0/99 | 0/99 |
| Colestipol + loperamide PRN | 7/104 | 0/86 | 0/85 | 0/84 | 0/82 | 0/81 | 0/80 | 0/79 | 0/79 | 0/77 | 0/77 | 1/75 |
| Neratinib DE1 | 2/60 | 0/86 | 0/53 | 0/53 | 0/51 | 0/51 | 0/50 | 0/50 | 0/50 | 0/49 | 0/47 | 0/46 |
| Neratinib DE2 | 2/62 | 0/56 | 0/49 | 0/49 | 1/48 | 0/46 | 0/42 | 0/40 | 0/37 | 0/32 | 0/28 | 0/25 |

Chan A et al. ESMO Breast 2022;Abstract P73.

# CONTROL: Diarrhea Profile

| Outcome | L (n=137) | BL (n=64) | CL (n=136) | CL-PRN (n=104) | DE1 (n=60) | DE2 (n=62) |
|---|---|---|---|---|---|---|
| **Any grade diarrhea**, n (%) | 109 (80) | 55 (86) | 113 (83) | 99 (95) | 59 (98) | 61 (98) |
| Grade 1 | 33 (24) | 15 (23) | 38 (28) | 34 (33) | 24 (40) | 23 (37) |
| Grade 2 | 34 (25) | 22 (34) | 47 (35) | 31 (30) | 27 (45) | 21 (34) |
| Grade 3 | 42 (31) | 18 (28) | 28 (21) | 34 (33) | 8 (13) | 17 (27) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Median episodes of grade 3 diarrhea**, n | 1 | 1 | 1 | 1 | 2 | 1 |
| **Median time to first onset of grade 3 diarrhea**, days | 7.0 | 19.0 | 41.0 | 19.0 | 45.0 | 19.0 |
| **Median cumulative duration of grade 3 diarrhea per patient**, days | 3.0 | 3.0 | 3.5 | 2.0 | 2.5 | 2.0 |
| **Dose holds due to diarrhea**, n (%) | 20 (15) | 12 (19) | 22 (16) | 15 (14) | 7 (12) | 8 (13) |
| **Discontinuations due to diarrhea**, n (%) | 28 (20) | 7 (11) | 5 (4) | 8 (8) | 2 (3) | 4 (6) |
| **Hospitalizations due to diarrhea**, n (%) | 2 (2) | 0 | 0 | 0 | 0 | 0 |

Chan A et al. ESMO Breast 2022;Abstract P73.

# CONTROL: Conclusions

- These final findings from the CONTROL study show improved tolerability of neratinib with all diarrhea prophylaxis and DE schedules. These results demonstrate that neratinib is well tolerated as extended-adjuvant treatment for patients with HER2+ breast cancer after 1 year of trastuzumab.
- Adoption of neratinib DE with loperamide PRN during the first 2 weeks of treatment (DE1 cohort) was associated with a lower rate of Grade 3 diarrhea compared to the CONTROL prophylaxis strategies, the DE2 strategy and the neratinib arm in the ExteNET trial.
- The DE1 cohort also had the lowest rate of diarrhea-related discontinuations (3%) and dose holds (12%) compared to the other strategies investigated in the CONTROL trial and the neratinib arm in the ExteNET trial.
- These findings suggest that several modalities, most notably neratinib DE1 with loperamide PRN, allow patients to stay on treatment longer and receive the full benefit of neratinib therapy.
- The US package label for neratinib now includes both the mandatory loperamide prophylaxis regimen and the DE1 strategy from CONTROL as diarrhea-mitigation strategies.

Chan A et al. ESMO Breast 2022;Abstract P73.

# Evolving Treatment Paradigms for Patients with Metastatic HER2-Positive BC

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ASCO special articles

# Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Guideline Update

Sharon H. Giordano, MD, MPH[1]; Maria Alice B. Franzoi, MD[2]; Sarah Temin, MSPH[3]; Carey K. Anders, MD[4]; Sarat Chandarlapaty, MD, PhD[5]; Jennie R. Crews, MD[6]; Jeffrey J. Kirshner, MD[7]; Ian E. Krop, MD, PhD[8]; Nancy U. Lin, MD[8]; Aki Morikawa, MD, PhD[9]; Debra A. Patt, MD, MPH, MBA[10]; Jane Perlmutter, PhD[11]; Naren Ramakrishna, MD, PhD[12]; and Nancy E. Davidson, MD[13]

*J Clin Oncol* 2022 August;40:2612-35.

RTP RESEARCH TO PRACTICE

# Trastuzumab Deruxtecan (T-DXd) and DESTINY-Breast Studies

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# Trastuzumab Deruxtecan Significantly Delayed Disease Progression in Comparison to Physician's Choice of Treatment for HER2-Positive Metastatic Breast Cancer in the DESTINY-Breast02 Phase III Trial

## Press Release – August 15, 2022

Positive high-level results from the DESTINY-Breast02 Phase III trial of trastuzumab deruxtecan versus physician's choice of treatment showed the trial met the primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in progression-free survival in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab emtansine. The trial also met the key secondary endpoint of improved overall survival.

The trial evaluated a similar later-line patient population as the single-arm DESTINY-Breast01 Phase II trial, which was the basis for initial approvals in advanced HER2-positive metastatic breast cancer. The safety profile of trastuzumab deruxtecan in DESTINY-Breast02 was consistent with previous Phase III clinical trials with no new safety concerns identified. Interstitial lung disease (ILD) rates and severity were consistent with those observed in other metastatic breast cancer trials of trastuzumab deruxtecan, with a low rate of Grade 5 ILD events observed as determined by an independent adjudication committee.

https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improved-pfs-in-mbc-in-destiny-breast02.html

# Fam-Trastuzumab Deruxtecan-Nxki Approved in the United States for HER2-Positive Metastatic Breast Cancer Treated with a Prior Anti-HER2 Regimen

## Press Release – May 5, 2022

"Fam-trastuzumab deruxtecan-nxki has been approved in the US for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.

The approval by the Food and Drug Administration (FDA) was based on positive results from the DESTINY-Breast03 Phase III trial that showed fam-trastuzumab deruxtecan-nxki reduced the risk of disease progression or death by 72% versus trastuzumab emtansine (T-DM1) (hazard ratio [HR] 0.28; 95% confidence interval [CI]: 0.22-0.37; $p<0.0001$) in patients with HER2-positive unresectable and/or metastatic breast cancer previously treated with trastuzumab and a taxane.

The approval was granted under the FDA's Real-Time Oncology Review (RTOR) program and converts the accelerated approval of fam-trastuzumab deruxtecan-nxki in later line HER2-positive metastatic breast cancer to standard approval, broadening fam-trastuzumab deruxtecan-nxki's breast cancer indication in the US to earlier lines of use in patients with HER2-positive metastatic breast cancer."

https://finance.yahoo.com/news/enhertu-fam-trastuzumab-deruxtecan-nxki-110000498.html

RTP RESEARCH TO PRACTICE

*N Engl J Med* 2022 March 24;386:1143-54.

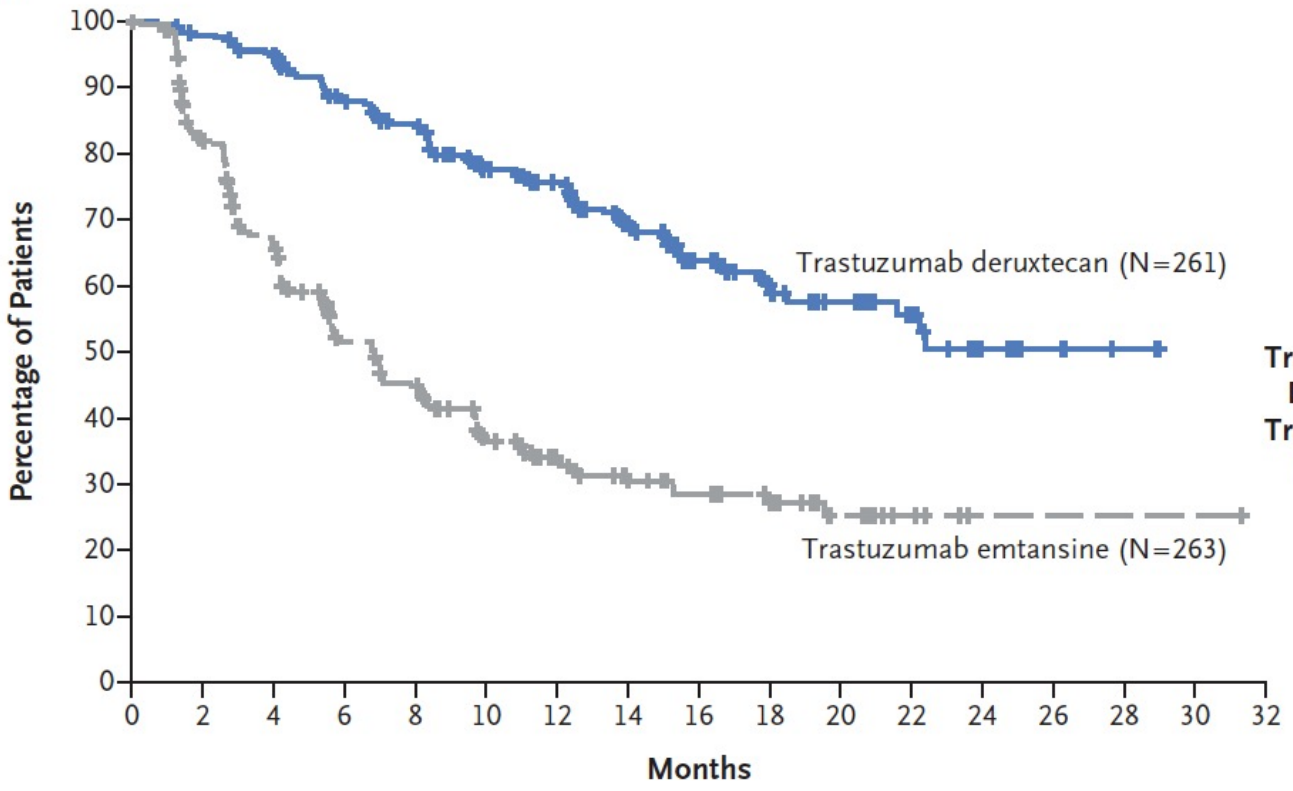
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

# DESTINY-Breast03: Progression-Free Survival




| | Median Progression-free Survival (95% CI) | 12-Mo Progression-free Survival (95% CI) |
|---|---|---|
| | *mo* | % |
| **Trastuzumab Deruxtecan** | NR (18.5–NE) | 75.8 (69.8–80.7) |
| **Trastuzumab Emtansine** | 6.8 (5.6–8.2) | 34.1 (27.7–40.5) |

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

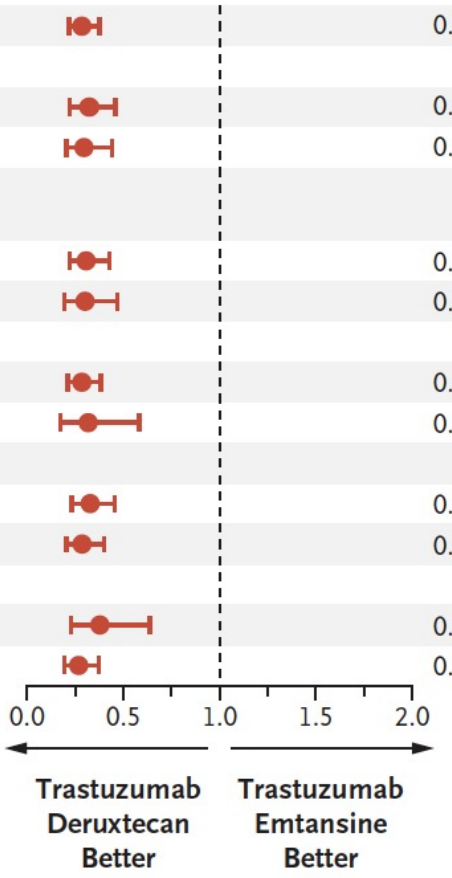
**No. at Risk**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 261 | 250 | 240 | 214 | 200 | 168 | 150 | 112 | 79 | 53 | 36 | 25 | 10 | 5 | 2 | |
| Trastuzumab emtansine | 263 | 200 | 155 | 108 | 93 | 65 | 51 | 37 | 29 | 21 | 12 | 6 | 1 | 1 | 1 | 0 |

Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

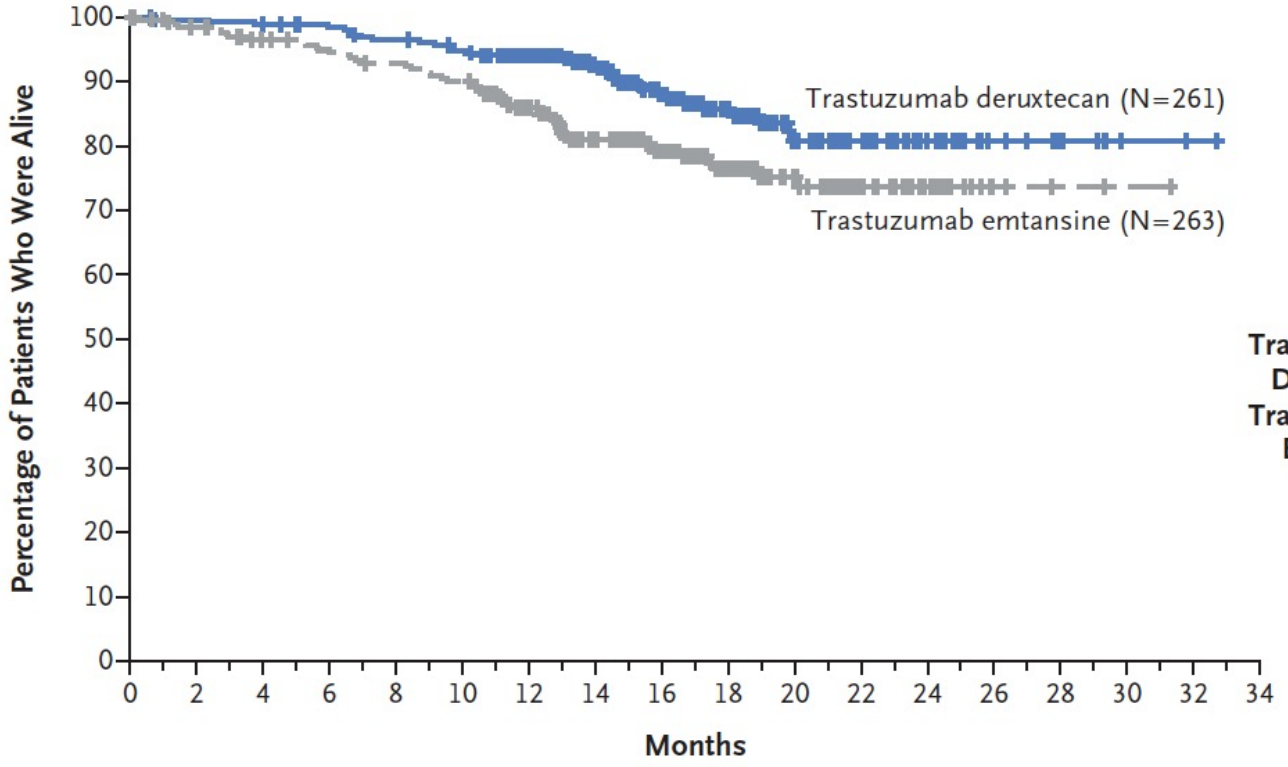
# DESTINY-Breast03: Progression-Free Survival in Prespecified Subgroups

| Subgroup | No. of Patients | No. of Events/No. of Patients | | Median Progression-free Survival (95% CI) | | Hazard Ratio for Disease Progression or Death (95% CI) |
|---|---|---|---|---|---|---|
| | | | | *mo* | | |
| | | Trastuzumab deruxtecan | Trastuzumab emtansine | Trastuzumab deruxtecan | Trastuzumab emtansine | |
| All patients | | 87/261 | 158/263 | NE (18.5–NE) | 6.8 (5.6–8.2) | 0.28 (0.22–0.37) |
| Hormone-receptor status | | | | | | |
| Positive | 272 | 46/133 | 84/139 | 22.4 (17.7–NE) | 6.9 (4.2–9.8) | 0.32 (0.22–0.46) |
| Negative | 248 | 41/126 | 73/122 | NE (18.0–NE) | 6.8 (5.4–8.3) | 0.30 (0.20–0.44) |
| Previous pertuzumab treatment | | | | | | |
| Yes | 320 | 57/162 | 98/158 | NE (18.5–NE) | 6.8 (5.4–8.3) | 0.30 (0.22–0.43) |
| No | 204 | 30/99 | 60/105 | NE (16.5–NE) | 7.0 (4.2–9.7) | 0.30 (0.19–0.47) |
| Visceral disease | | | | | | |
| Yes | 384 | 72/195 | 123/189 | 22.2 (16.5–NE) | 5.7 (4.2–7.0) | 0.28 (0.21–0.38) |
| No | 140 | 15/66 | 35/74 | NE (NE–NE) | 11.3 (6.8–NE) | 0.32 (0.17–0.58) |
| Lines of previous therapy | | | | | | |
| 0 or 1 | 258 | 46/132 | 75/126 | 22.4 (17.9–NE) | 8.0 (5.7–9.7) | 0.33 (0.23–0.48) |
| ≥2 | 266 | 41/129 | 83/137 | NE (16.8–NE) | 5.6 (4.2–7.1) | 0.28 (0.19–0.41) |
| Stable brain metastases | | | | | | |
| Yes | 114 | 31/62 | 31/52 | 15.0 (12.6–22.2) | 5.7 (2.9–7.1) | 0.38 (0.23–0.64) |
| No | 410 | 56/199 | 127/211 | NE (22.4–NE) | 7.0 (5.5–9.7) | 0.27 (0.19–0.37) |




Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

# DESTINY-Breast03: First Interim Analysis of Overall Survival




| | Median Overall Survival (95% CI) | 12-Mo Overall Survival (95% CI) |
|---|---|---|
| | *mo* | % |
| **Trastuzumab Deruxtecan** | NE (NE–NE) | 94.1 (90.3–96.4) |
| **Trastuzumab Emtansine** | NE (NE–NE) | 85.9 (80.9–89.7) |

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

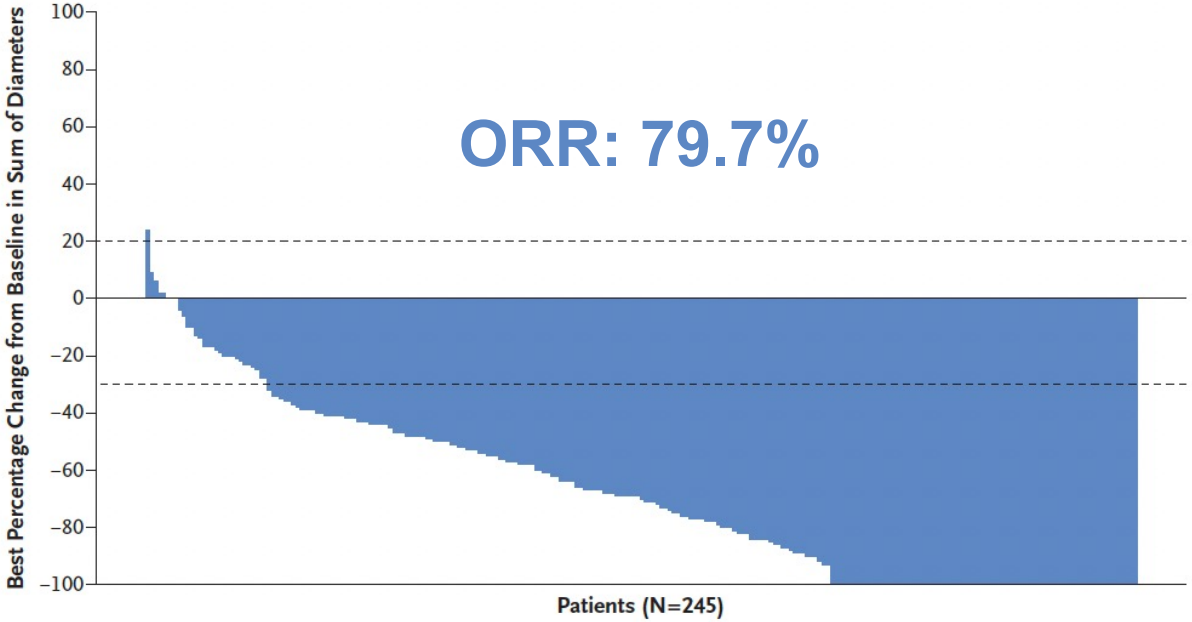
**No. at Risk**

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trastuzumab deruxtecan | 261 | 256 | 254 | 249 | 243 | 237 | 218 | 180 | 133 | 86 | 56 | 42 | 24 | 11 | 7 | 6 | 2 | 2 | 1 | 0 |
| Trastuzumab emtansine | 263 | 253 | 243 | 236 | 231 | 224 | 188 | 151 | 120 | 75 | 52 | 32 | 18 | 5 | 3 | 3 | 1 | 1 | 0 | |

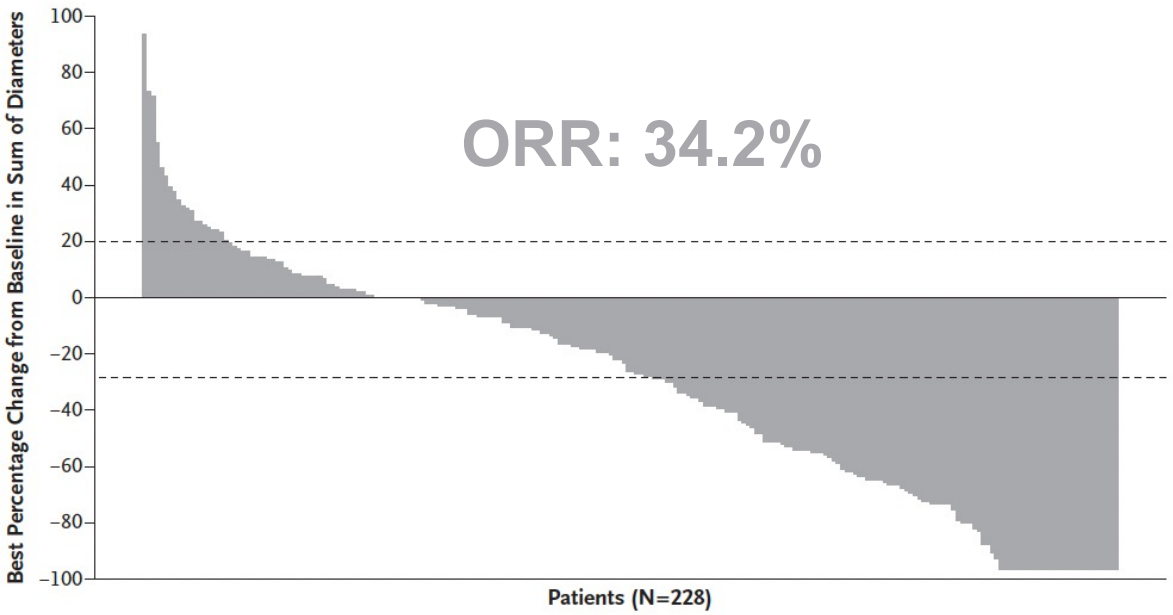
Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

# DESTINY-Breast03: Antitumor Activity

## Trastuzumab deruxtecan




## Trastuzumab emtansine




ORR = overall response rate

Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

RTP RESEARCH TO PRACTICE

2022 ASCO® ANNUAL MEETING

Abstract 1000

# Trastuzumab Deruxtecan vs Trastuzumab Emtansine in Patients With HER2-Positive Unresectable and/or Metastatic Breast Cancer: Safety Follow-up of the Randomized, Phase 3 Study DESTINY-Breast03

**Erika Hamilton, MD**,[a] Vanessa Petry, Winnie Yeo, Sung-Bae Kim, Giampaolo Bianchini, Toshinari Yamashita, Kan Yonemori, Kenichi Inoue, Giuseppe Curigliano, Sara A. Hurvitz, Javier Cortés, Hiroji Iwata, Jillian Cathcart, Yali Liu, Caleb Lee, Emarjola Bako, Rachel Kim, Seock-Ah Im
**On behalf of the DESTINY-Breast03 investigators**

[a]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

# DESTINY-Breast03: Safety Update Overview

| n (%) | T-DXd n = 257 | T-DM1 n = 261 |
|---|---|---|
| Patients discontinued from study treatment | 141 (54.9) | 222 (85.1) |
| Any grade TEAE | 256 (99.6) | 249 (95.4) |
| Grade ≥3 TEAE | 137 (53.3) | 130 (49.8) |
| Any grade serious TEAE | 54 (21.0) | 50 (19.2) |
| Grade ≥3 serious TEAE | 39 (15.2) | 38 (14.6) |
| TEAE associated with drug discontinuation | 38 (14.8) | 19 (7.3) |
| TEAE associated with dose reduction | 59 (23.0) | 36 (13.8) |

- Rates of TEAEs (any grade and grade ≥3) and serious TEAEs were similar between the T-DXd and T-DM1 arms
- TEAEs associated with drug discontinuation occurred in 38 patients (14.8%) in the T-DXd arm and 19 patients (7.3%) in the T-DM1 arm

TEAE = treatment-emergent adverse event

Hamilton E et al. ASCO 2022;Abstract 1000.

