Meet The Professor

Optimizing the Management of HER2-Positive Breast Cancer

Tuesday, October 4, 2022
5:00 PM – 6:00 PM ET

Faculty

Nancy U Lin, 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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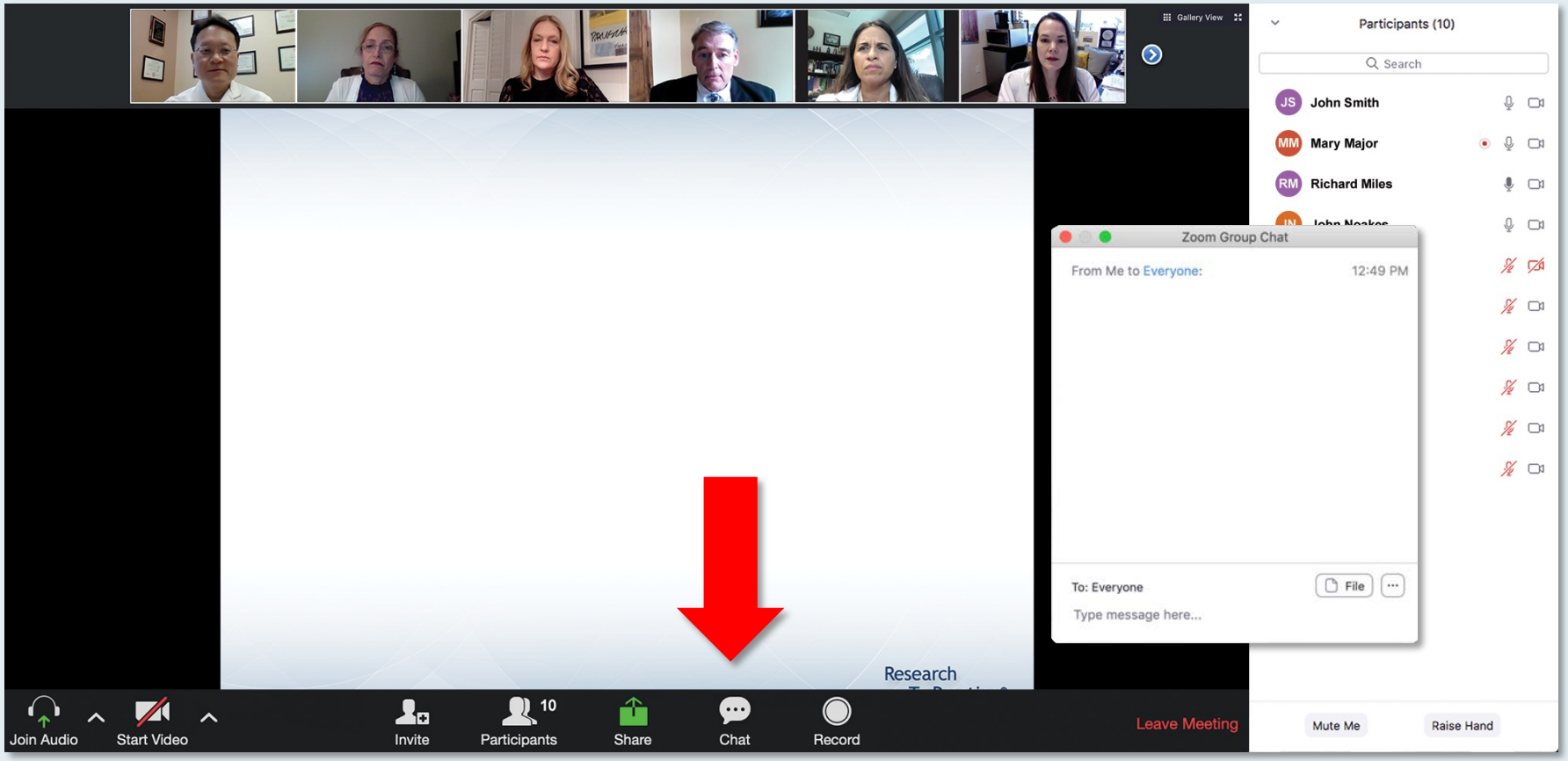
Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Lin — Disclosures

Consulting Agreements	Affinia Therapeutics, Aleta Biotherapeutics, AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Daiichi Sankyo Inc, Denali Therapeutics, Janssen Biotech Inc, Olema Oncology, Prelude Therapeutics, Puma Biotechnology Inc, Seagen Inc, Voyager Therapeutics
Contracted Research	AstraZeneca Pharmaceuticals LP, Genentech, a member of the Roche Group, Merck, Olema Oncology, Pfizer Inc, Seagen Inc, Zion Pharmaceuticals