# DESTINY-Breast03: Drug-Related TEAEs in ≥20% of Patients

| | T-DXd n = 257 | | T-DM1 n = 261 | |
|---|---|---|---|---|
| n (%) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Nausea | 189 (73.5) | 17 (6.6) | 72 (27.6) | 1 (0.4) |
| Fatigue | 118 (45.9) | 16 (6.2) | 76 (29.1) | 2 (0.8) |
| Vomiting | 114 (44.4) | 4 (1.6) | 15 (5.7) | 1 (0.4) |
| Neutropenia | 111 (43.2) | 51 (19.8) | 30 (11.5) | 8 (3.1) |
| Alopecia | 97 (37.7) | 1 (0.4) | 7 (2.7) | 0 |
| Anemia | 82 (31.9) | 16 (6.2) | 37 (14.2) | 11 (4.2) |
| Leukopenia | 79 (30.7) | 17 (6.6) | 21 (8.0) | 2 (0.8) |
| Decreased appetite | 68 (26.5) | 3 (1.2) | 34 (13.0) | 0 |
| Thrombocytopenia | 65 (25.3) | 19 (7.4) | 137 (52.5) | 65 (24.9) |
| Diarrhea | 61 (23.7) | 1 (0.4) | 11 (4.2) | 2 (0.8) |
| Constipation | 60 (23.3) | 0 | 25 (9.6) | 0 |

Hamilton E et al. ASCO 2022;Abstract 1000.

# DESTINY-Breast03: Time to First Onset of TEAEs

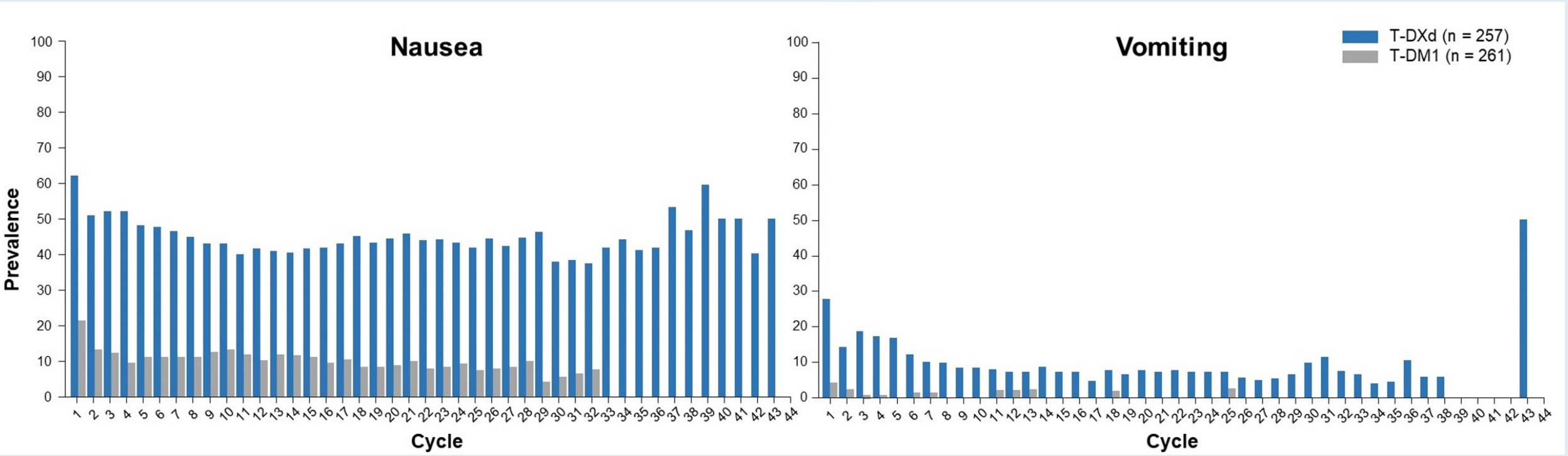
| Median time to event, days | T-DXd n = 257 | T-DM1 n = 261 |
|---|---|---|
| TEAE associated with treatment discontinuation | 224 | 147 |
| TEAE associated with first dose reduction | 96 | 19 |
| Selected TEAEs | | |
| Anemia | 70.0 | 42.0 |
| Lymphopenia | 196.0 | 168.0 |
| Thrombocytopenia | 132.0 | 8.0 |
| Fatigue | 22.0 | 24.0 |
| Leukopenia | 74.5 | 92.0 |
| Neutropenia[a] | 64.0 | 105.0 |
| Nausea | 2.0 | 3.0 |
| Vomiting | 10.0 | 6.0 |
| Alopecia | 27.0 | 43.0 |

- TEAEs associated with first drug discontinuation or first dose reduction occurred later with T-DXd treatment than with T-DM1 treatment
- Median time to any TEAE associated with first dose reduction was longer in the T-DXd arm at 96 days compared with the T-DM1 arm at 19 days

ILD = interstitial lung disease

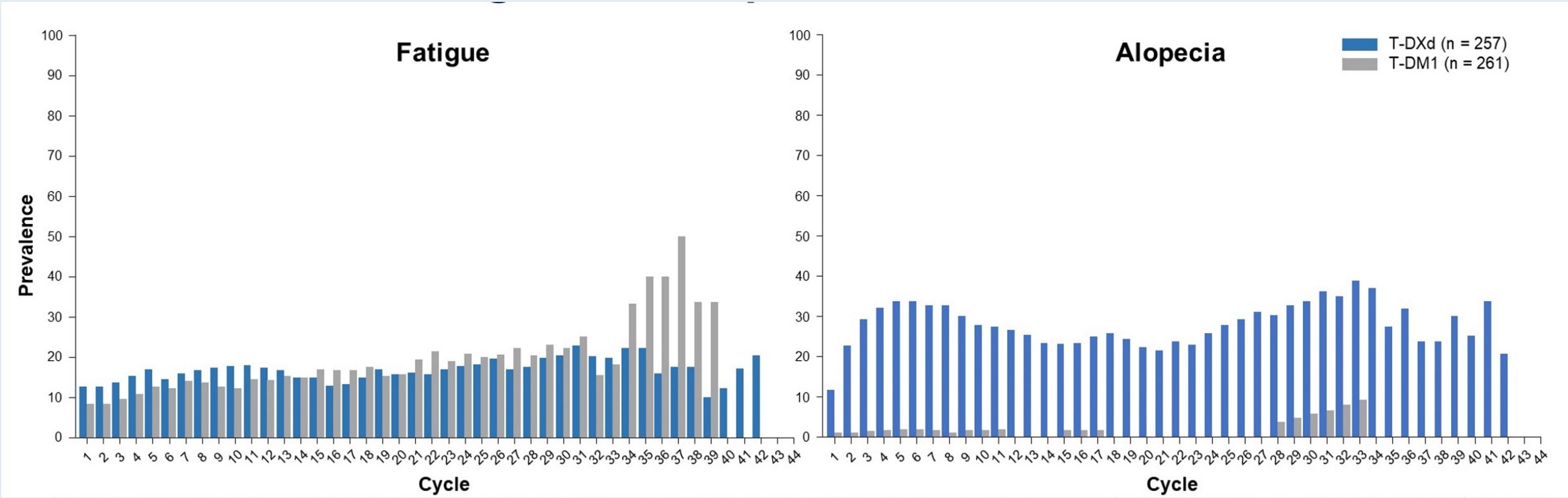
Hamilton E et al. ASCO 2022;Abstract 1000.

# DESTINY-Breast03: Prevalence of Nausea and Vomiting




Hamilton E et al. ASCO 2022;Abstract 1000.

# DESTINY-Breast03: Prevalence of Fatigue and Alopecia




Hamilton E et al. ASCO 2022;Abstract 1000.

# DESTINY-Breast03: Adjudicated Drug-Related ILD/Pneumonitis

| | T-DXd n = 257 | T-DM1 n = 261 |
|---|---|---|
| Any grade, n (%) | 28 (10.9) | 5 (1.9) |
| Grade 1 | 7 (2.7) | 4 (1.5) |
| Grade 2 | 19 (7.4) | 1 (0.4) |
| Grade 3 | 2 (0.8) | 0 |
| Grade 4 | 0 | 0 |
| Grade 5 | 0 | 0 |
| Time to first onset, median (range), days | 181 (33-507) | 289 (80-499) |
| Outcome of worst event, n (%) | | |
| Fatal | 0 | 1 (20.0)[a] |
| Not recovered/not resolved | 8 (28.6) | 0 |
| Ongoing | 0 | 0 |
| Recovering/resolving | 2 (7.1) | 0 |
| Recovered/resolved with sequelae | 2 (7.1) | 0 |
| Recovered/resolved | 16 (57.1) | 4 (80.0) |

For this safety update:

- Majority of adjudicated ILD/pneumonitis cases were low grade and no new grade 4 or 5 events occurred in either treatment arm
- One additional grade 2 adjudicated drug-related ILD/pneumonitis occurred
- The majority of events resolved with ongoing follow-up

Hamilton E et al. ASCO 2022;Abstract 1000.

# DESTINY-Breast09 Phase III Trial Design

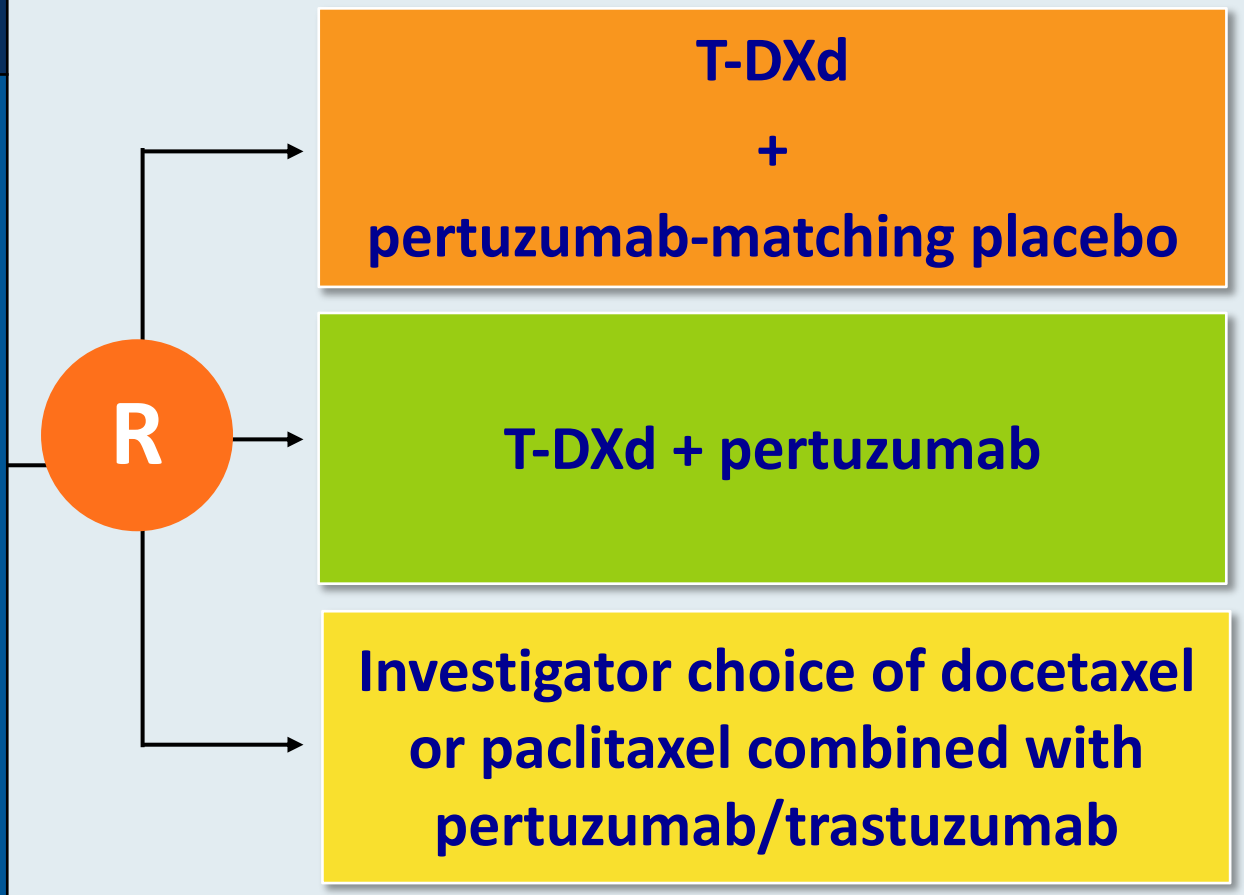
**Estimated enrollment: N = 1,134**

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




www.clinicaltrials.gov. NCT04784715. Accessed August 2022.

# Trastuzumab Deruxtecan Granted FDA Approval for HER2-Low Breast Cancer

## Press Release – August 5, 2022

"Today, the US Food and Drug Administration approved fam-trastuzumab-deruxtecan-nxki, an IV infusion for the treatment of patients with unresectable (unable to be removed) or metastatic (spread to other parts of the body) HER2-low breast cancer. This is the first approved therapy targeted to patients with the HER2-low breast cancer subtype, which is a newly defined subset of HER2-negative breast cancer.

Patients with HER2-low breast cancer are eligible for fam-trastuzumab-deruxtecan-nxki if they have received a prior chemotherapy in the metastatic setting, or their cancer returned during, or within 6 months of completing, adjuvant chemotherapy.

This approval is based on DESTINY-Breast04, a randomized, multicenter, open label clinical trial that enrolled 557 adult patients with unresectable or metastatic HER2-low breast cancer."

https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-her2-low-breast-cancer

RTP RESEARCH TO PRACTICE

2022 ASCO ANNUAL MEETING **Abstract LBA3** DESTINY-Breast04

# Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

**Shanu Modi** Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

June 5, 2022

***Additional authors***: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

**On behalf of the DESTINY-Breast04 investigators**





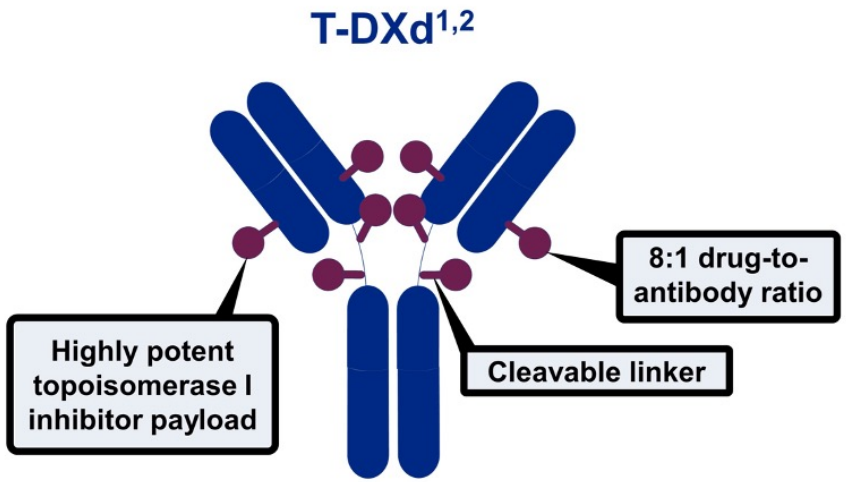
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

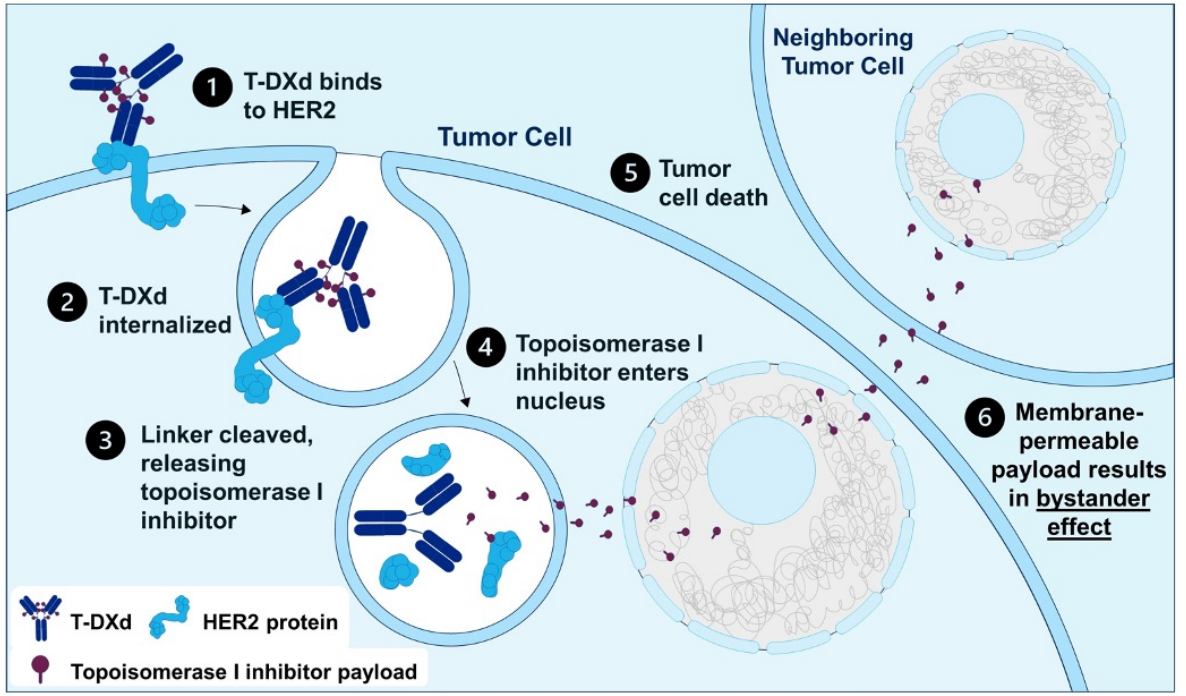
# Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

# T-DXd Mechanism of Action, Bystander Effect and Rationale for Targeting HER2-Low Breast Cancer




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[1,2]

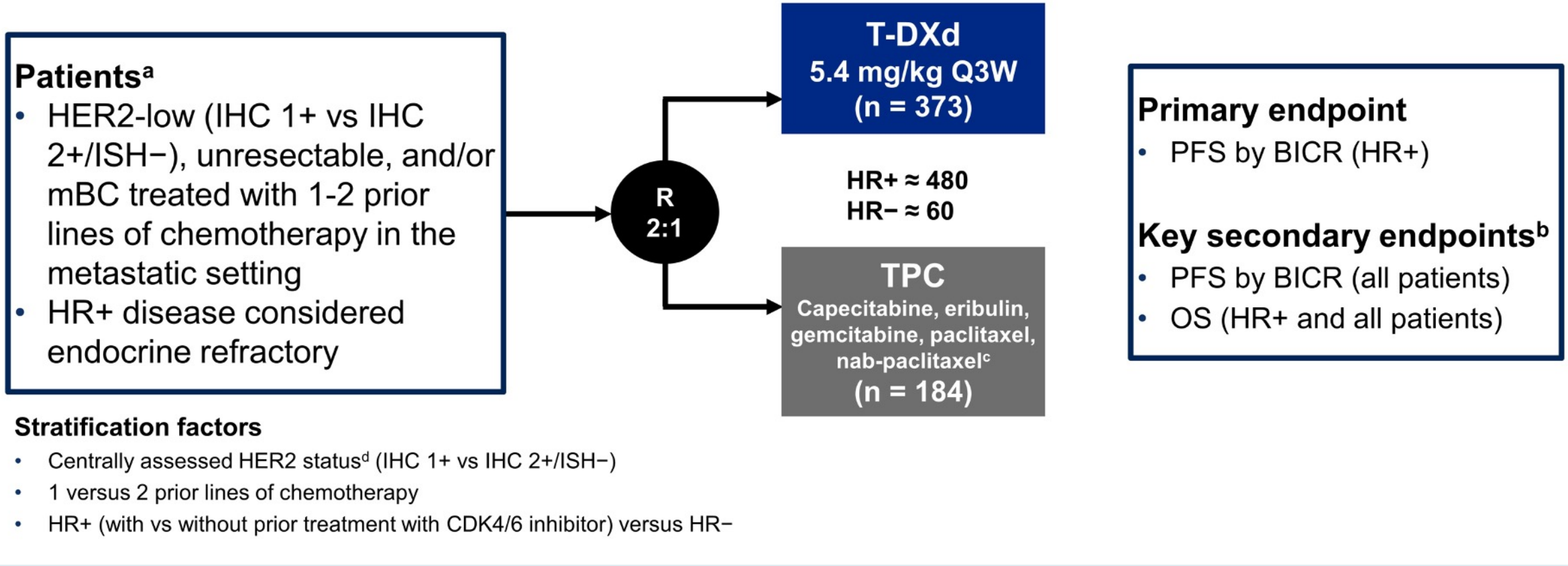



Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

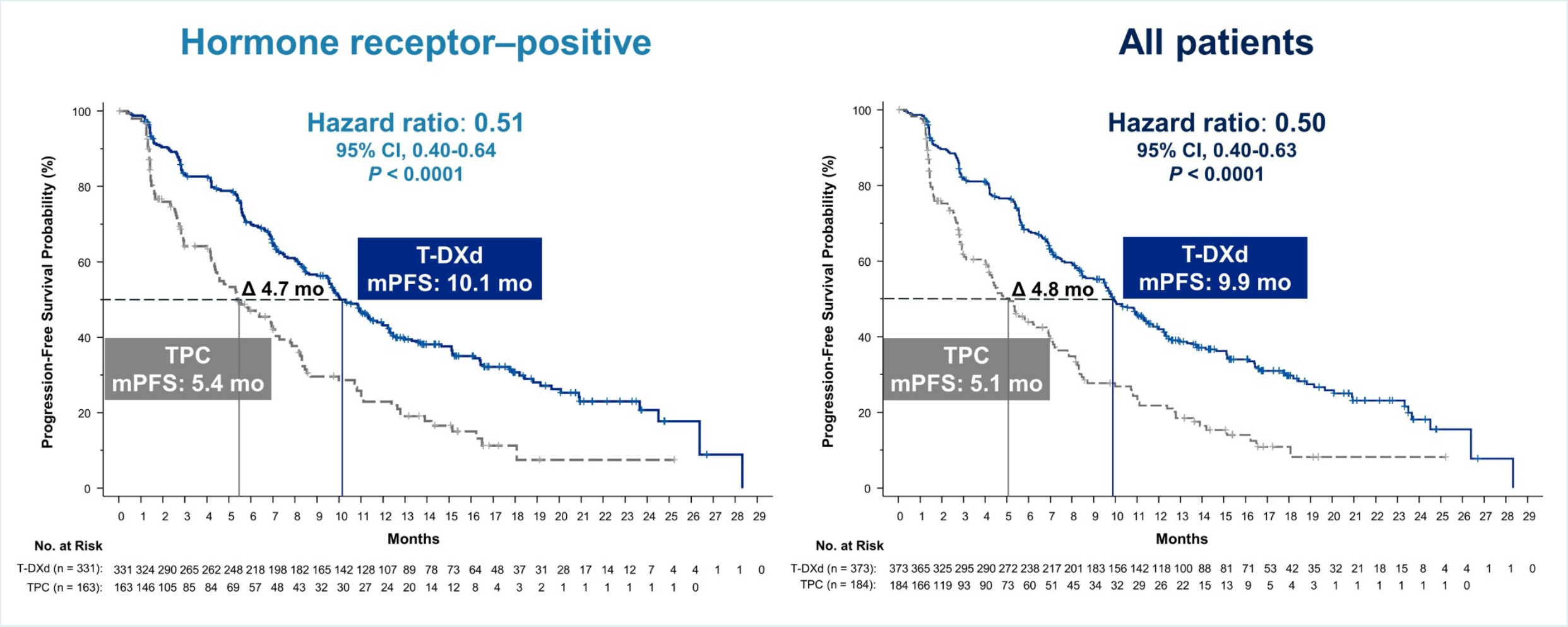
# DESTINY-Breast04 Phase III Trial Schema




TPC = treatment of physician's choice; PFS = progression-free survival; BICR = blinded independent central review; OS = overall survival

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

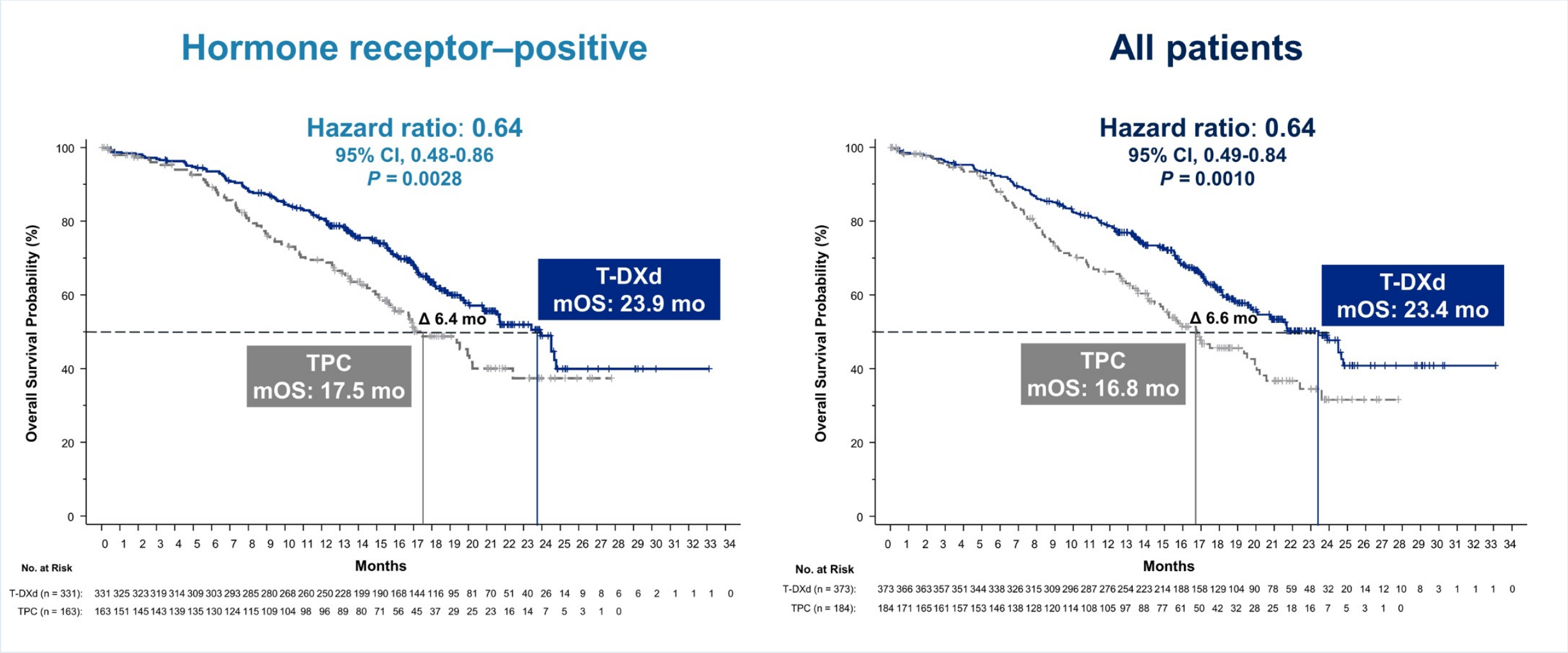
# DESTINY-Breast04: PFS for HR-Positive (Primary Endpoint) and All Patients




mPFS = median progression-free survival

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

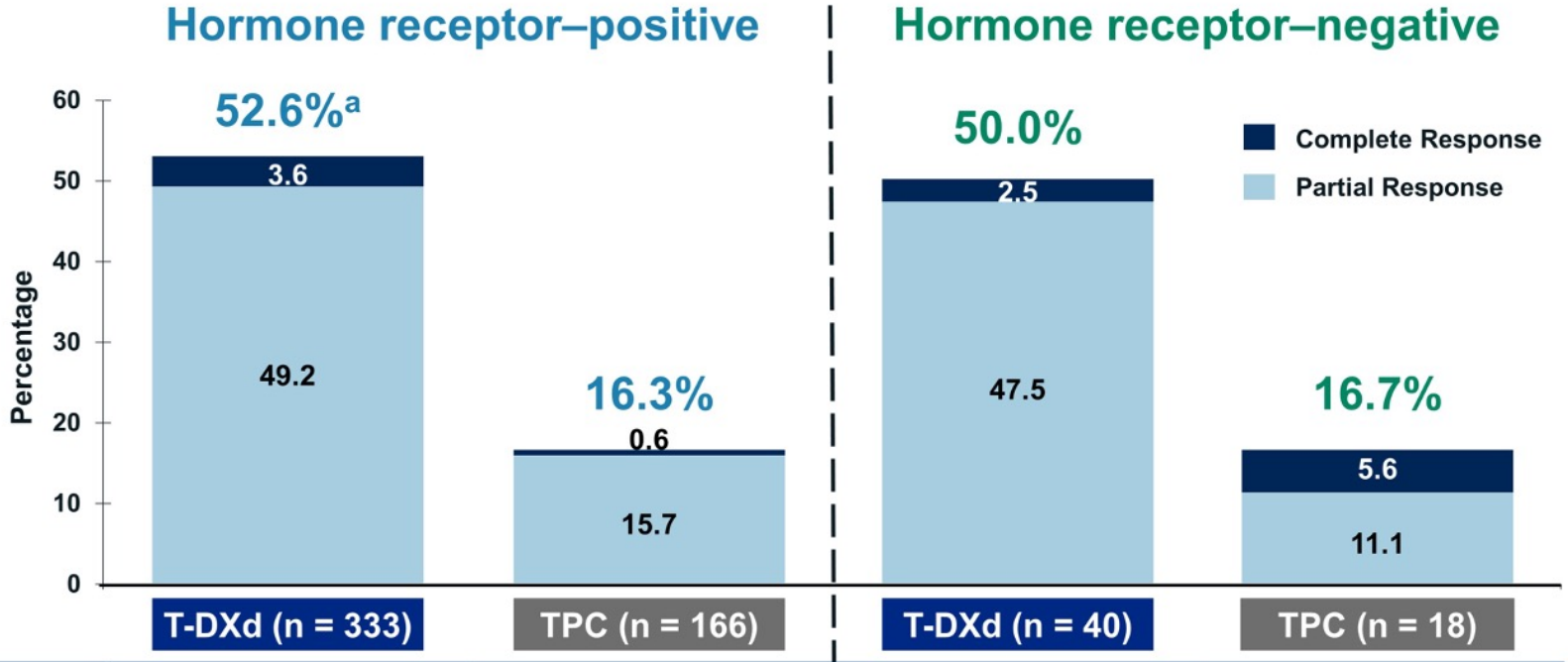
# DESTINY-Breast04: OS for HR-Positive and All Patients




mOS = median overall survival

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

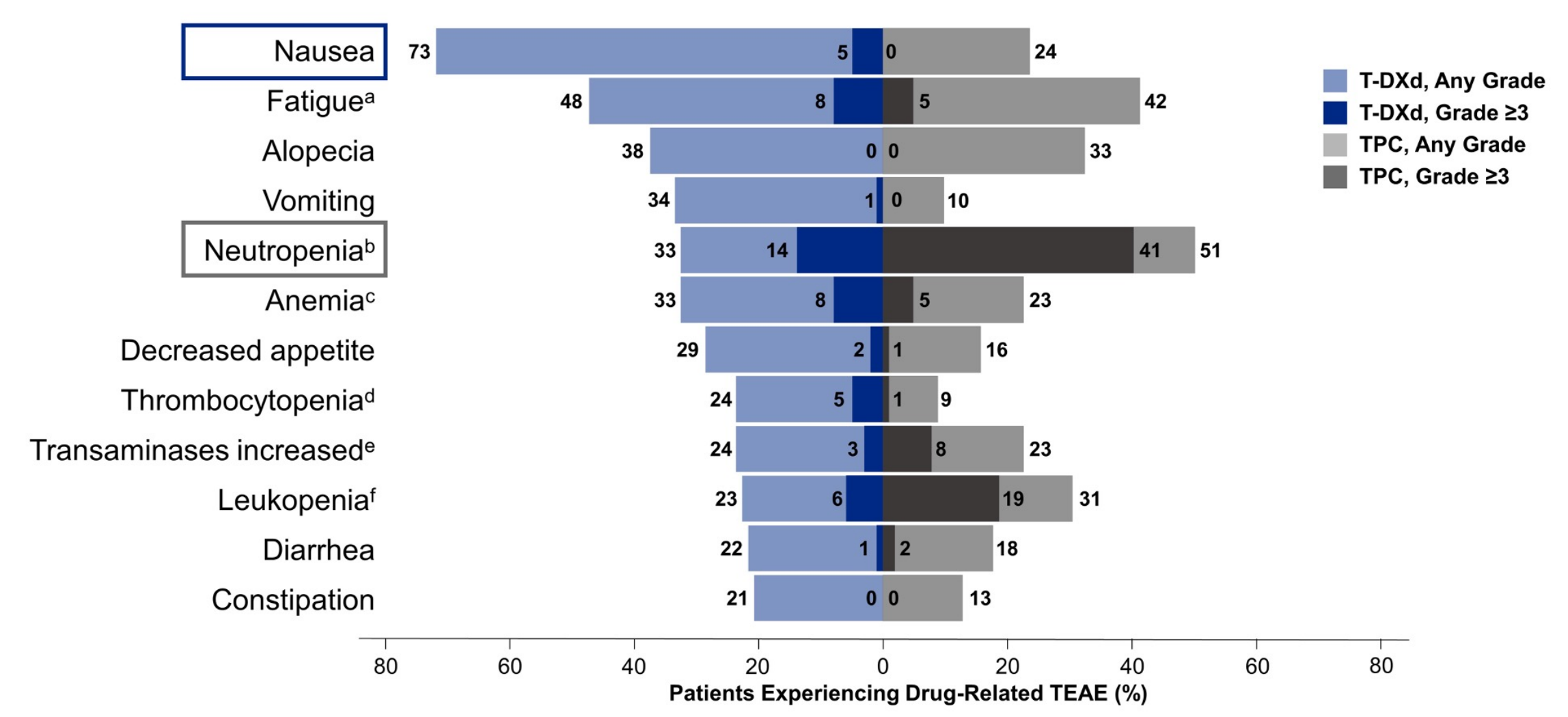
# DESTINY-Breast04: Confirmed Objective Response Rate




| | T-DXd (n = 333) | TPC (n = 166) | T-DXd (n = 40) | TPC (n = 18) |
|---|---|---|---|---|
| Progressive disease, % | 7.8 | 21.1 | 12.5 | 33.3 |
| Not evaluable, % | 4.2 | 12.7 | 7.5 | 5.6 |
| **Clinical benefit rate,[b] %** | 71.2 | 34.3 | 62.5 | 27.8 |
| **Duration of response, months** | 10.7 | 6.8 | 8.6 | 4.9 |

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

# DESTINY-Breast04: Common Drug-Related TEAEs




Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

# DESTINY-Breast04: Adverse Events of Special Interest

## Adjudicated as drug-related ILD/pneumonitis[a]

| n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade |
|---|---|---|---|---|---|---|
| T-DXd (n = 371) | 13 (3.5) | 24 (6.5) | 5 (1.3) | 0 | 3 (0.8) | 45 (12.1) |
| TPC (n = 172) | 1 (0.6) | 0 | 0 | 0 | 0 | 1 (0.6) |

## Left ventricular dysfunction[b]

| n (%) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any Grade |
|---|---|---|---|---|---|---|
| Ejection fraction decreased | | | | | | |
| T-DXd (n = 371) | 1 (0.3) | 14 (3.8) | 1 (0.3) | 0 | 0 | 16 (4.3) |
| TPC (n = 172) | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac failure[c] | | | | | | |
| T-DXd (n = 371) | 0 | 1 (0.3) | 1 (0.3) | 0 | 0 | 2 (0.5) |
| TPC (n = 172) | 0 | 0 | 0 | 0 | 0 | 0 |

Modi S et al. ASCO 2022;Abstract LBA3. Modi S et al. *N Engl J Med* 2022 July 7;387(1):9-20.

# DESTINY-Breast06 Phase III Trial Design

**Estimated enrollment: N = 850**

- Metastatic breast cancer
- HER2-low or negative by local test IHC 2+/ISH- or IHC 1/ISH- or IHC 0/ISH-
- HER2-low or HER2 IHC >0 <1 by central lab
- HR-positive
- No prior chemotherapy for advanced or metastatic disease
- PD within 6 months of starting first-line therapy with ET/CDK4/6 OR PD on at least 2 prior line of ET +/- targeted therapy

R

**Trastuzumab deruxtecan**

**Physician's choice:**

**Capecitabine or paclitaxel or *nab* paclitaxel**

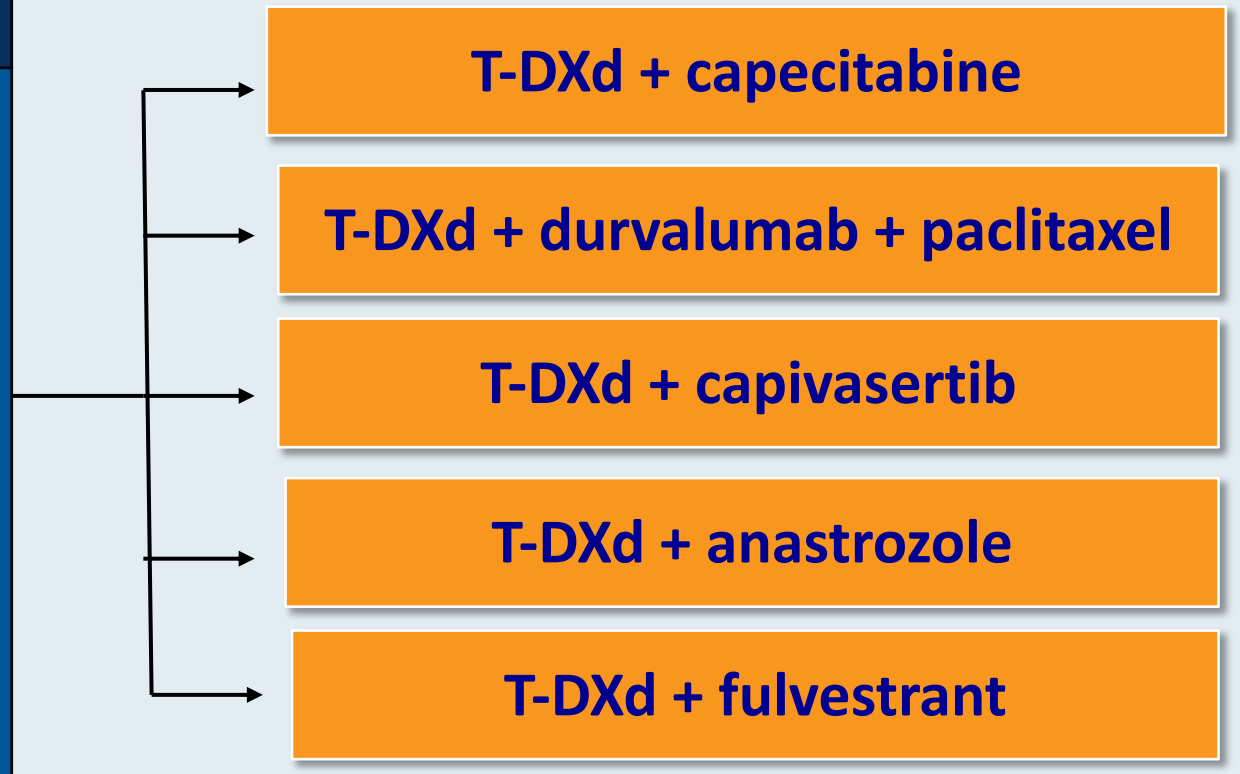
**Primary endpoint:** PFS in HR-positive, HER2-low population

www.clinicaltrials.gov. NCT04494425. Accessed August 2022.

# DESTINY-Breast08 Phase I Trial Design

**Estimated enrollment: N = 182**

- Metastatic breast cancer (mBC)
- HER2-low (IHC 2+/ISH- or IHC 1+/ISH- or untested)
- HR-positive
- At least 1 prior line of ET +/- targeted therapy and 1 prior line of chemotherapy for mBC (Part 1)
- Only 1 prior line of ET +/- targeted therapy and no prior chemotherapy for mBC (Part 2)




**Primary endpoints:** Adverse events, serious adverse events

**Secondary endpoints:** Objective response rate, progression-free survival, duration of response, overall response

www.clinicaltrials.gov. NCT04538742. Accessed August 2022.

# Tucatinib and HER2CLIMB Studies

*Ann Oncol* 2022 March;33(3):321-9.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

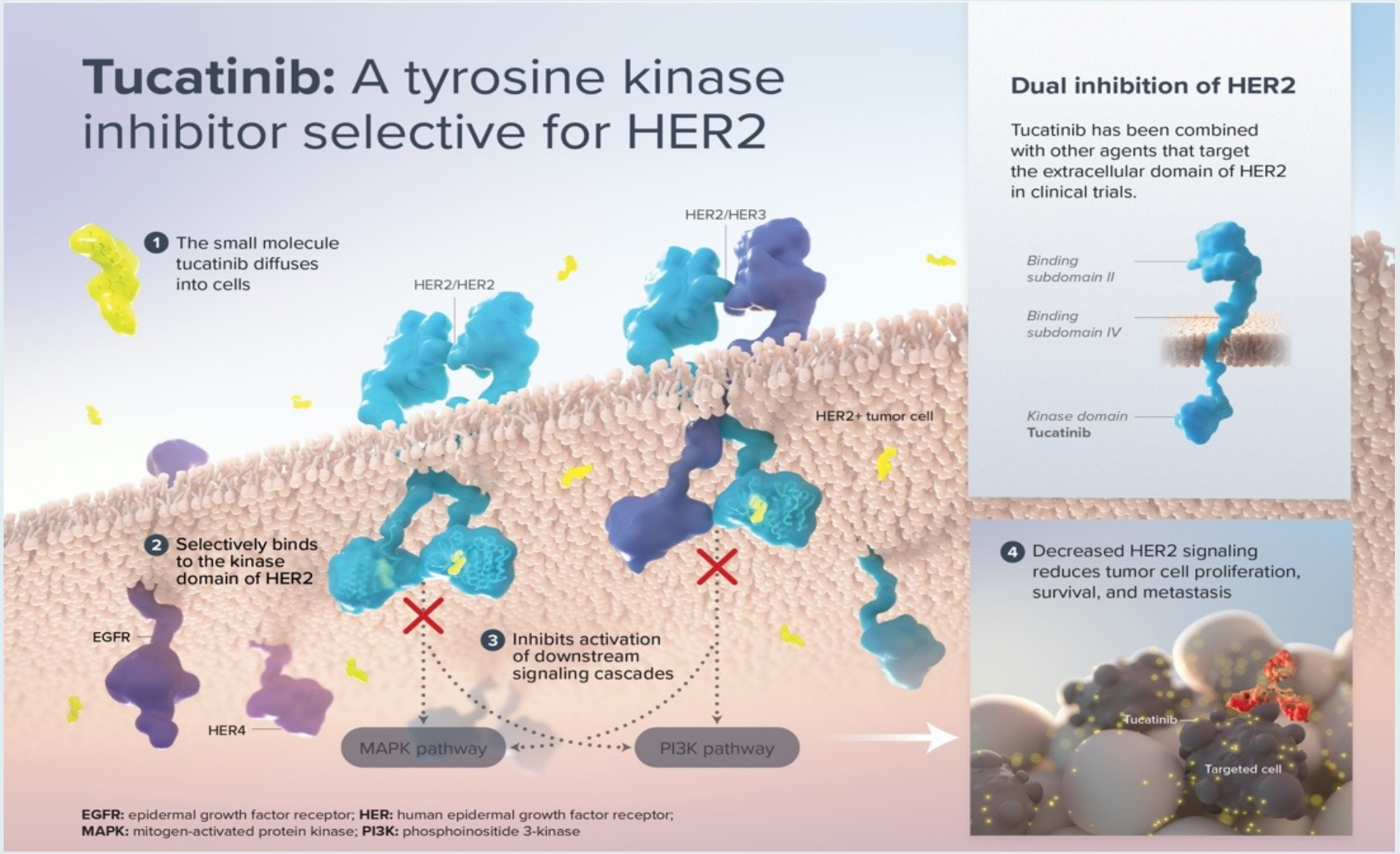
ORIGINAL ARTICLE

# Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis

G. Curigliano[1*], V. Mueller[2], V. Borges[3], E. Hamilton[4], S. Hurvitz[5], S. Loi[6], R. Murthy[7], A. Okines[8], E. Paplomata[9†], D. Cameron[10], L. A. Carey[11], K. Gelmon[12], G. N. Hortobagyi[7], I. Krop[13], S. Loibl[14], M. Pegram[15], D. Slamon[5], J. Ramos[16], W. Feng[16] & E. Winer[13]