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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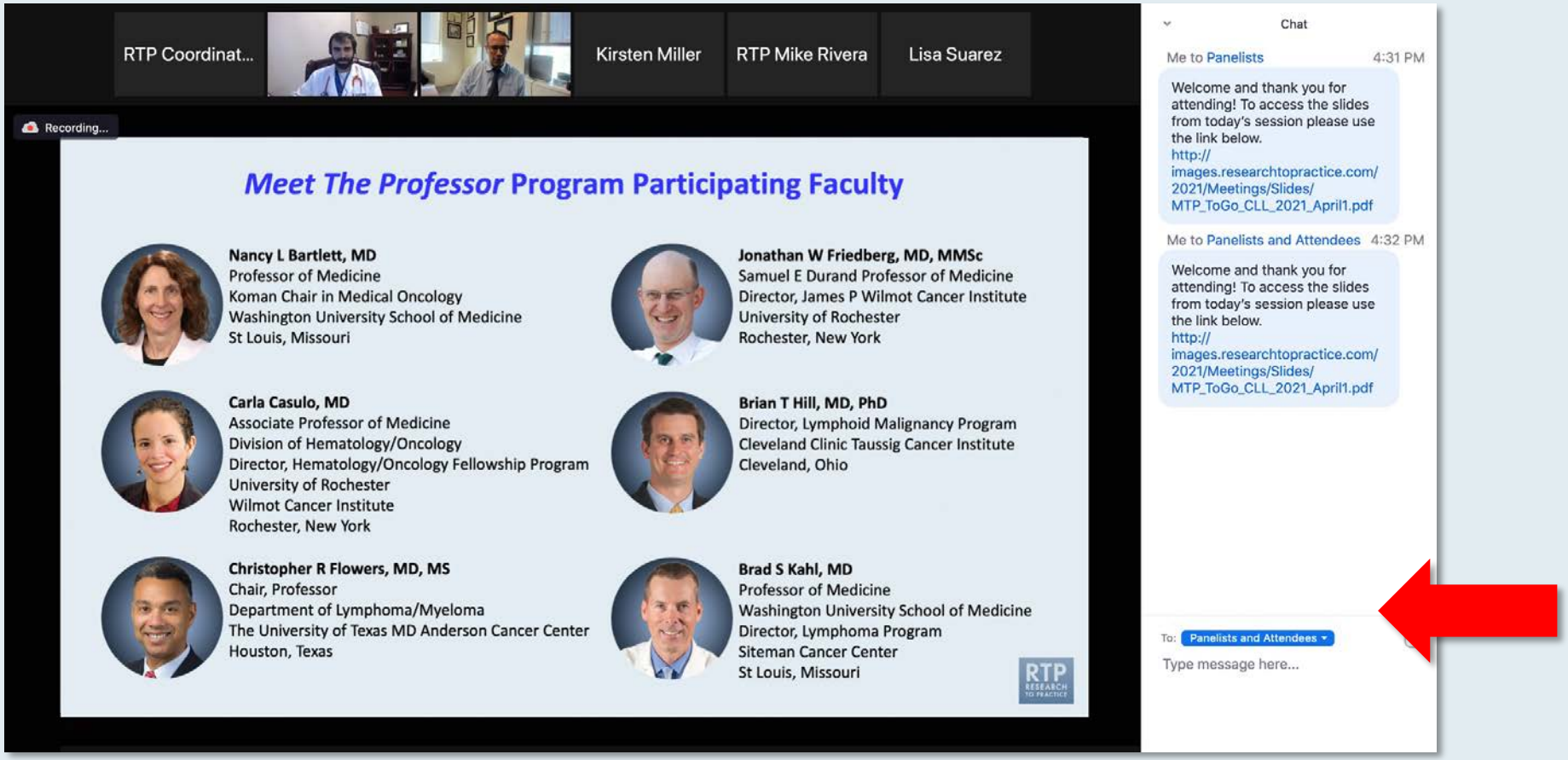
Expand chat submission box