RTP RESEARCH TO PRACTICE

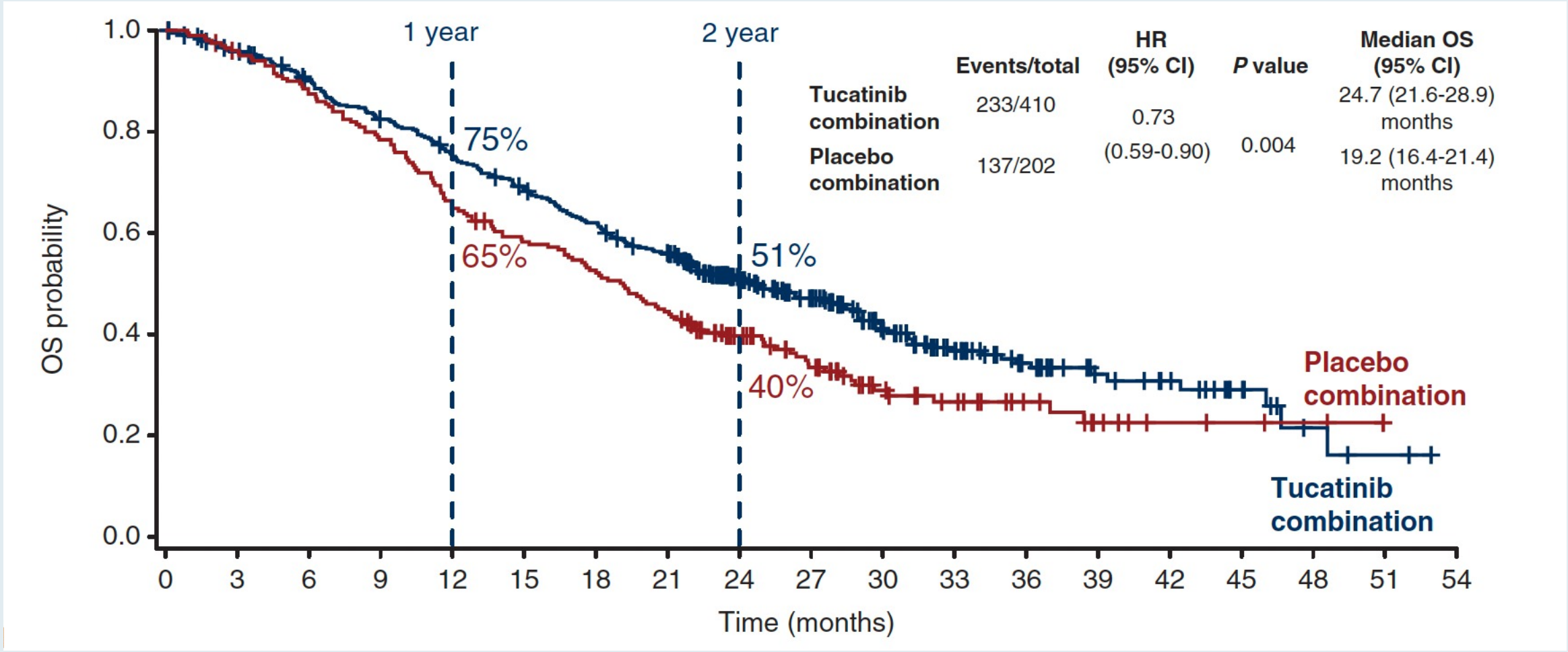
# Tucatinib Mechanism of Action




www.seagen.com/science/pipeline/tucatinib

RTP RESEARCH TO PRACTICE

# HER2CLIMB: Overall Survival

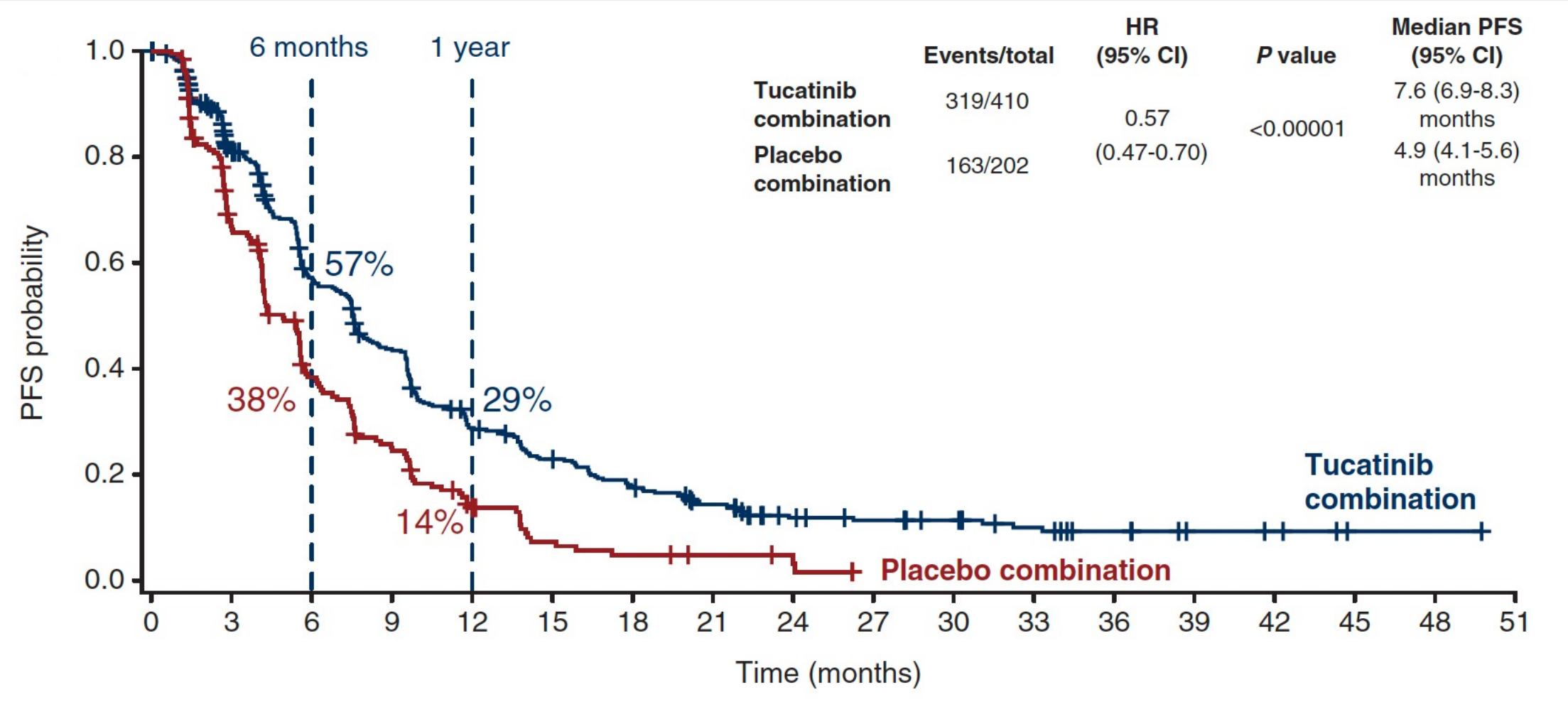



| | Events/total | HR (95% CI) | *P* value | Median OS (95% CI) |
|---|---|---|---|---|
| Tucatinib combination | 233/410 | 0.73 (0.59-0.90) | 0.004 | 24.7 (21.6-28.9) months |
| Placebo combination | 137/202 | | | 19.2 (16.4-21.4) months |

Curigliano G et al. *Ann Oncol* 2022 March;33(3):321-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: Progression-Free Survival



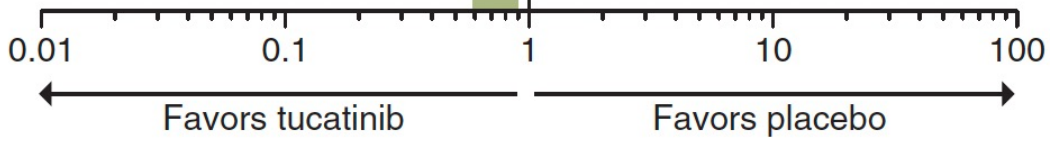

| | Events/total | HR (95% CI) | *P* value | Median PFS (95% CI) |
|---|---|---|---|---|
| Tucatinib combination | 319/410 | 0.57 (0.47-0.70) | <0.00001 | 7.6 (6.9-8.3) months |
| Placebo combination | 163/202 | | | 4.9 (4.1-5.6) months |

Curigliano G et al. *Ann Oncol* 2022 March;33(3):321-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: Forest Plot of Overall Survival

| Subgroups | Event/*N* | HR (95% CI) |
|---|---|---|
| **All patients** | **370/612** | **0.73 (0.59-0.90)** |
| Age | | |
| ≥65 years | 76/116 | 0.64 (0.38-1.06) |
| <65 years | 294/496 | 0.76 (0.60-0.96) |
| Race | | |
| White | 268/444 | 0.75 (0.58-0.96) |
| Non-White | 102/168 | 0.57 (0.37-0.89) |
| Hormone receptor status | | |
| Positive | 226/370 | 0.81 (0.61-1.06) |
| Not positive | 144/242 | 0.61 (0.43-0.87) |
| Baseline brain metastases | | |
| Yes | 189/291 | 0.60 (0.44-0.81) |
| No | 180/319 | 0.85 (0.63-1.16) |
| ECOG performance status | | |
| 0 | 155/298 | 0.60 (0.43-0.83) |
| 1 | 215/314 | 0.85 (0.64-1.13) |
| Region | | |
| North America | 240/369 | 0.78 (0.60-1.02) |
| Rest of world | 130/243 | 0.63 (0.44-0.91) |




Curigliano G et al. *Ann Oncol* 2022 March;33(3):321-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: Summary of Adverse Events

| 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) |

Curigliano G et al. *Ann Oncol* 2022 March;33(3):321-9.

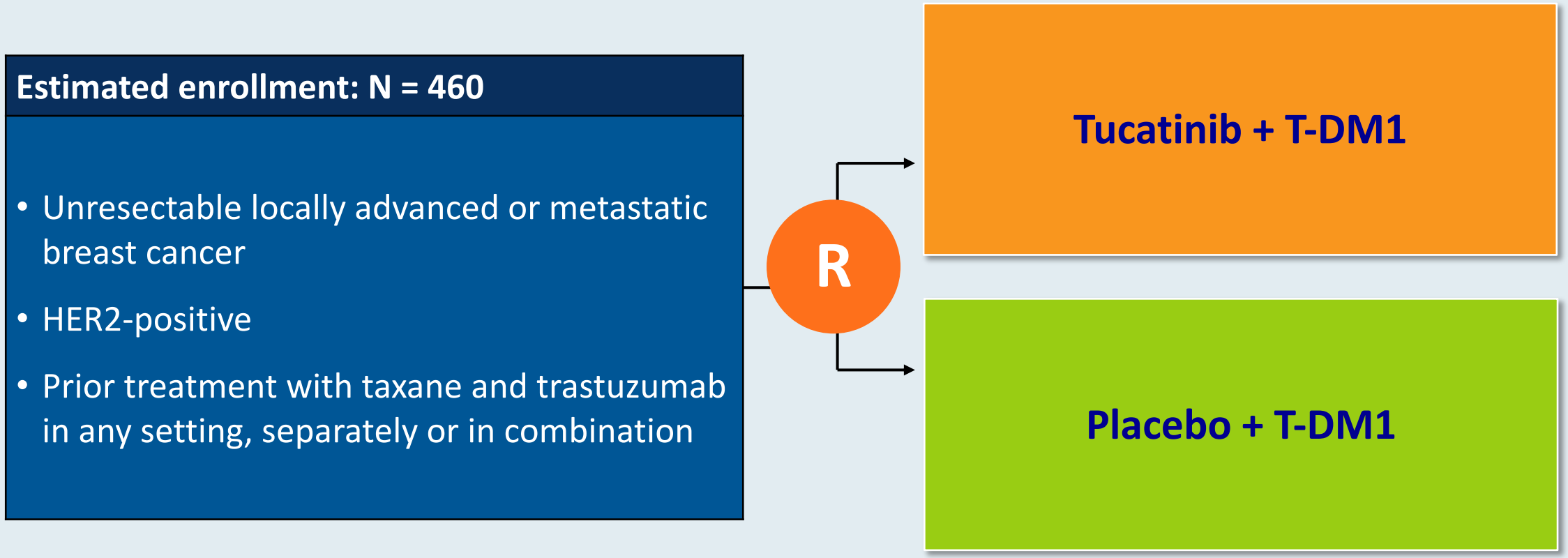
# HER2CLIMB: Adverse Events

| 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 March;33(3):321-9.

RTP RESEARCH TO PRACTICE

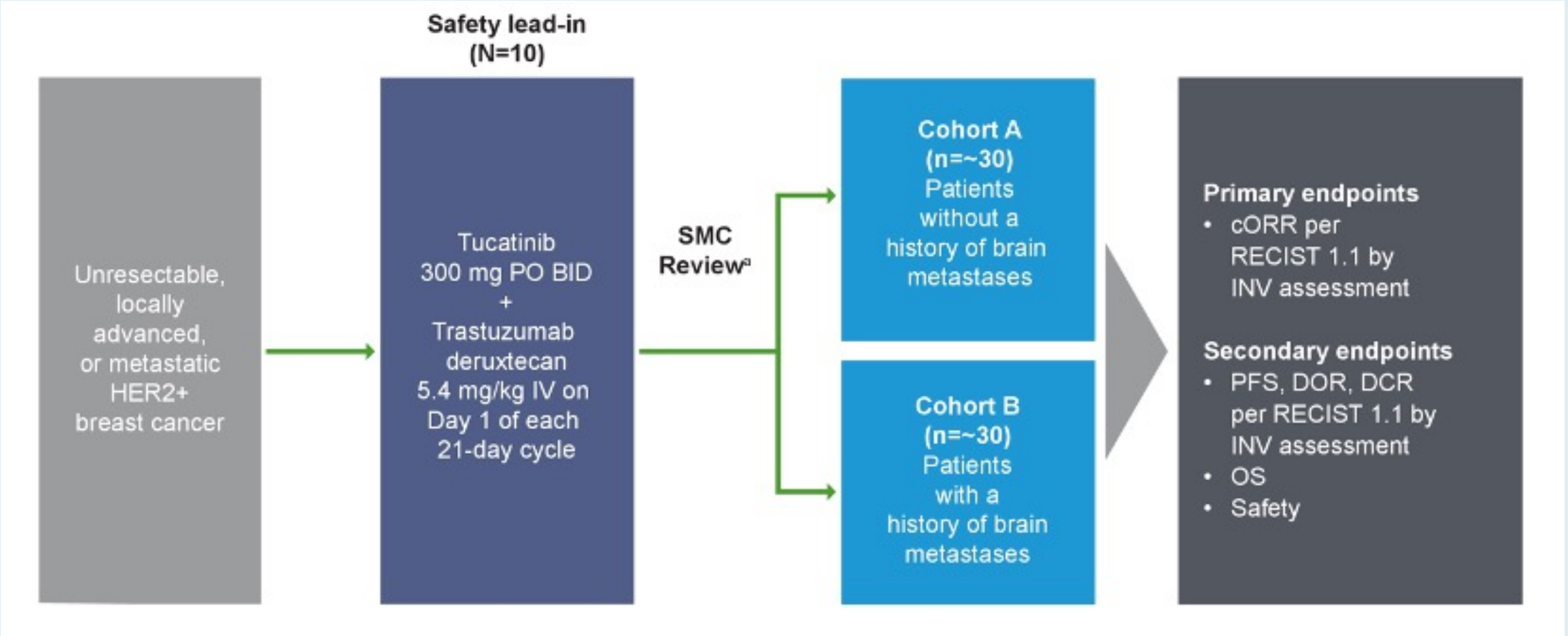
# HER2CLIMB-02 Phase III Trial Design




**Primary endpoint:** PFS by investigator assessment

www.clinicaltrials.gov. NCT03975647. Accessed August 2022.

# HER2CLIMB-04 Phase II Study Schema



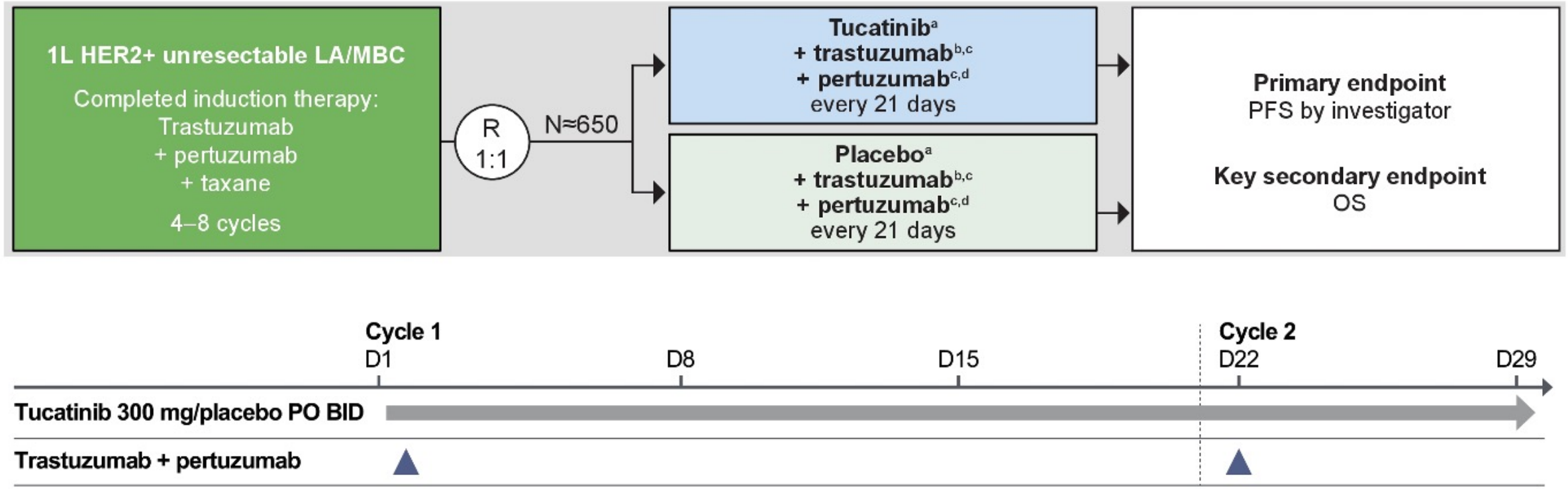

**Eligibility**

- HER2-positive locally advanced or metastatic breast cancer
- Prior treatment with taxane and trastuzumab (+/- pertuzumab) in the locally advanced or metastatic setting or disease progression within 6 months of (neo)adjuvant therapy with taxane and trastuzumab (+/- pertuzumab)

cORR = confirmed objective response rate

Krop I et al. ASCO 2022;Abstract TPS1111.

# HER2CLIMB-05 Phase III Study Schema




Hamilton E et al. ASCO 2022;Abstract TPS1108.

# Neratinib and the NALA Study

original reports

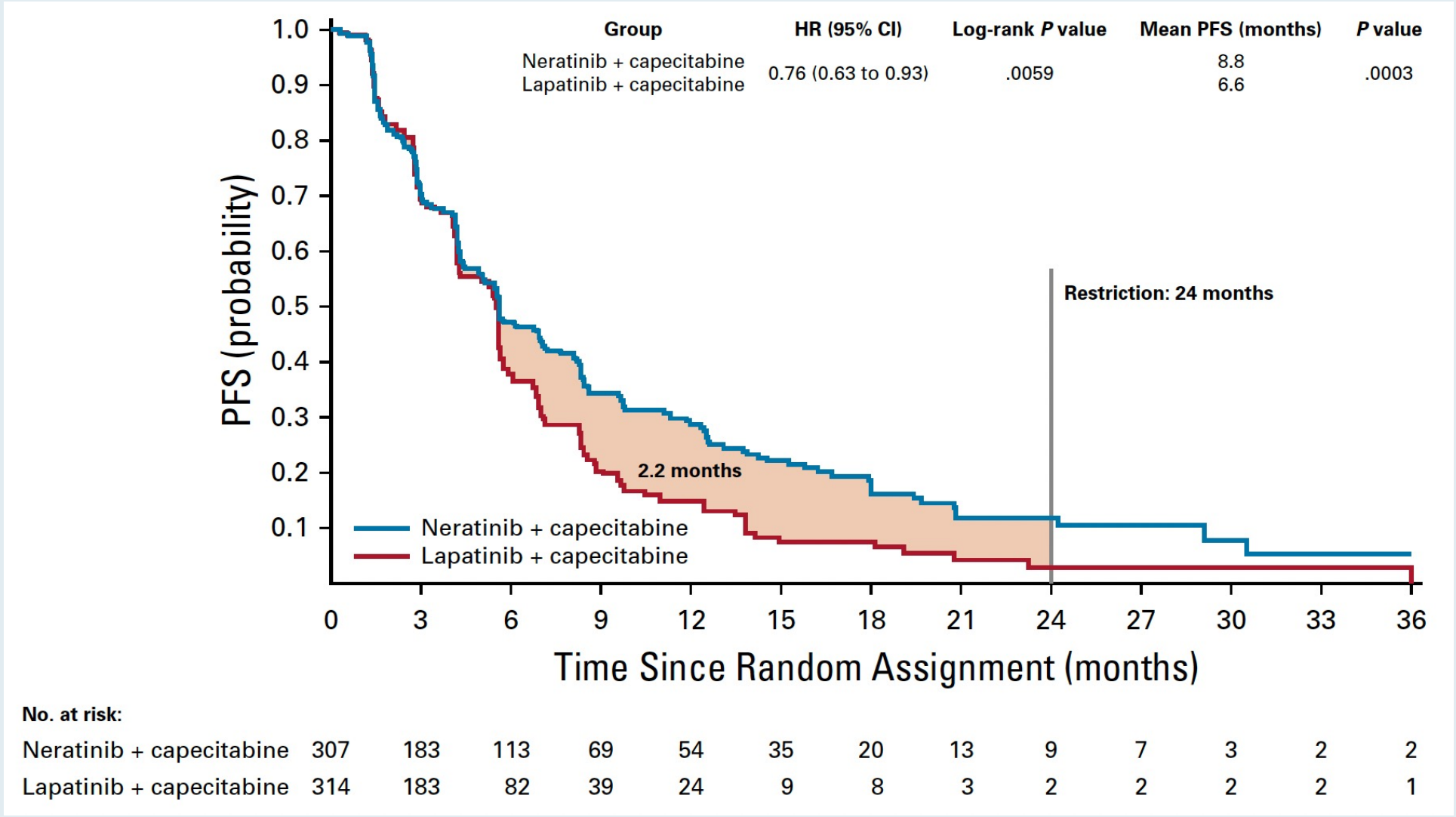
# Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial

Cristina Saura, MD[1]; Mafalda Oliveira, MD, PhD[1]; Yin-Hsun Feng, MD, PhD[2]; Ming-Shen Dai, MD, PhD[2]; Shang-Wen Chen, MD[2]; Sara A. Hurvitz, MD[3]; Sung-Bae Kim, MD, PhD[4]; Beverly Moy, MD, PhD[5]; Suzette Delaloge, MD, MSc[6]; William Gradishar, MD[7]; Norikazu Masuda, MD, PhD[8]; Marketa Palacova, MD[9]; Maureen E. Trudeau, MD[10]; Johanna Mattson, MD, PhD[11]; Yoon Sim Yap, MBBS[12]; Ming-Feng Hou, MD[13]; Michelino De Laurentiis, MD, PhD[14]; Yu-Min Yeh, MD[15]; Hong-Tai Chang, MD[16]; Thomas Yau, MBBS, MD[17]; Hans Wildiers, MD, PhD[18,19]; Barbara Haley, MD[20]; Daniele Fagnani, MD[21]; Yen-Shen Lu, MD, PhD[22]; John Crown, MBBCh, MD[23]; Johnson Lin, MD[24]; Masato Takahashi, MD, PhD[25]; Toshimi Takano, MD[26]; Miki Yamaguchi, MD, PhD[27]; Takaaki Fujii, MD, PhD[28]; Bin Yao, MS[29]; Judith Bebchuk, ScD[29]; Kiana Keyvanjah, PharmD[29]; Richard Bryce, MBChB[29]; and Adam Brufsky, MD, PhD[30]; for the NALA Investigators

*J Clin Oncol* 2020;38:3138-49.

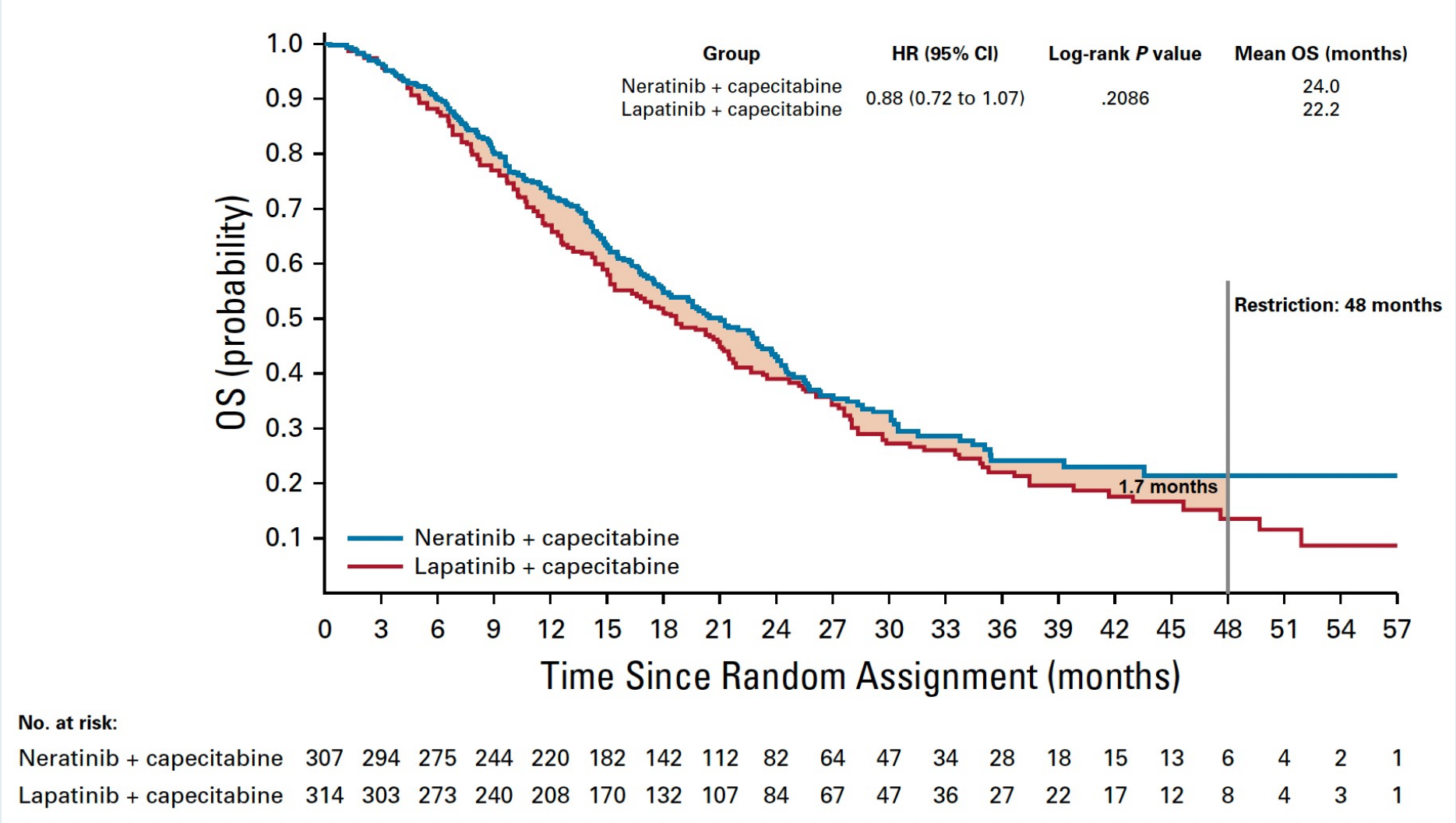
RTP RESEARCH TO PRACTICE

# NALA: Centrally Assessed PFS




Saura C et al. *J Clin Oncol* 2020;38:3138-49.

# NALA: Overall Survival (ITT Population)




Saura C et al. *J Clin Oncol* 2020;38:3138-49.

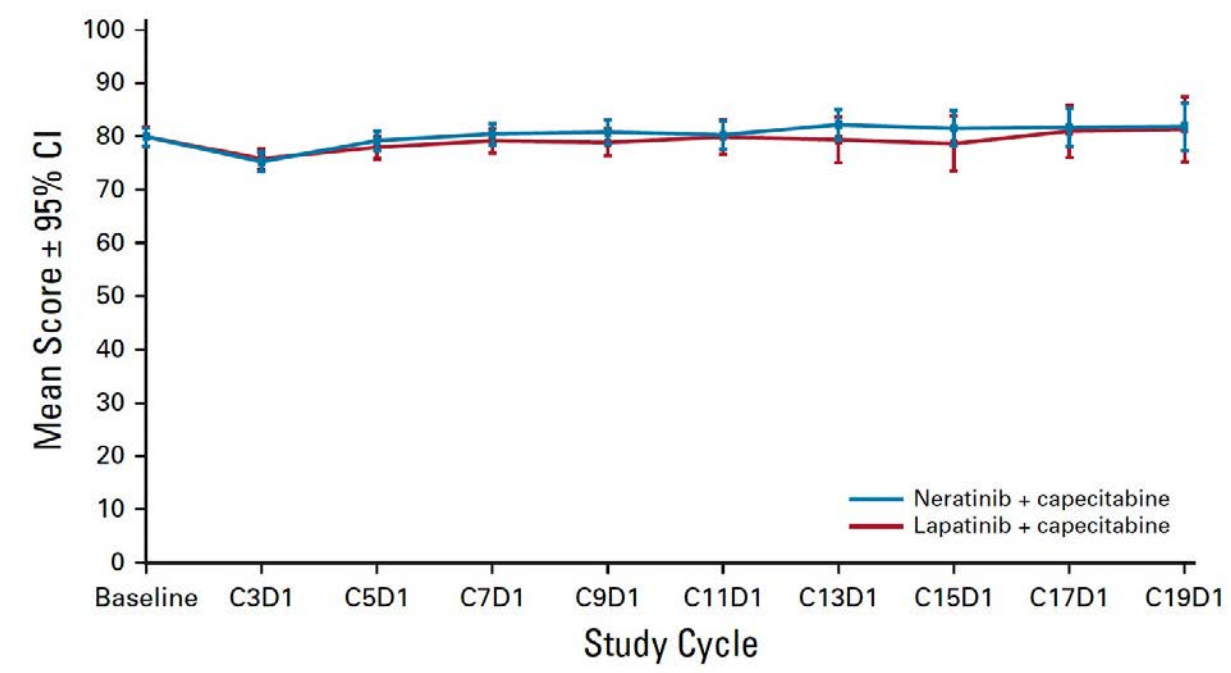
# NALA: Treatment-Emergent AEs in >15% of Patients

| | N+C (n = 303) | | L+C (n = 311) | |
|---|---|---|---|---|
| AE | All Grade | Grade 3/4 | All Grade | Grade 3/4 |
| Diarrhea | 252 (83.2) | 74 (24.4) | 206 (66.2) | 39 (12.5) |
| Nausea | 161 (53.1) | 13 (4.3) | 132 (42.4) | 9 (2.9) |
| PPE syndrome | 139 (45.9) | 29 (9.6) | 175 (56.3) | 35 (11.3) |
| Vomiting | 138 (45.5) | 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) | 51 (16.4) | 11 (3.5) |

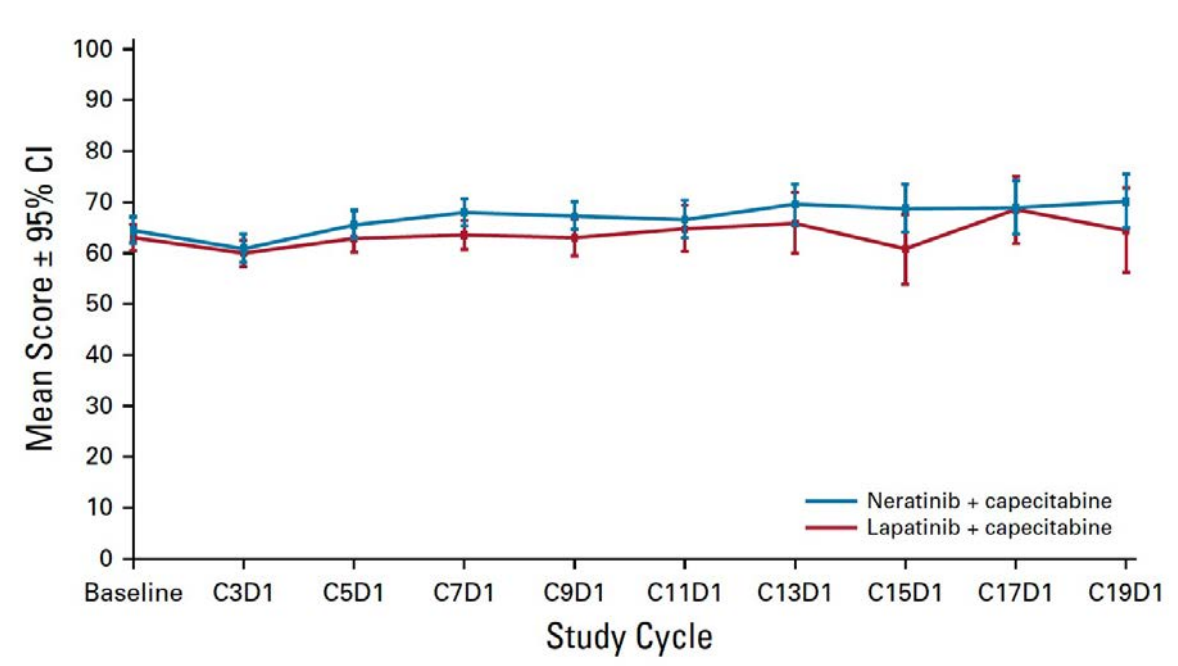
Saura C et al. *J Clin Oncol* 2020;38:3138-49.

# NALA: Changes Over Time in Global Quality of Life and Functioning

## EORTC QoL




## Global Health Status Score




Saura C et al. *J Clin Oncol* 2020;38:3138-49.

RTP RESEARCH TO PRACTICE

# Key Considerations in the Care of Patients with HER2-Positive BC with Brain Metastasis

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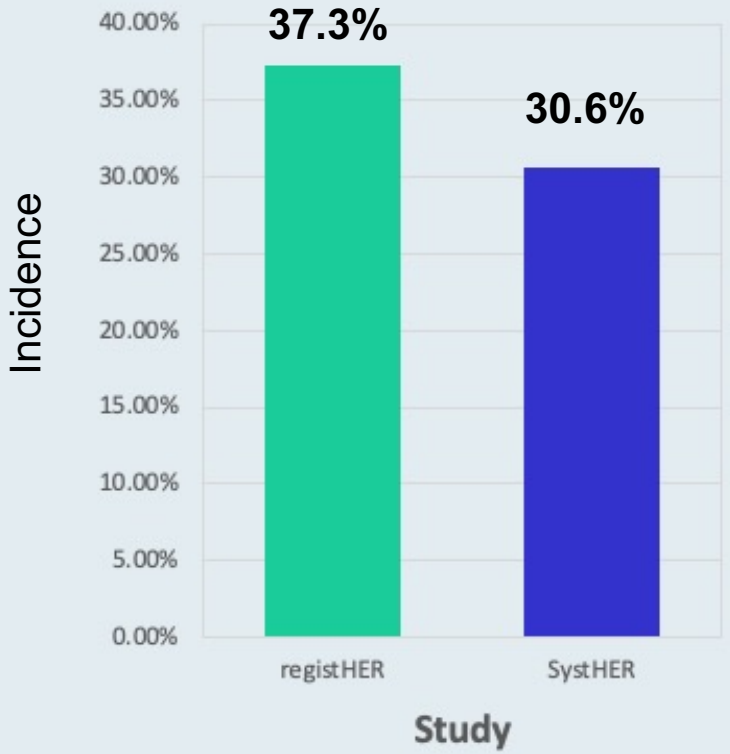
TO PRACTICE

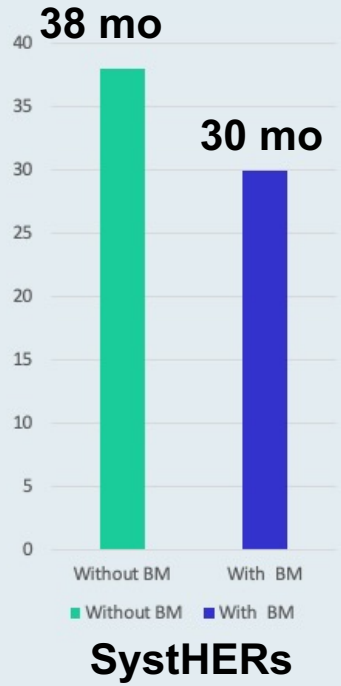
# Incidence and Prognosis of HER2-Positive CNS Metastases

- **registHER (N = 1,012) and SystHERs (N = 997) observational studies for patients with HER2-Positive breast cancer treated with trastuzumab and other anti-HER2 therapies**

## Incidence




## Prognosis


Brufsky AM et al. *Clin Cancer Res* 2011;17(14):4834-43. Hurvitz SA et al. *Clin Cancer Res* 2019;25(8): 2433-41.

RTP RESEARCH TO PRACTICE

ASCO special articles

# Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Guideline Update

Naren Ramakrishna, MD, PhD[1]; Carey K. Anders, MD[2]; Nancy U. Lin, MD[3]; Aki Morikawa, MD, PhD[4]; Sarah Temin, MSPH[5]; Sarat Chandarlapaty, MD, PhD[6]; Jennie R. Crews, MD[7]; Nancy E. Davidson, MD[8]; Maria Alice B. Franzoi, MD[9]; Jeffrey J. Kirshner, MD[10]; Ian E. Krop, MD, PhD[3]; Debra A. Patt, MD, MPH, MBA[11]; Jane Perlmutter, PhD[12]; and Sharon H. Giordano, MD, MPH[13]

*J Clin Oncol* 2022 August;40:2636-55.

RTP RESEARCH TO PRACTICE

*Ann Oncol* 2020 October;31(10):1350-8.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

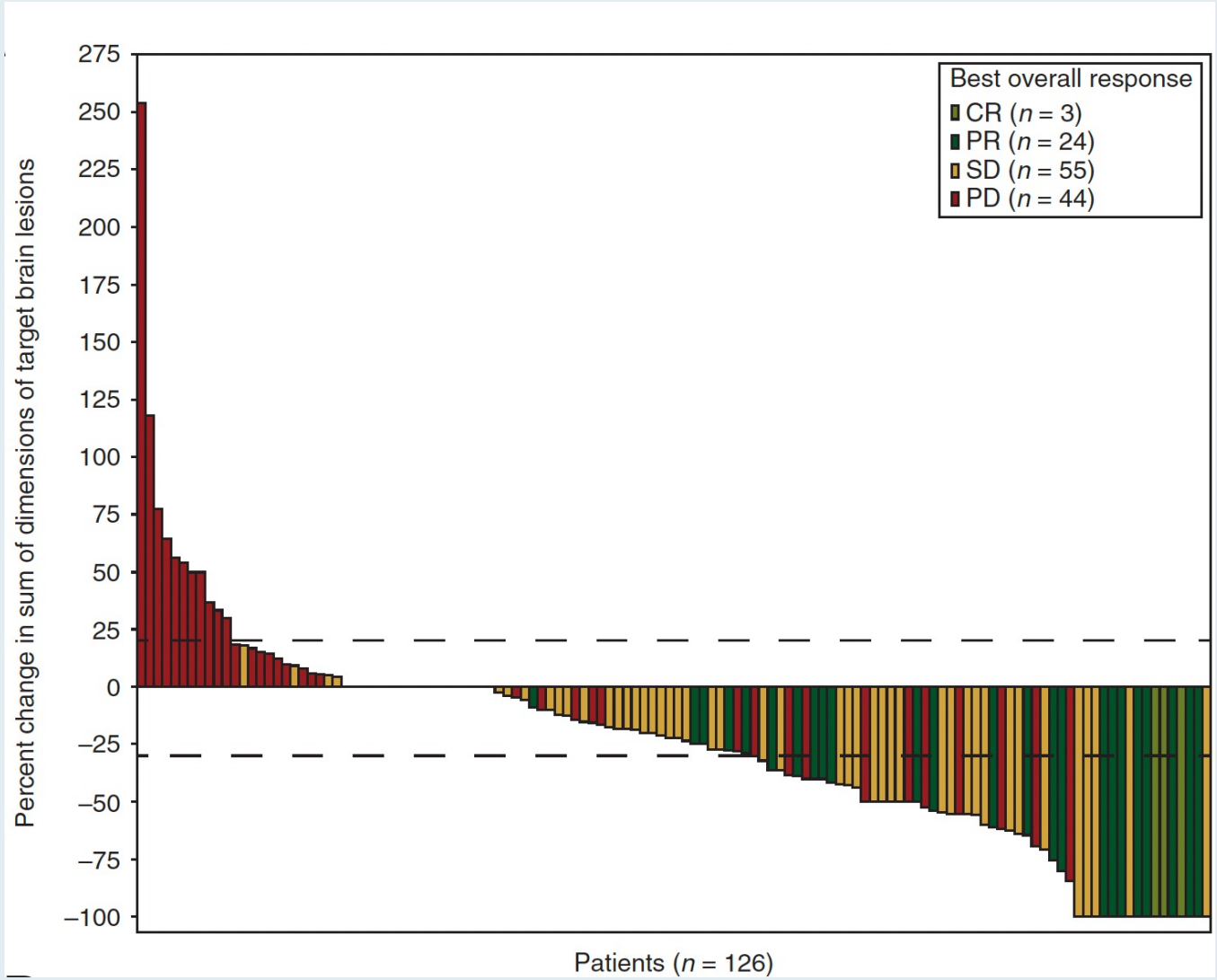
ORIGINAL ARTICLE

# Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆

F. Montemurro[1*], S. Delaloge[2], C. H. Barrios[3], R. Wuerstlein[4], A. Anton[5], E. Brain[6], T. Hatschek[7], C. M. Kelly[8], C. Peña-Murillo[9], M. Yilmaz[10], M. Donica[11] & P. Ellis[12,13]

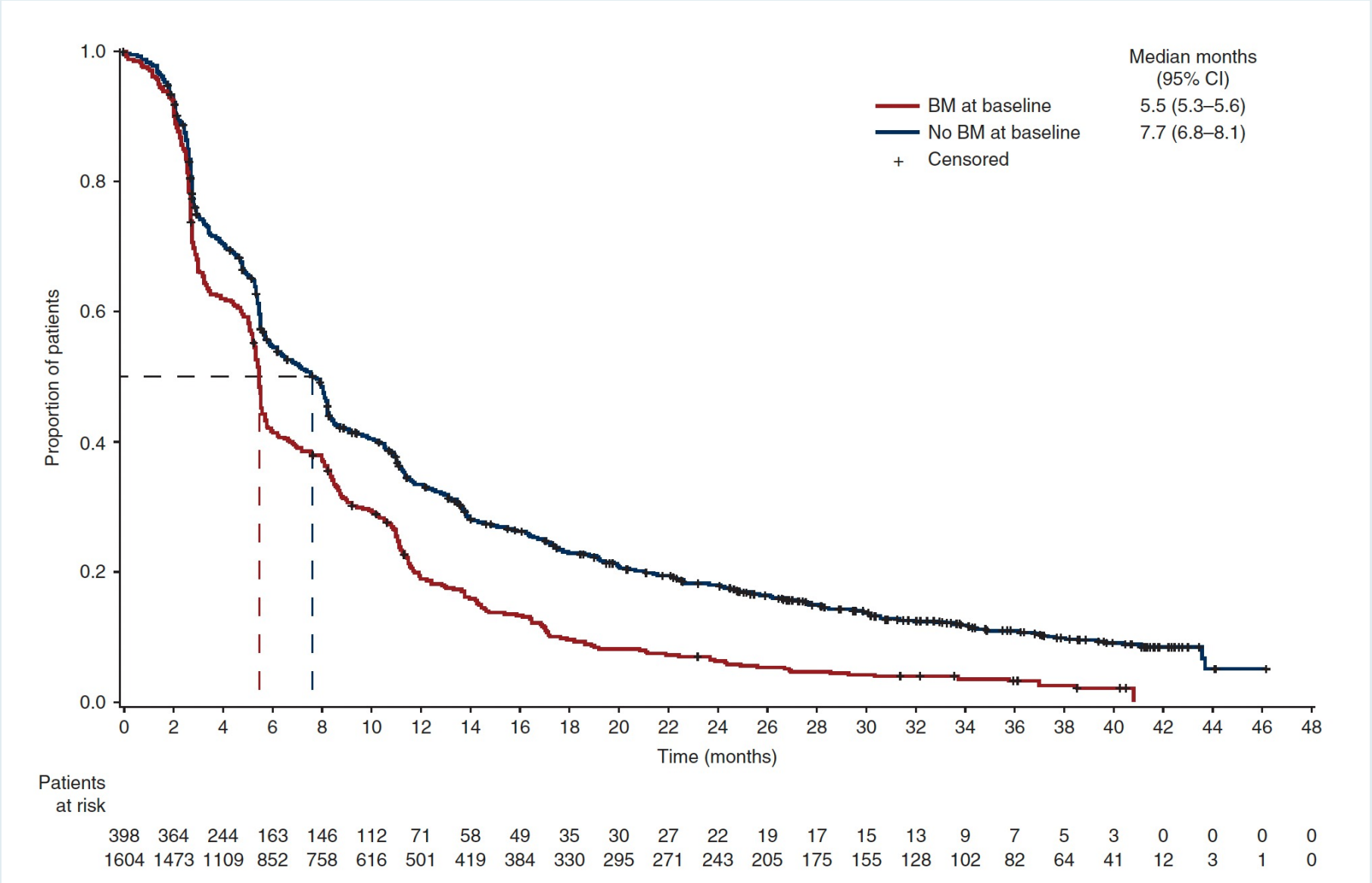
RTP RESEARCH TO PRACTICE

# KAMILLA: Percent Change in Sum of Dimensions of Target Brain Lesions




Montemurro F et al. *Ann Oncol* 2020 October;31(10):1350-8.

# KAMILLA: Progression-Free Survival




BM = brain metastases

Montemurro F et al. *Ann Oncol* 2020 October;31(10):1350-8.

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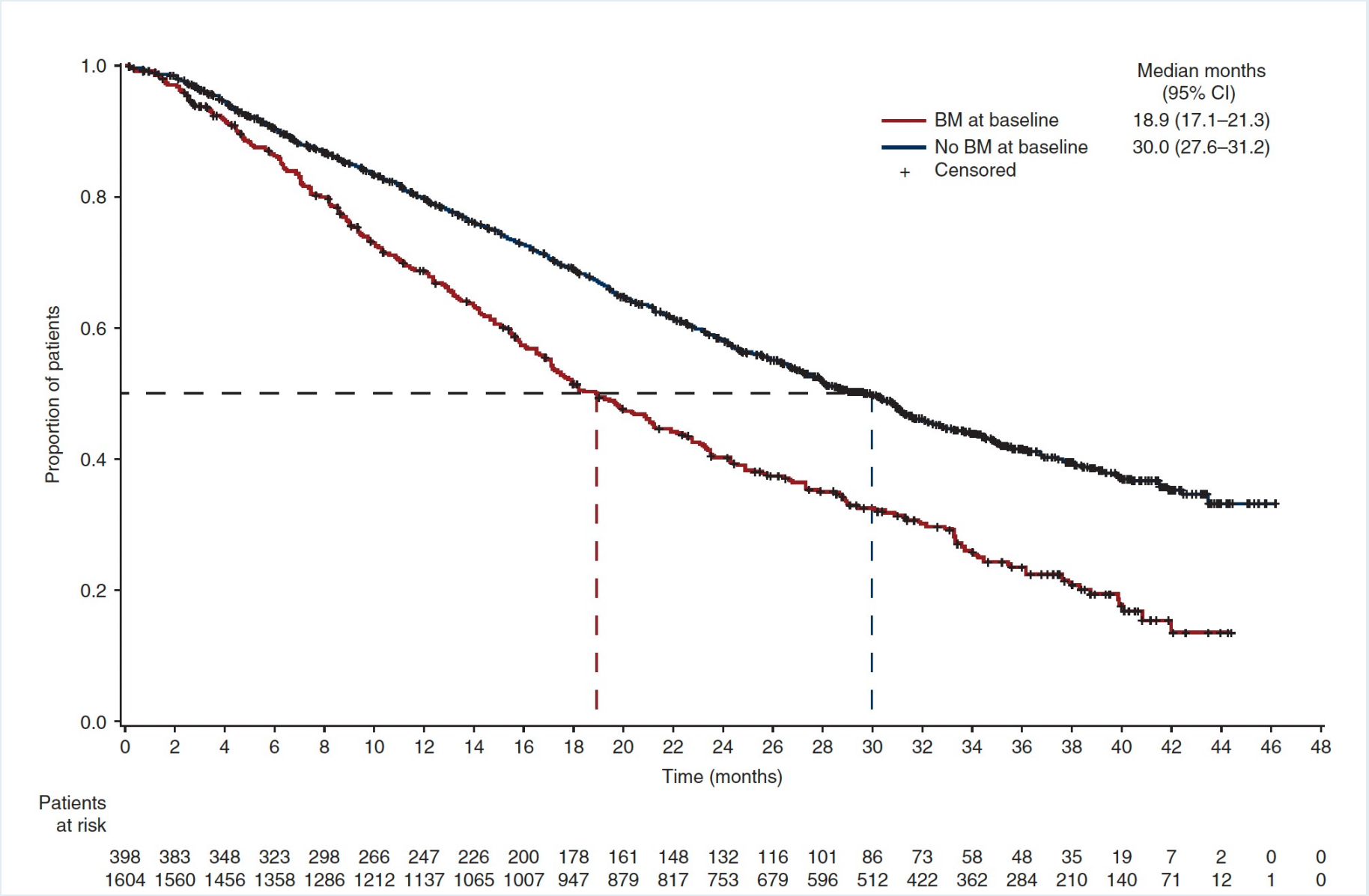
# KAMILLA: Overall Survival




Montemurro F et al. *Ann Oncol* 2020 October;31(10):1350-8.

*Oncologist* 2021 August;26(8):e1327-38.

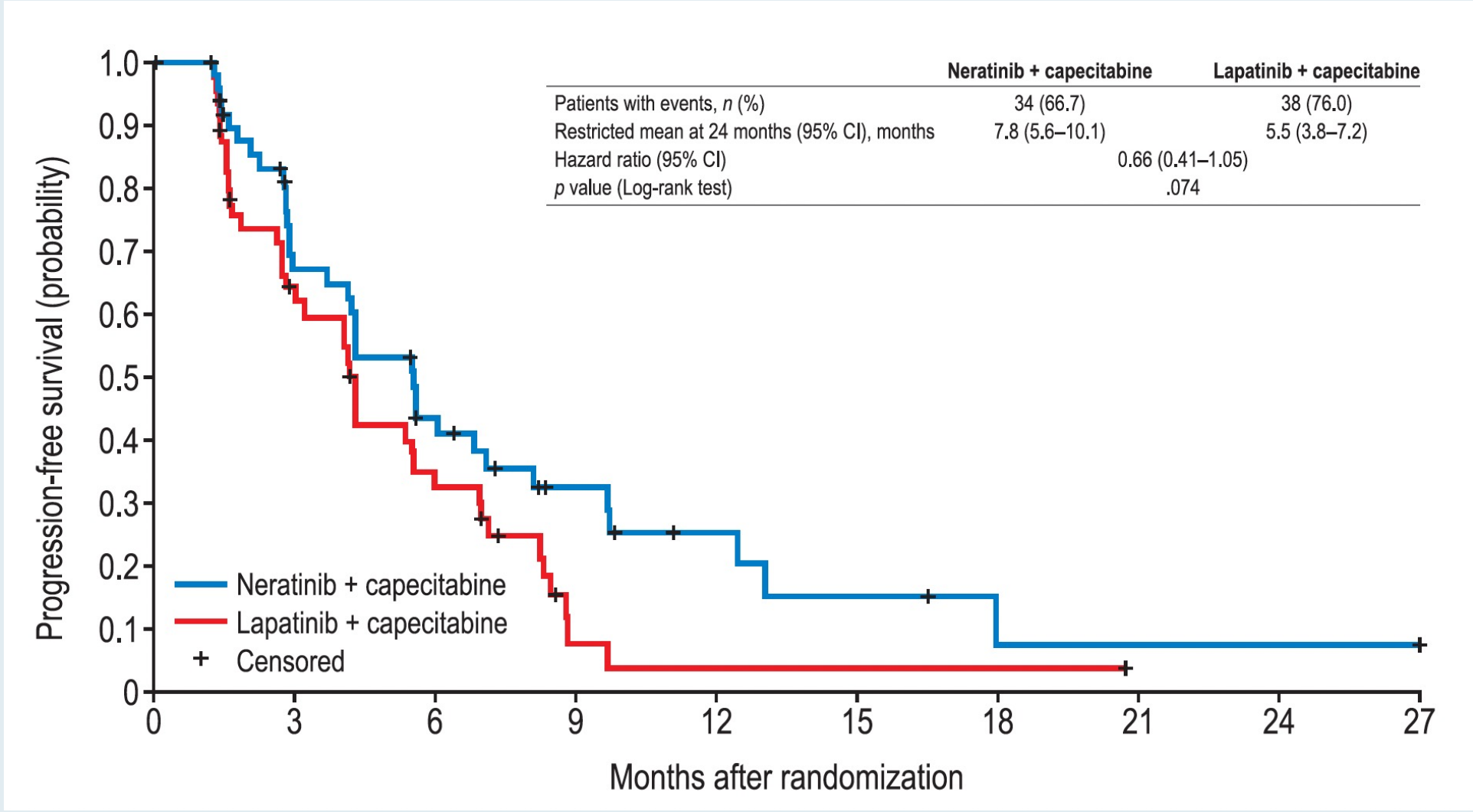
The Oncologist®

Breast Cancer

# Efficacy of Neratinib Plus Capecitabine in the Subgroup of Patients with Central Nervous System Involvement from the NALA Trial

Sara A. Hurvitz,[a] Cristina Saura,[b] Mafalda Oliveira,[b] Maureen E. Trudeau,[c] Beverly Moy,[d] Suzette Delaloge,[e] William Gradishar,[f] Sung-Bae Kim,[g] Barbara Haley,[h] Larisa Ryvo,[i] Ming-Shen Dai,[j] Vladimir Milovanov,[k] Jesús Alarcón,[l] Sujith Kalmadi,[m] Eduardo Cronemberger,[n] Cristiano Souza,[o] Luciana Landeiro,[p] Ron Bose,[q] Judith Bebchuk,[r] Fairooz Kabbinavar,[r] Richard Bryce,[r] Kiana Keyvanjah,[r] Adam M. Brufsky[s]

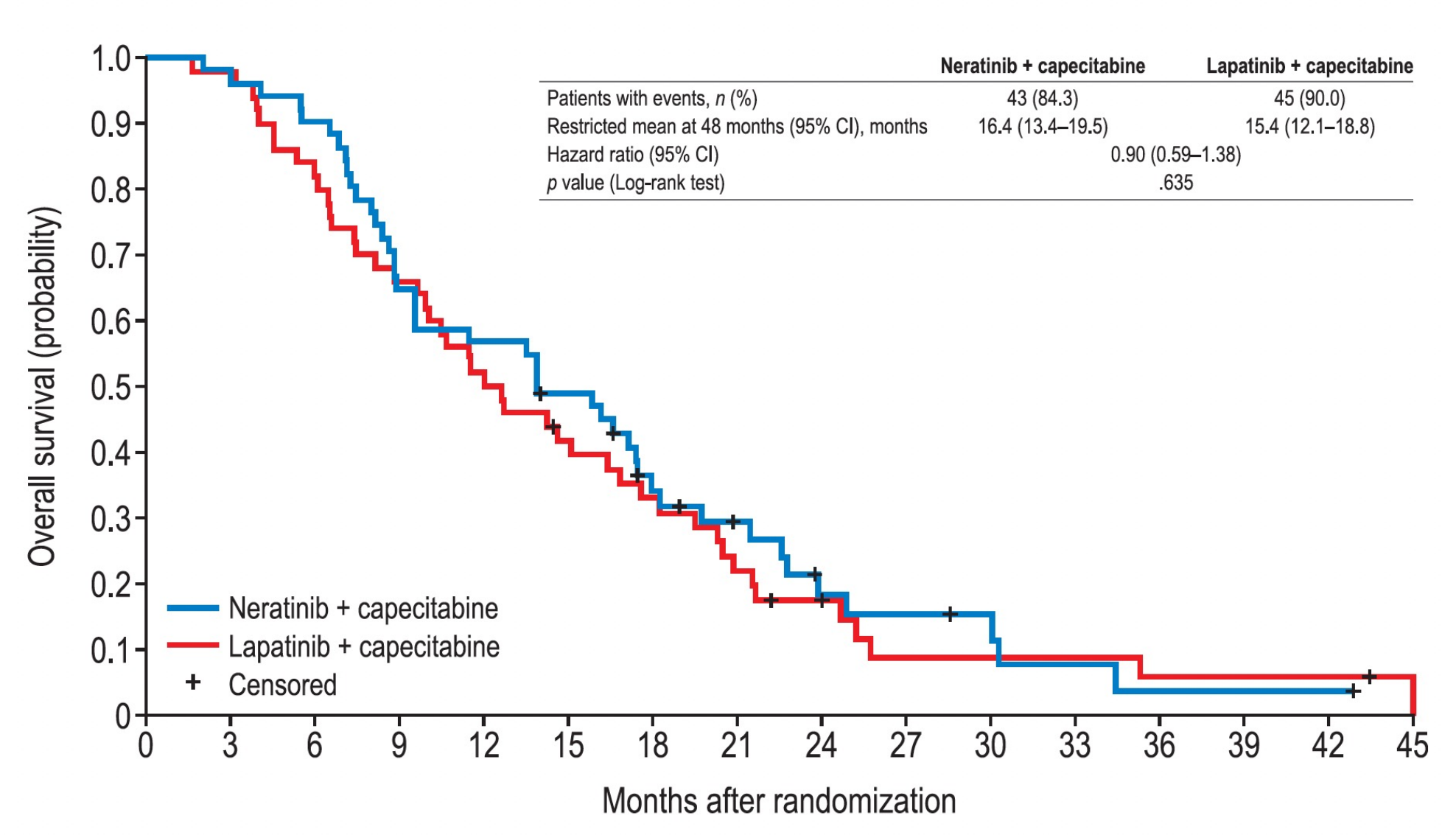
# NALA: PFS for Patients with CNS Metastases at Baseline




| | Neratinib + capecitabine | Lapatinib + capecitabine |
|---|---|---|
| Patients with events, *n* (%) | 34 (66.7) | 38 (76.0) |
| Restricted mean at 24 months (95% CI), months | 7.8 (5.6–10.1) | 5.5 (3.8–7.2) |
| Hazard ratio (95% CI) | 0.66 (0.41–1.05) | |
| *p* value (Log-rank test) | .074 | |

Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

# NALA: OS for Patients with CNS Metastases at Baseline




| | Neratinib + capecitabine | Lapatinib + capecitabine |
|---|---|---|
| Patients with events, *n* (%) | 43 (84.3) | 45 (90.0) |
| Restricted mean at 48 months (95% CI), months | 16.4 (13.4–19.5) | 15.4 (12.1–18.8) |
| Hazard ratio (95% CI) | 0.90 (0.59–1.38) | |
| *p* value (Log-rank test) | .635 | |

Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

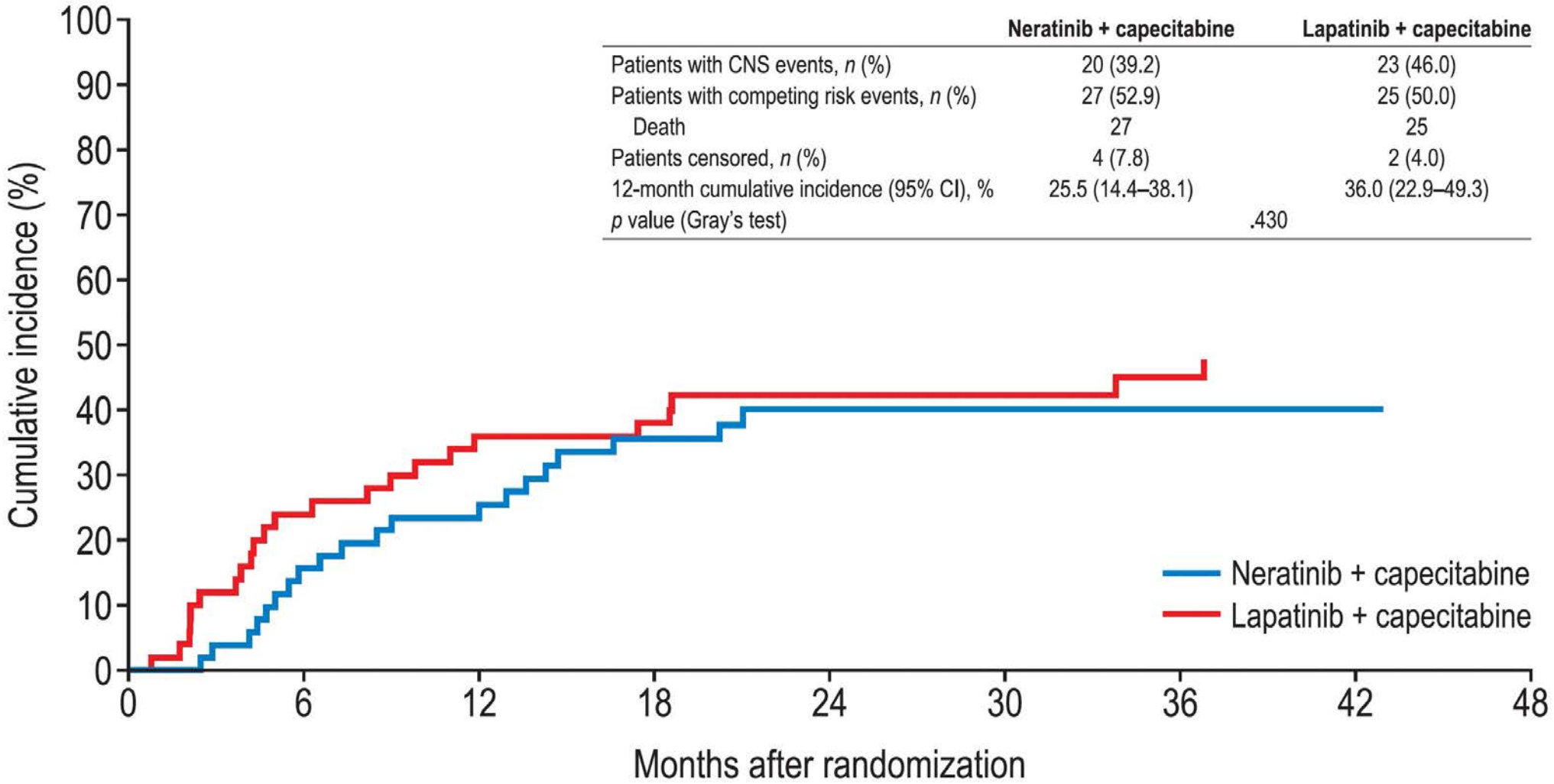
# NALA: Efficacy in Patients with CNS Metastases at Baseline

| Endpoint | Neratinib + capecitabine (n = 51) | Lapatinib + capecitabine (n = 50) | Hazard ratio | *p*-value |
|---|---|---|---|---|
| Median PFS | 5.6 mo | 4.3 mo | 0.66 | 0.074 |
| Median OS | 13.9 mo | 12.4 mo | 0.90 | 0.635 |
| Time to intervention for CNS disease (12-month cumulative incidence) | 25.5% | 36.0% | — | 0.430 |
| Progressive CNS disease (12-month cumulative incidence) | 26.2% | 41.6% | — | 0.364 |
| Median CNS PFS | 12.4 mo | 8.3 mo | 0.62 | 0.143 |
| Objective response rate | 28.6% | 28.2% | — | 0.972 |
| Median duration of response | 8.3 mo | 5.3 mo | 0.47 | 0.252 |
| Clinical benefit rate | 40.0% | 30.8% | — | 0.410 |

Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

# NALA: Time to Intervention for CNS Disease – Progressive CNS Disease

| | Neratinib + capecitabine | Lapatinib + capecitabine |
|---|---|---|
| Patients with CNS events, *n* (%) | 20 (39.2) | 23 (46.0) |
| Patients with competing risk events, *n* (%) | 27 (52.9) | 25 (50.0) |
| Death | 27 | 25 |
| Patients censored, *n* (%) | 4 (7.8) | 2 (4.0) |
| 12-month cumulative incidence (95% CI), % | 25.5 (14.4–38.1) | 36.0 (22.9–49.3) |
| *p* value (Gray's test) | .430 | |

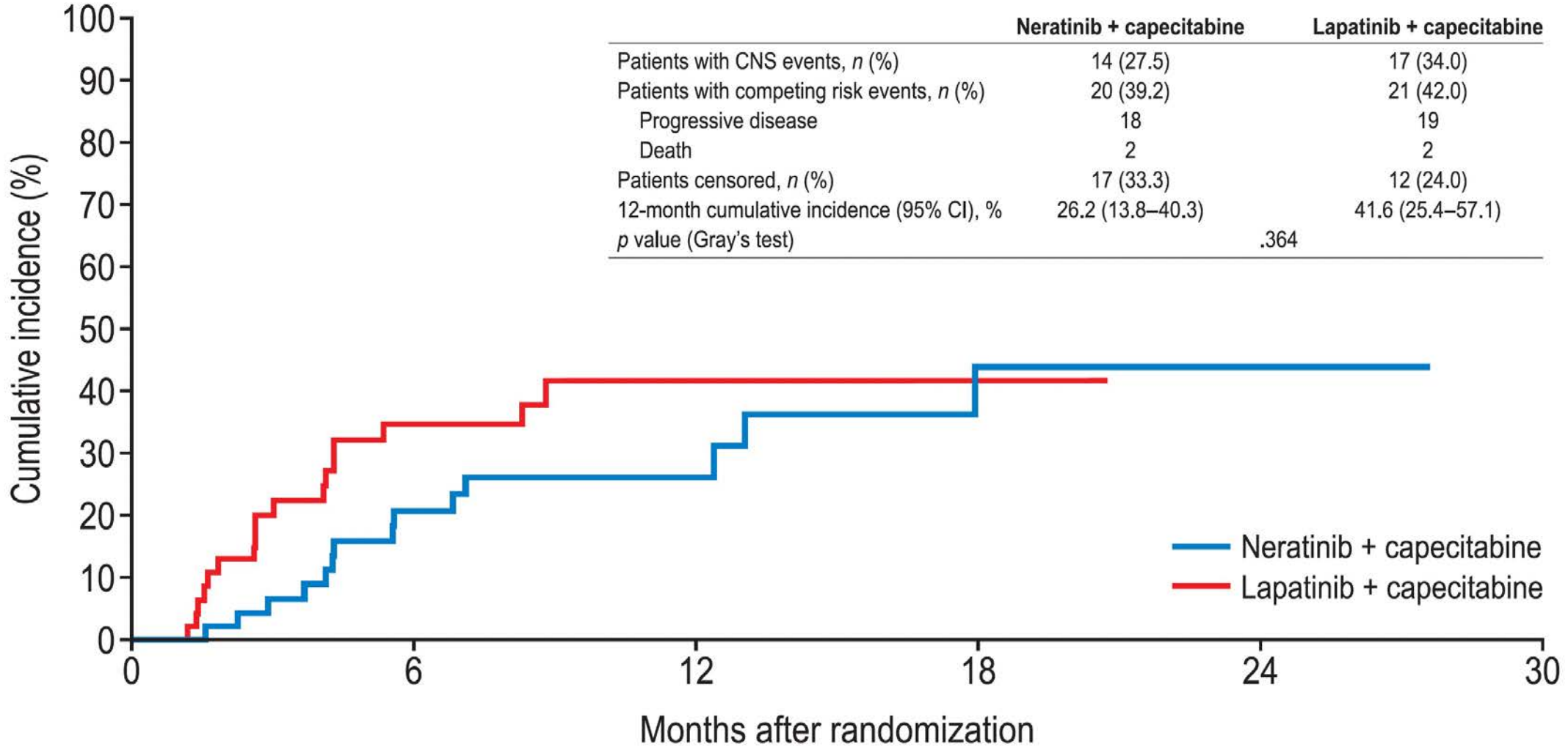



Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

RTP RESEARCH TO PRACTICE

# NALA: Time to Intervention for CNS Disease – CNS PFS

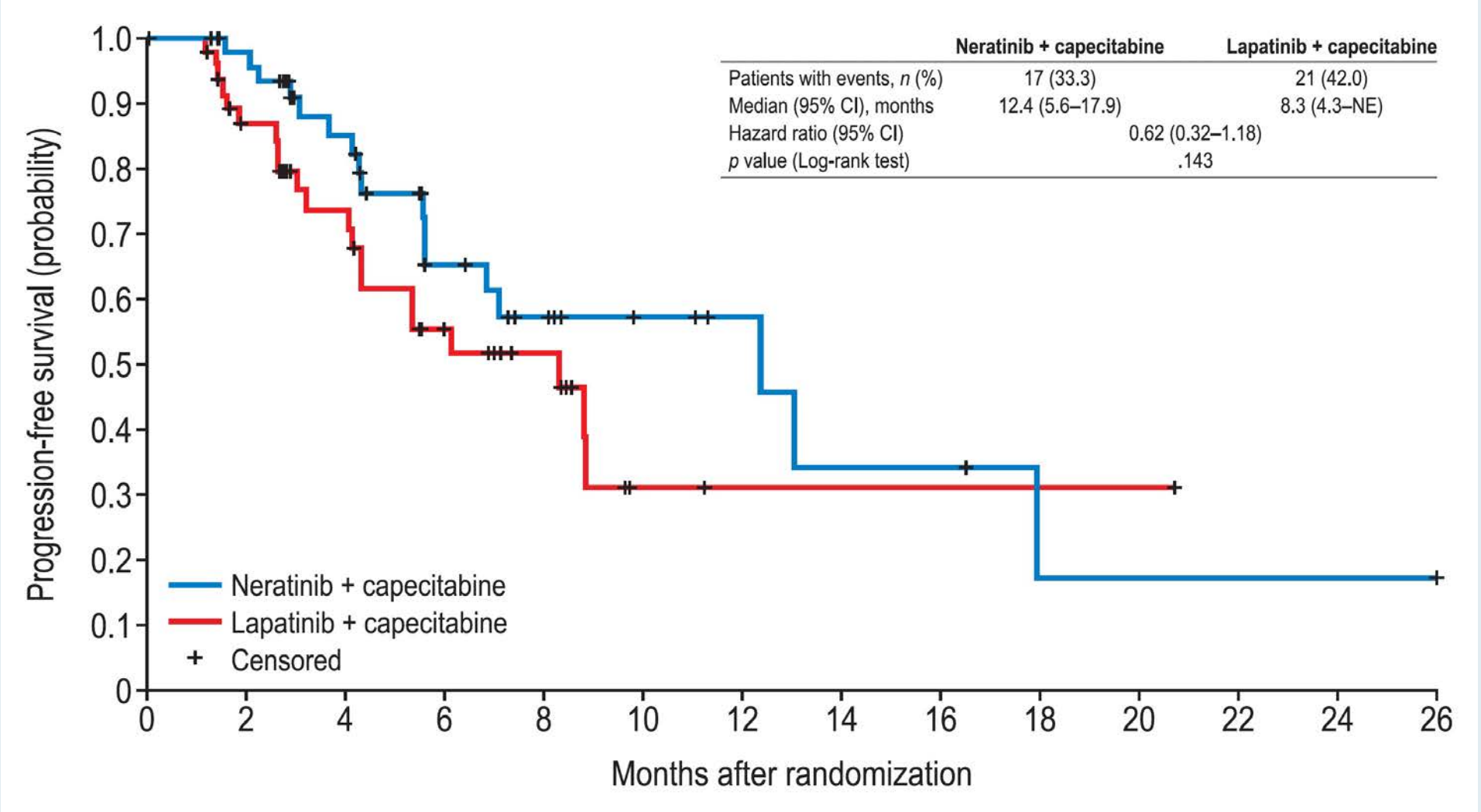
| | Neratinib + capecitabine | Lapatinib + capecitabine |
|---|---|---|
| Patients with CNS events, *n* (%) | 14 (27.5) | 17 (34.0) |
| Patients with competing risk events, *n* (%) | 20 (39.2) | 21 (42.0) |
| Progressive disease | 18 | 19 |
| Death | 2 | 2 |
| Patients censored, *n* (%) | 17 (33.3) | 12 (24.0) |
| 12-month cumulative incidence (95% CI), % | 26.2 (13.8–40.3) | 41.6 (25.4–57.1) |
| *p* value (Gray's test) | .364 | |




Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

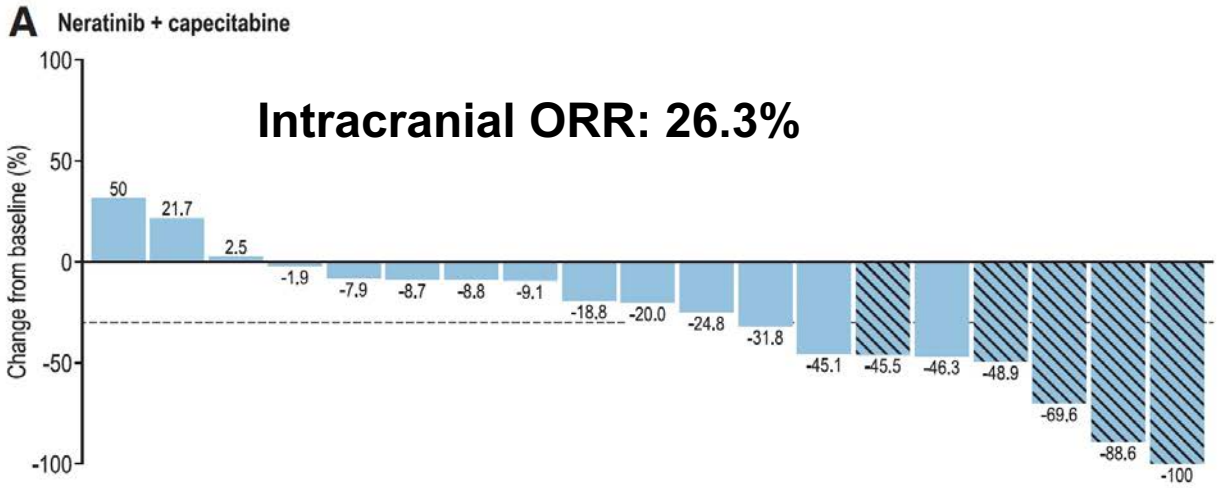
RTP RESEARCH TO PRACTICE

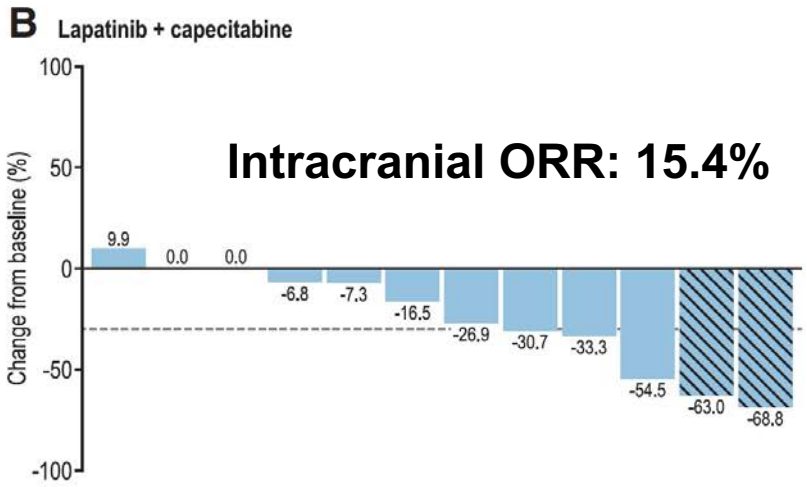
# NALA: Time to Intervention for CNS Disease – Patients with CNS Metastases at Baseline




Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

# NALA: Best Change in Intracranial Tumor Size from Baseline in Patients with Target CNS Lesions at Screening




| | N+C ($n$ = 19) | L+C ($n$ = 13) |
|---|---|---|
| **Best overall intracranial response (unconfirmed), *n* (%)** | | |
| Complete response | 1 (5.3) | 0 (0.0) |
| Partial response | 7 (36.8) | 5 (38.5) |
| Stable disease | 9 (47.4) | 6 (46.2) |
| Disease progression | 2 (10.5) | 1 (7.7) |
| Not evaluable | 0 (0.0) | 1 (7.7) |
| **Intracranial objective response (confirmed), *n* (%)** | 5 (26.3) | 2 (15.4) |
| Objective response rate (95% CI) | 26.3 (9.1–51.2) | 15.4 (1.9–45.4) |
| Difference (95% CI) | 10.9 (–23.3 to 40.1) | |

Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

*N Engl J Med* 2022 March 24;386:1143-54.

The NEW ENGLAND JOURNAL of MEDICINE

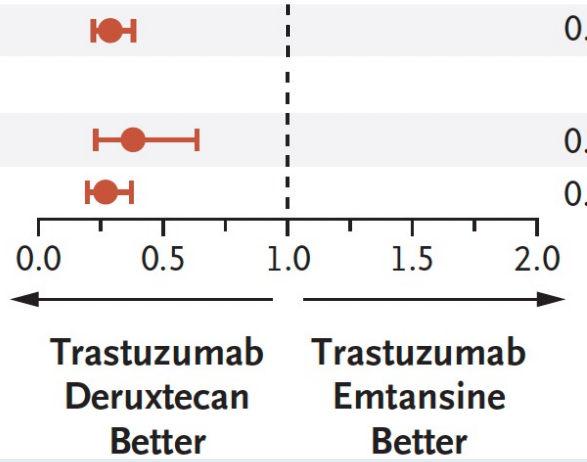
ORIGINAL ARTICLE

# Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

# DESTINY-Breast03: Progression-Free Survival for Patients with Brain Metastases

| Subgroup | No. of Patients | No. of Events/No. of Patients | | Median Progression-free Survival (95% CI) *mo* | | Hazard Ratio for Disease Progression or Death (95% CI) |
|---|---|---|---|---|---|---|
| | | Trastuzumab deruxtecan | Trastuzumab emtansine | Trastuzumab deruxtecan | Trastuzumab emtansine | |
| All patients | | 87/261 | 158/263 | NE (18.5–NE) | 6.8 (5.6–8.2) | 0.28 (0.22–0.37) |
| Stable brain metastases | | | | | | |
| Yes | 114 | 31/62 | 31/52 | 15.0 (12.6–22.2) | 5.7 (2.9–7.1) | 0.38 (0.23–0.64) |
| No | 410 | 56/199 | 127/211 | NE (22.4–NE) | 7.0 (5.5–9.7) | 0.27 (0.19–0.37) |




Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

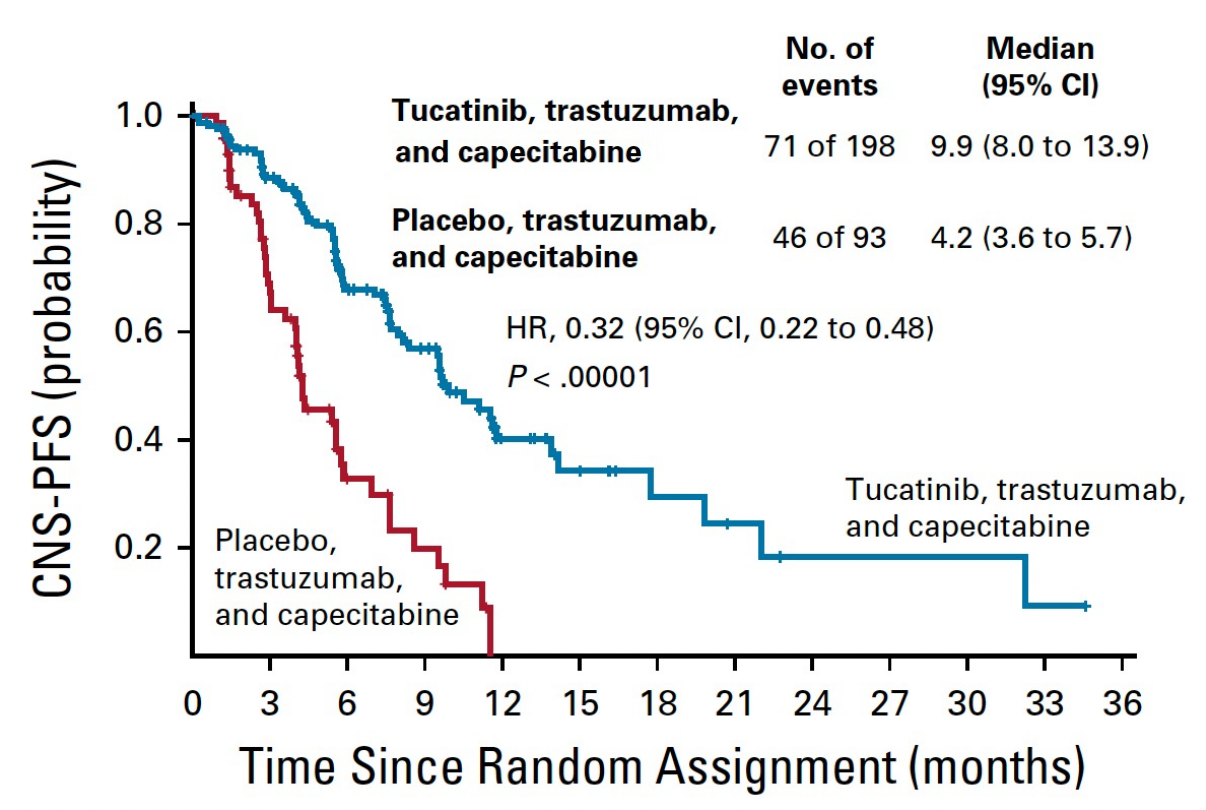
rapid communications

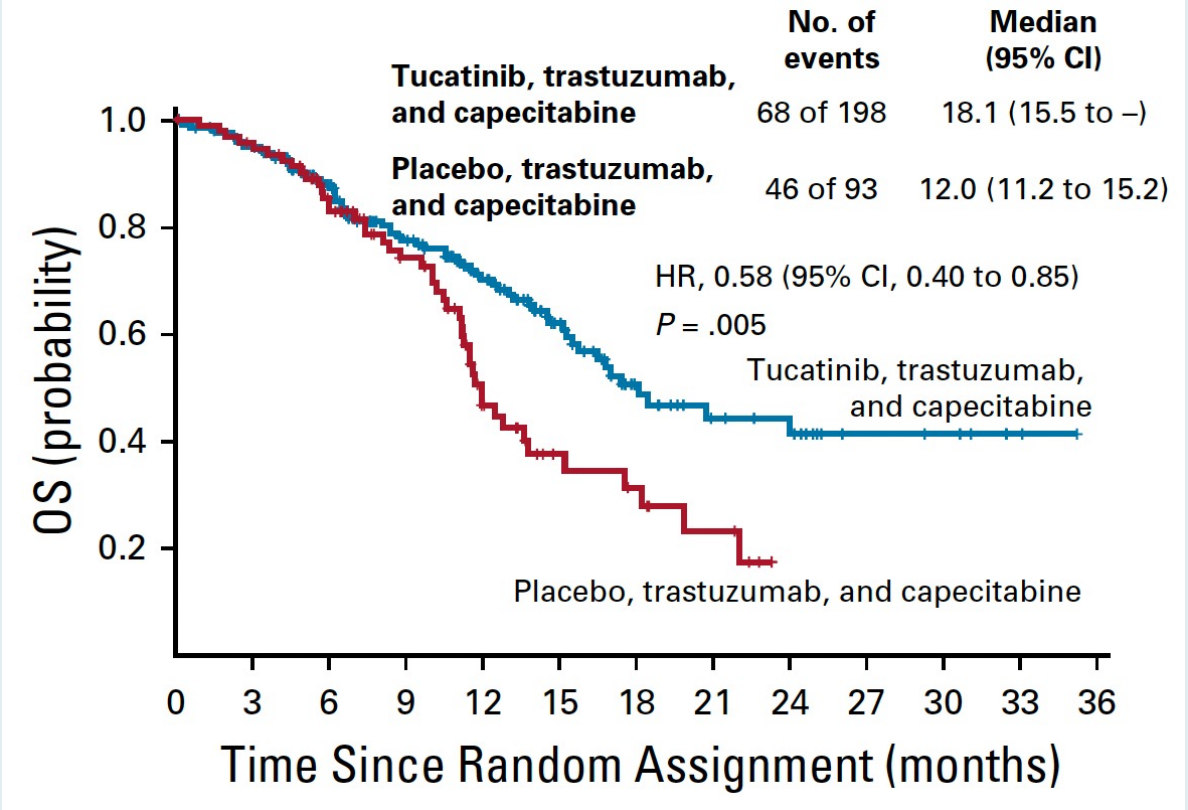
# Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

Nancy U. Lin, MD[1]; Virginia Borges, MMSc, MD[2]; Carey Anders, MD[3]; Rashmi K. Murthy, MD, MBE[4]; Elisavet Paplomata, MD[5]; Erika Hamilton, MD[6]; Sara Hurvitz, MD[7]; Sherene Loi, MD, PhD[8]; Alicia Okines, MBChB, MD[9]; Vandana Abramson, MD[10]; Philippe L. Bedard, MD[11]; Mafalda Oliveira, MD, PhD[12]; Volkmar Mueller, MD[13]; Amelia Zelnak, MD[14]; Michael P. DiGiovanna, MD, PhD[15]; Thomas Bachelot, MD[16]; A. Jo Chien, MD[17]; Ruth O'Regan, MD[5]; Andrew Wardley, MBChB, MSc, MD[18]; Alison Conlin, MD, MPH[19]; David Cameron, MD, MA[20]; Lisa Carey, MD[21]; Giuseppe Curigliano, MD, PhD[22]; Karen Gelmon, MD[23]; Sibylle Loibl, MD, PhD[24]; JoAl Mayor, PharmD[25]; Suzanne McGoldrick, MD, MPH[25]; Xuebei An, PhD[25]; and Eric P. Winer, MD[1]

Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

# HER2CLIMB: CNS Progression-Free Survival and Overall Survival for Patients with Brain Metastases

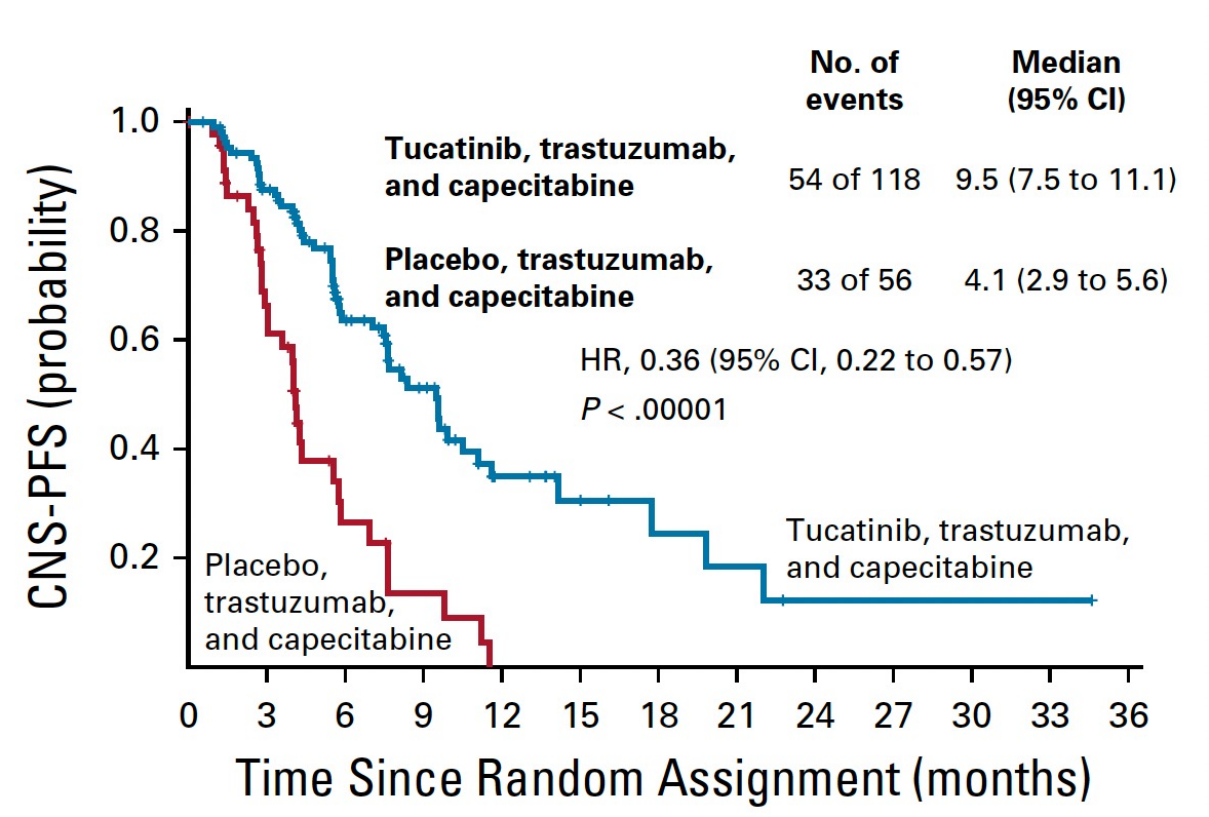


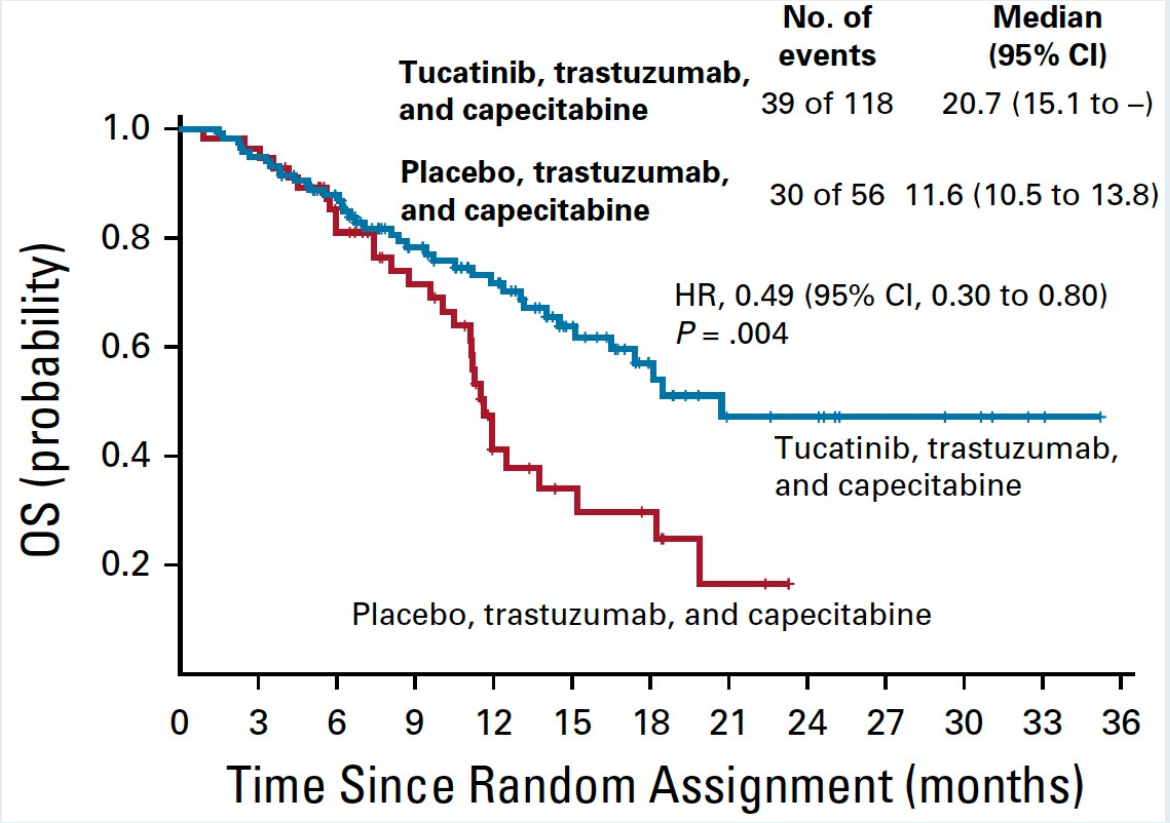




Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: CNS Progression-Free Survival and Overall Survival for Patients with Active Brain Metastases




Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: Intracranial Confirmed Objective Response Rate for Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

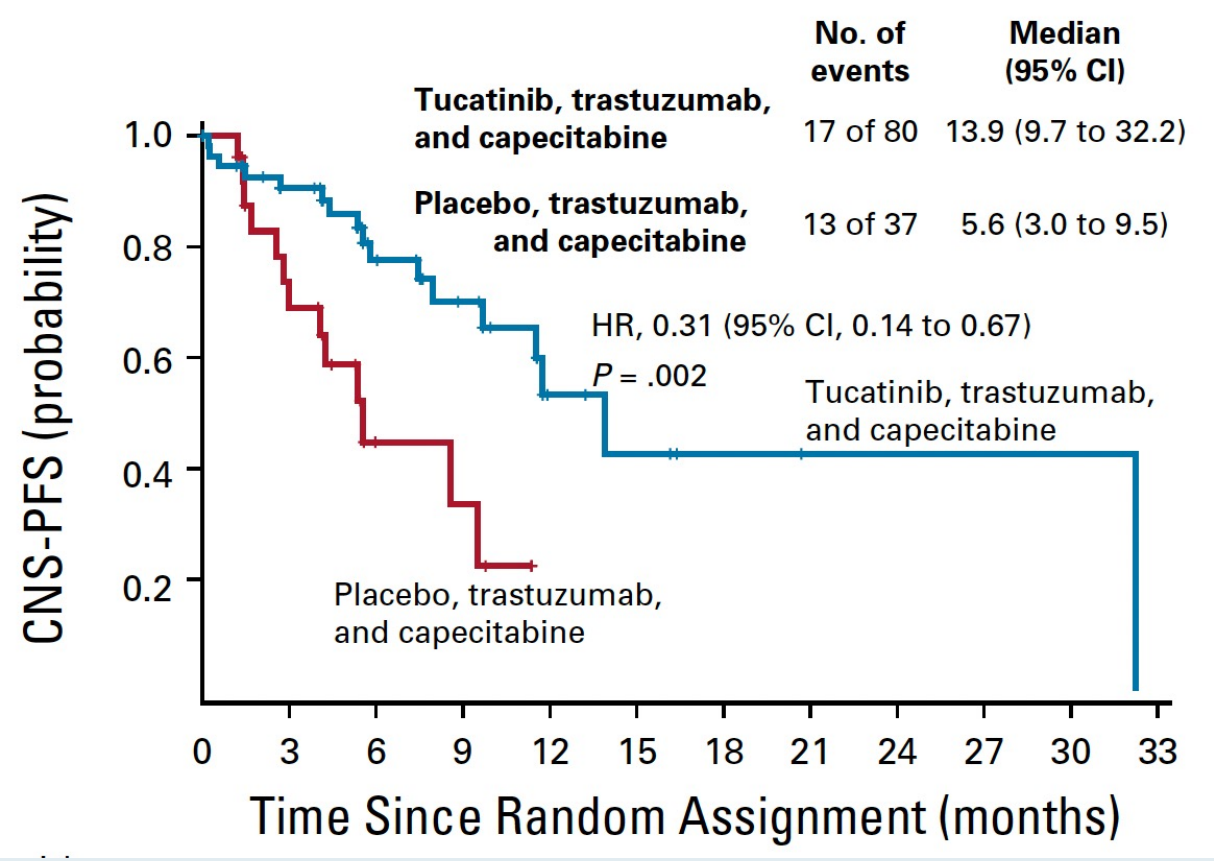
| Response | Tucatinib, trastuzumab and capecitabine (n = 55) | Placebo, trastuzumab and capecitabine (n = 20) |
|---|---|---|
| **Best overall intracranial response** | | |
| Complete response | 5.5% | 5% |
| Partial response | 41.8% | 15.0% |
| Stable disease | 43.6% | 80.0% |
| Progressive disease | 3.6% | 0 |
| Intracranial ORR | 47.3% | 20.0% |
| Intracranial DoR | 6.8 mo | 3.0 mo |

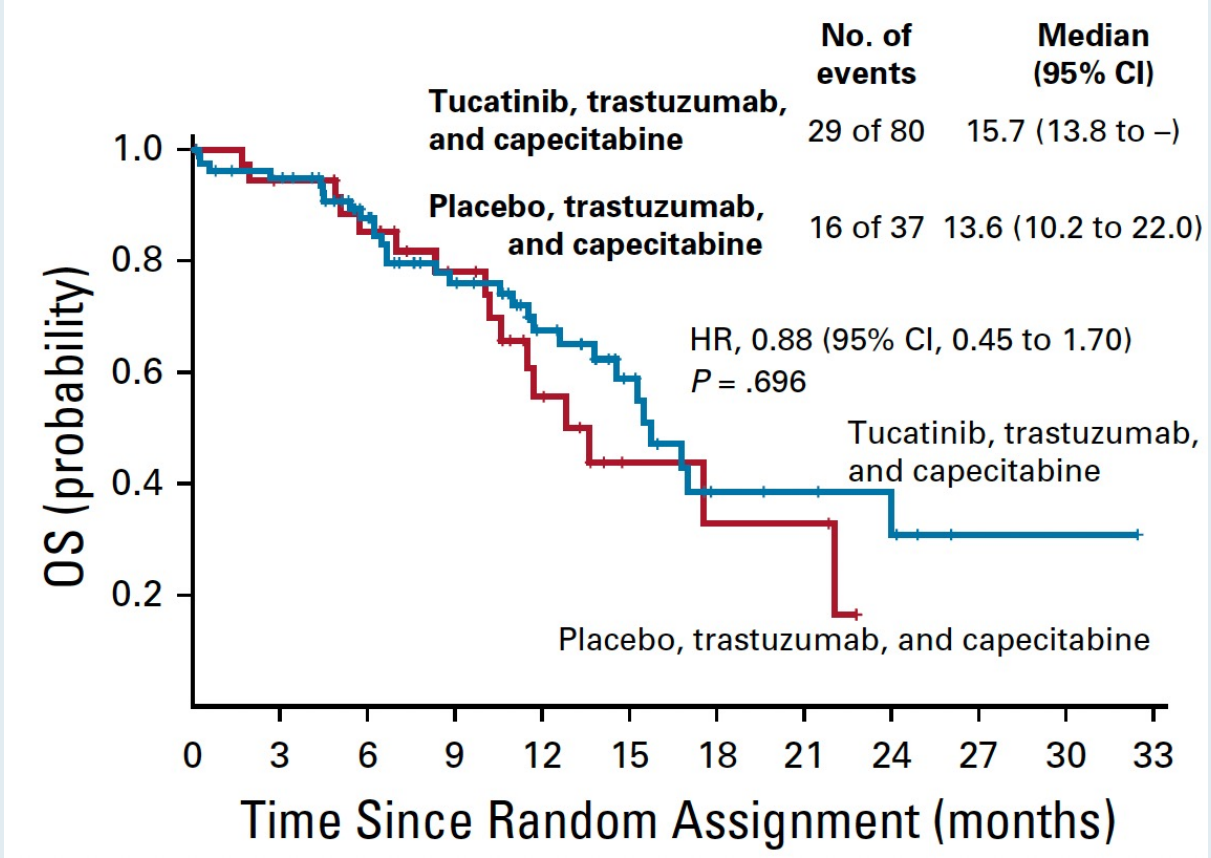
DoR = duration of response

Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: CNS Progression-Free Survival and Overall Survival for Patients with Stable Brain Metastases

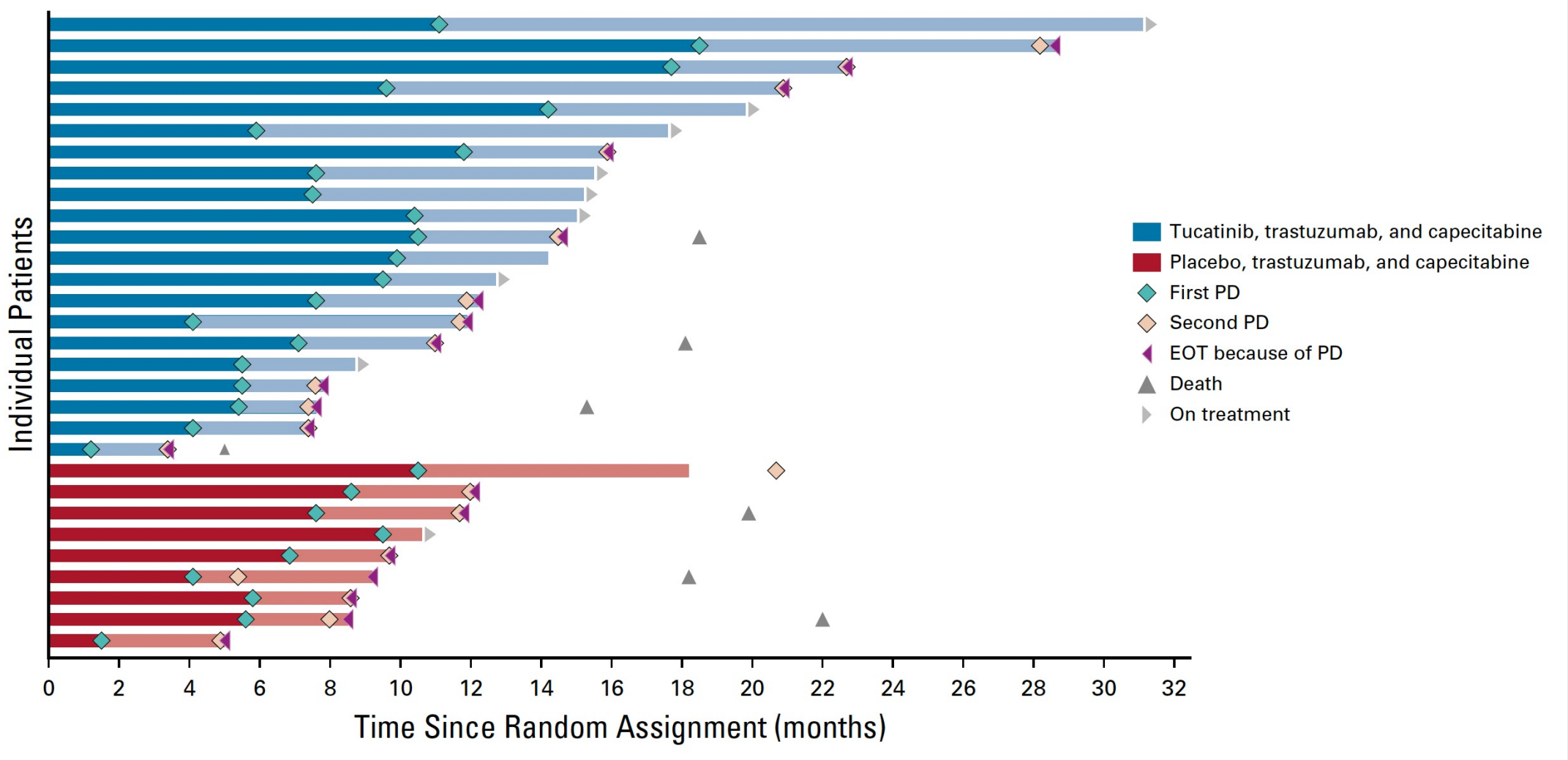



Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

RTP RESEARCH TO PRACTICE

# HER2CLIMB: Duration of Treatment for Patients with Isolated Progression in the Brain Who Continued Assigned Study Treatment




Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

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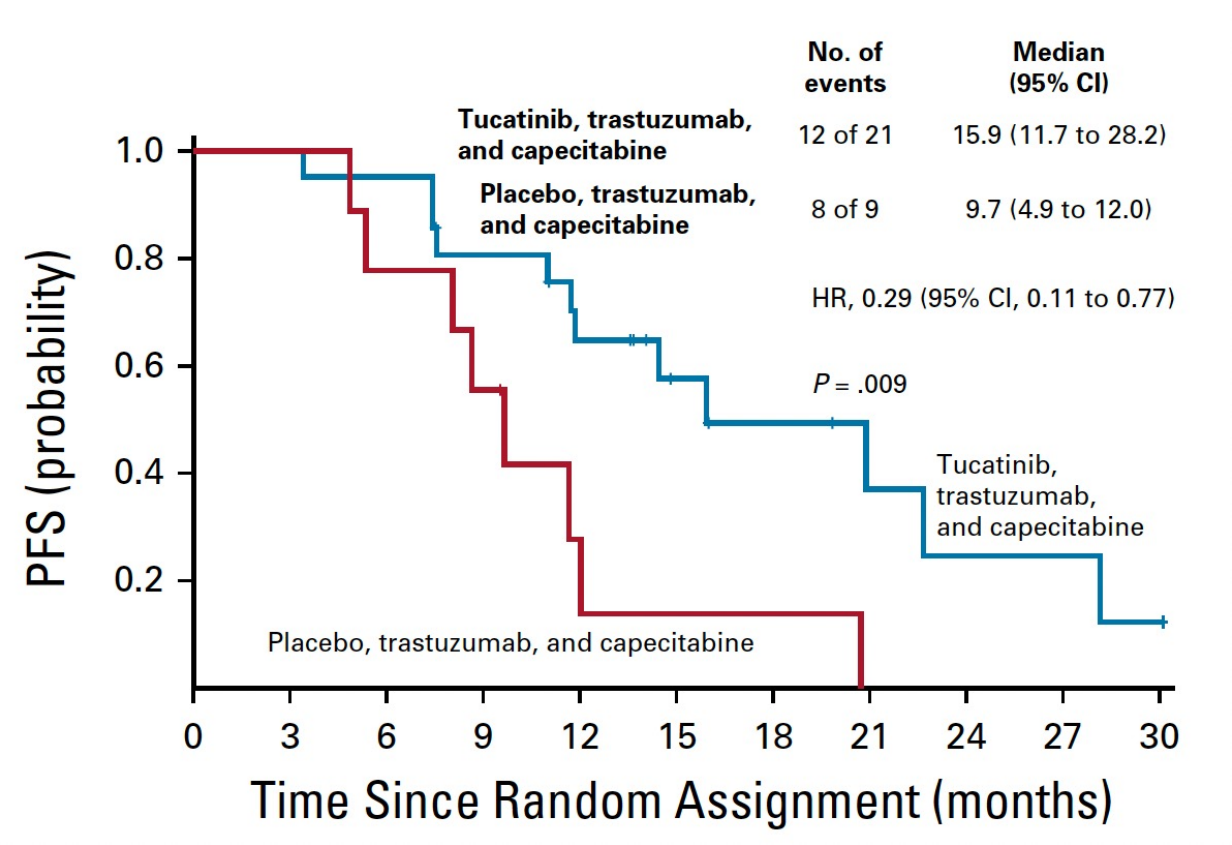
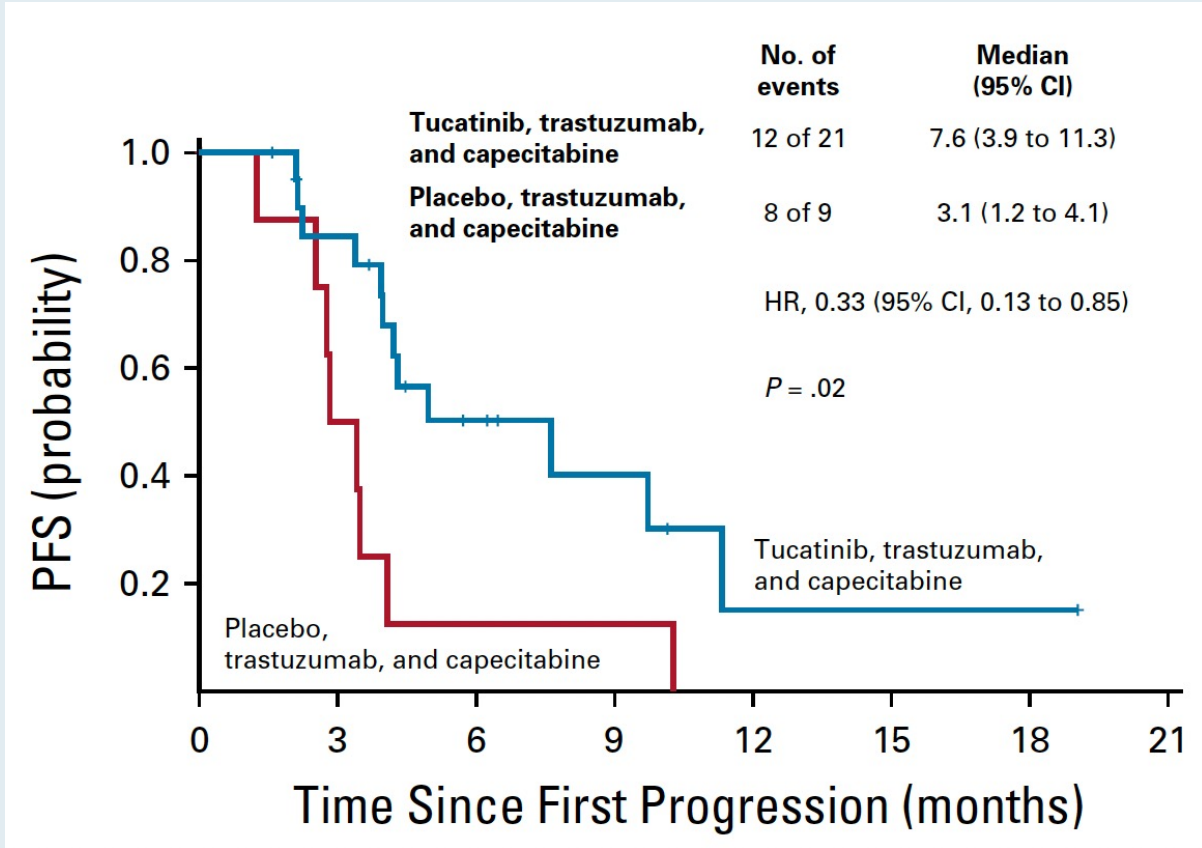
# HER2CLIMB: Time to Second Disease Progression

**Time from random assignment to second disease progression**




**Time from first PD to second disease progression**




Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

# Trastuzumab-Deruxtecan (T-DXd) in HER2-Positive Breast Cancer Patients (Pts) with Active Brain Metastases: Primary Outcome Analysis from the TUXEDO-1 Trial

Bartsch R et al.

ESMO Breast 2022;Abstract 165MO.

# Study Design

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

## TUXEDO-1 (NCT04752059)


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.

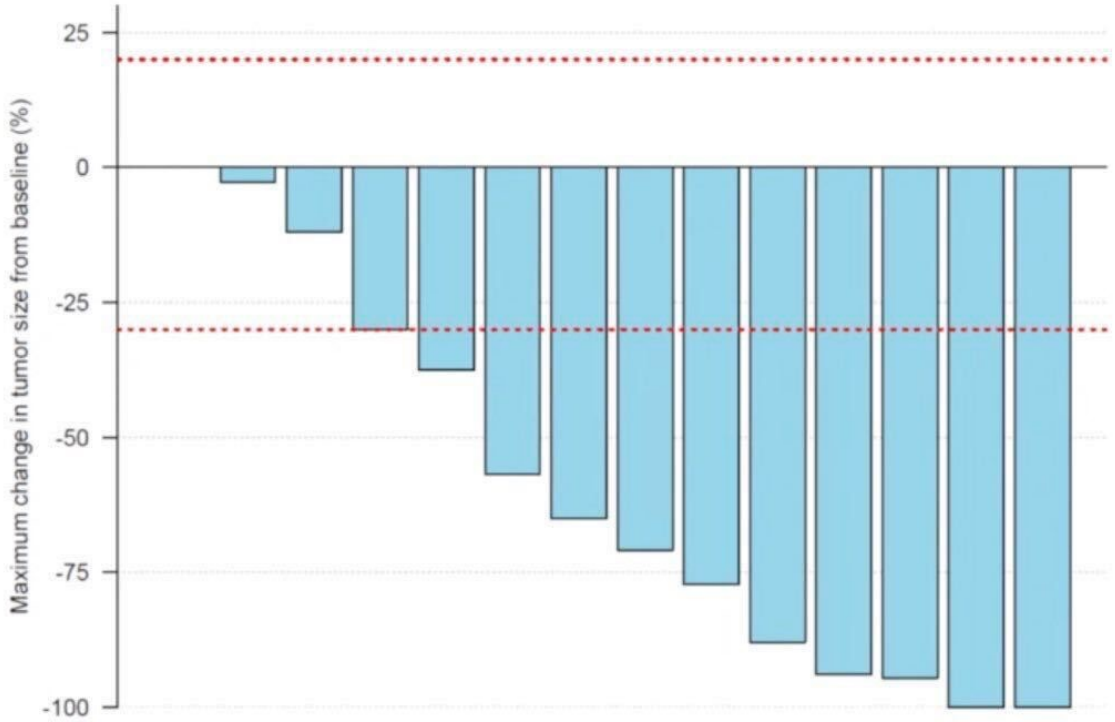
Simon Two Stage Design
- RR (CNS) >60% suggests clinically relevant activity
- RR (CNS) <26% suggests no benefit compared to previous systemic treatment options
- Stage 1: 6 pts. (at least three responses); Stage 2: 9 pts; overall 15 pts. (at least 7 responses)
- Type 1 error rate 5%; power 80%

Bartsch R et al. ESMO Breast 2022;Abstract 165MO.

# Primary Endpoint

**Objective Response Rate (RANO-BM criteria)**

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

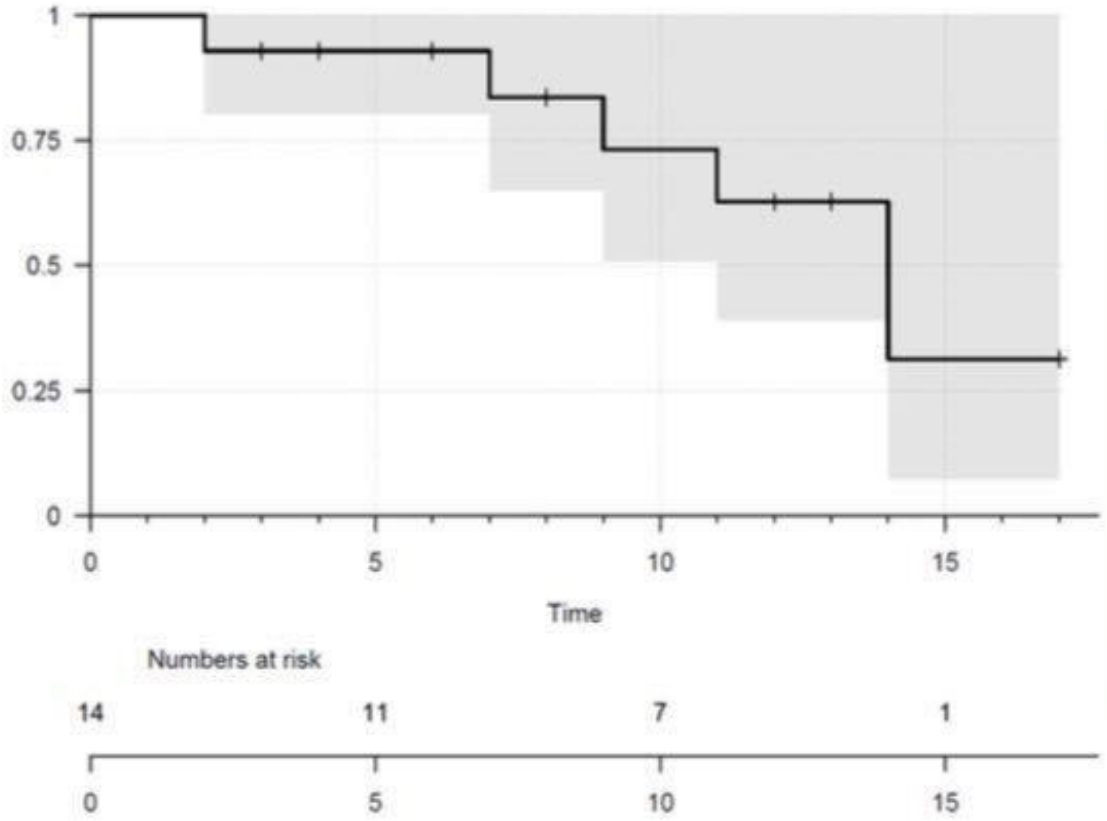



One patient with dural metastases

RR (per-protocol-population; *n*=14): 78.6%

Bartsch R et al. ESMO Breast 2022;Abstract 165MO.

# Secondary Endpoints

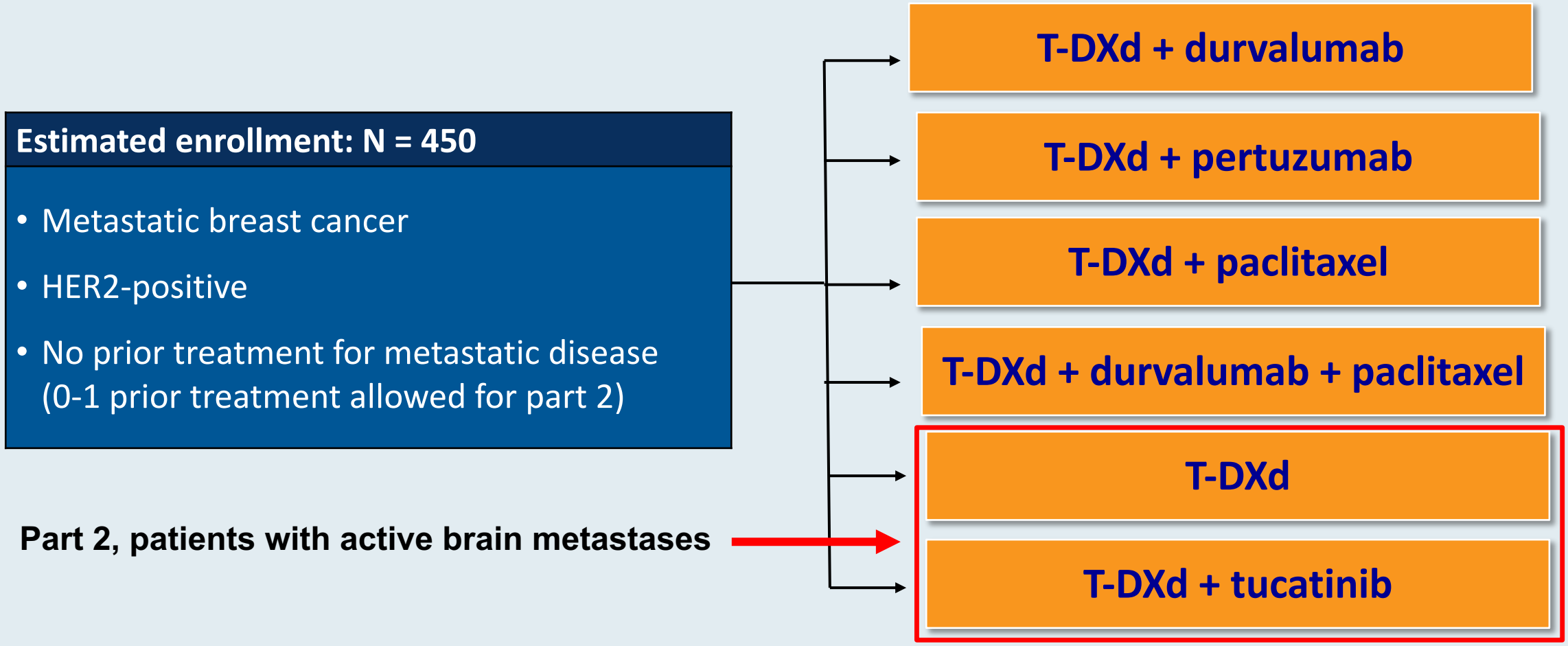



- PFS: 14 months (95% CI 11.0-n.r.)
- Median follow-up 11 months (range 3 – 17 months)

- Clinical Benefit Rate (CR+PR+SD ≥6 months): 13/15 (86.7%) in the ITT population and 13/14 (92.9%) in the PP population
- Median OS not reached
- Extracranial Response Rate:
- Pts. with extracranial metastases at baseline (*n*=13): PR 5/13 (27.8%)
- Pts with measurable extracranial disease at baseline (*n*=8): PR 5/8 (62.5%)

Bartsch R et al. ESMO Breast 2022;Abstract 165MO.

# DESTINY-Breast07 Phase I/II Trial Design

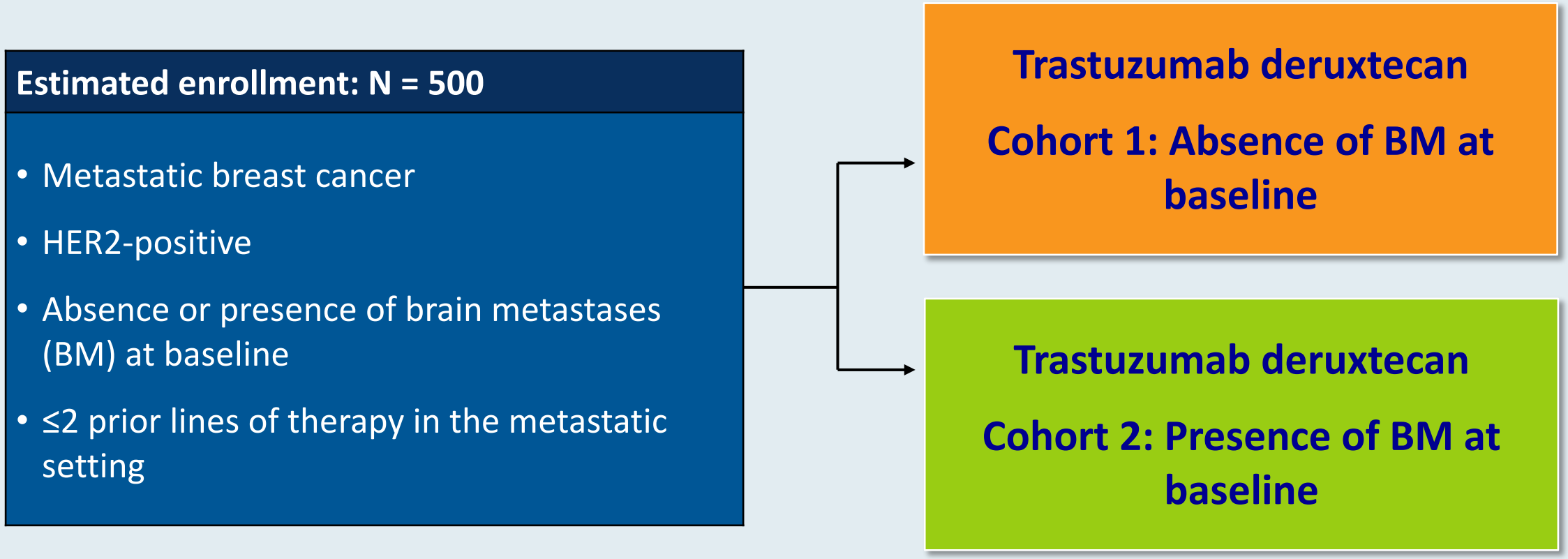



**Primary endpoints:** AEs, serious AEs

**Secondary endpoints:** Objective response rate, PFS, PFS2, DoR, OS

www.clinicaltrials.gov. NCT04538742. Accessed August 2022.

# DESTINY-Breast12 Phase IIIb/IV Trial Design




**Primary endpoints:** Objective response rate for patients without BM at baseline (Cohort 1), PFS for patients with BM at baseline (Cohort 2)

www.clinicaltrials.gov. NCT04739761. Accessed August 2022.

# Exploring Current Considerations and Promising Investigational Approaches for Patients with Myelodysplastic Syndromes

*A CME/MOC-Accredited Virtual Event*

**Thursday, September 8, 2022**

**5:00 PM – 6:00 PM ET**

## Faculty

**Guillermo Garcia-Manero, MD**
**Gail J Roboz, MD**
**David Sallman, MD**

## Moderator

**Neil Love, MD**

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*Thank you for joining us!*

*CME and MOC credit information will be emailed to each participant within 5 business days.*

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