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

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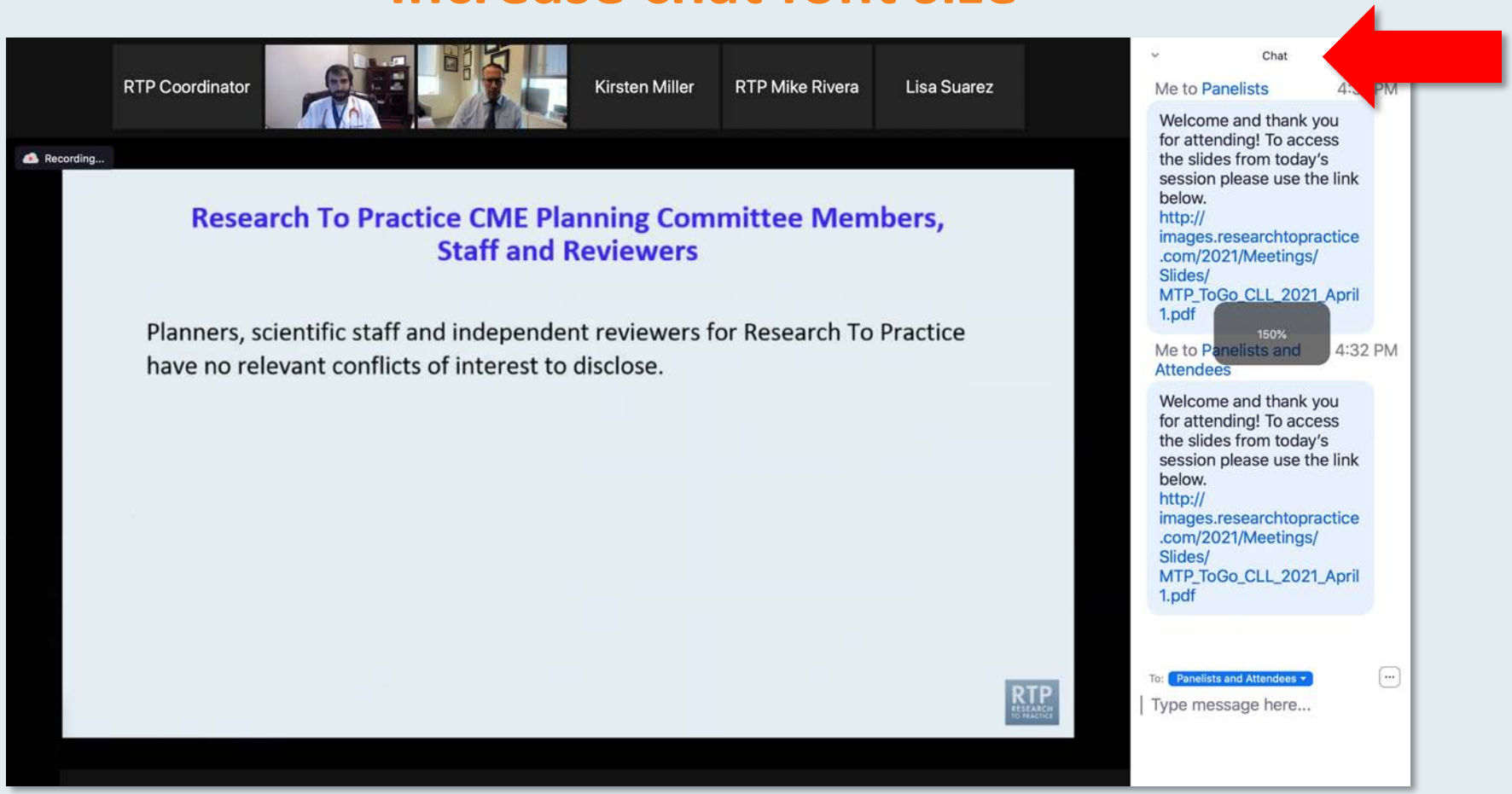
Increase chat font size



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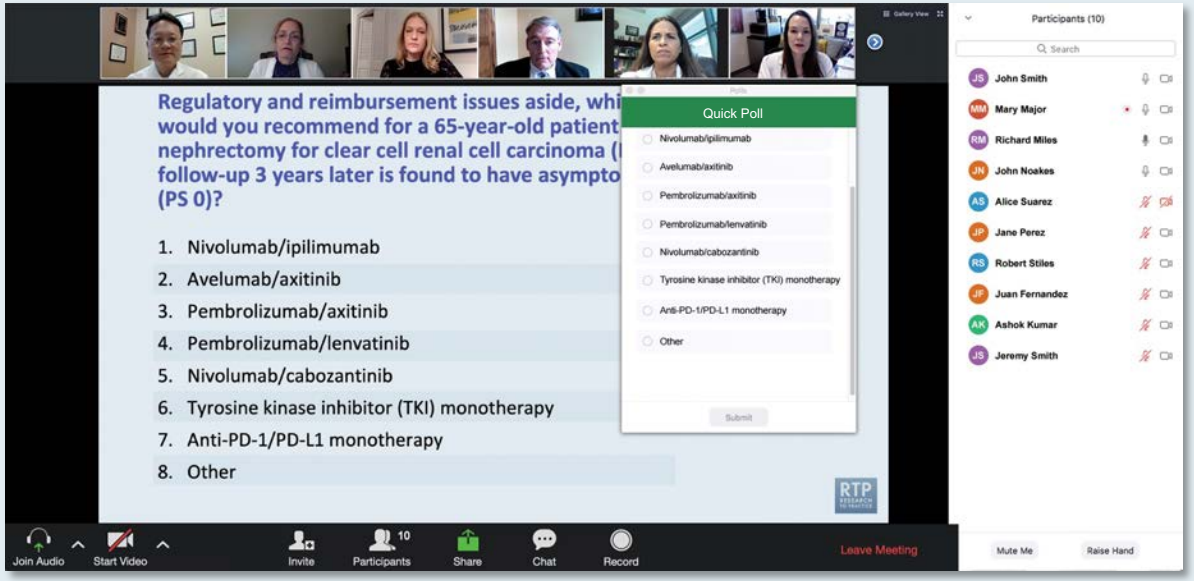
You may do this as many times as you need for readability.

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



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WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR SHANU MODI
MEMORIAL SLOAN KETTERING CANCER CENTER

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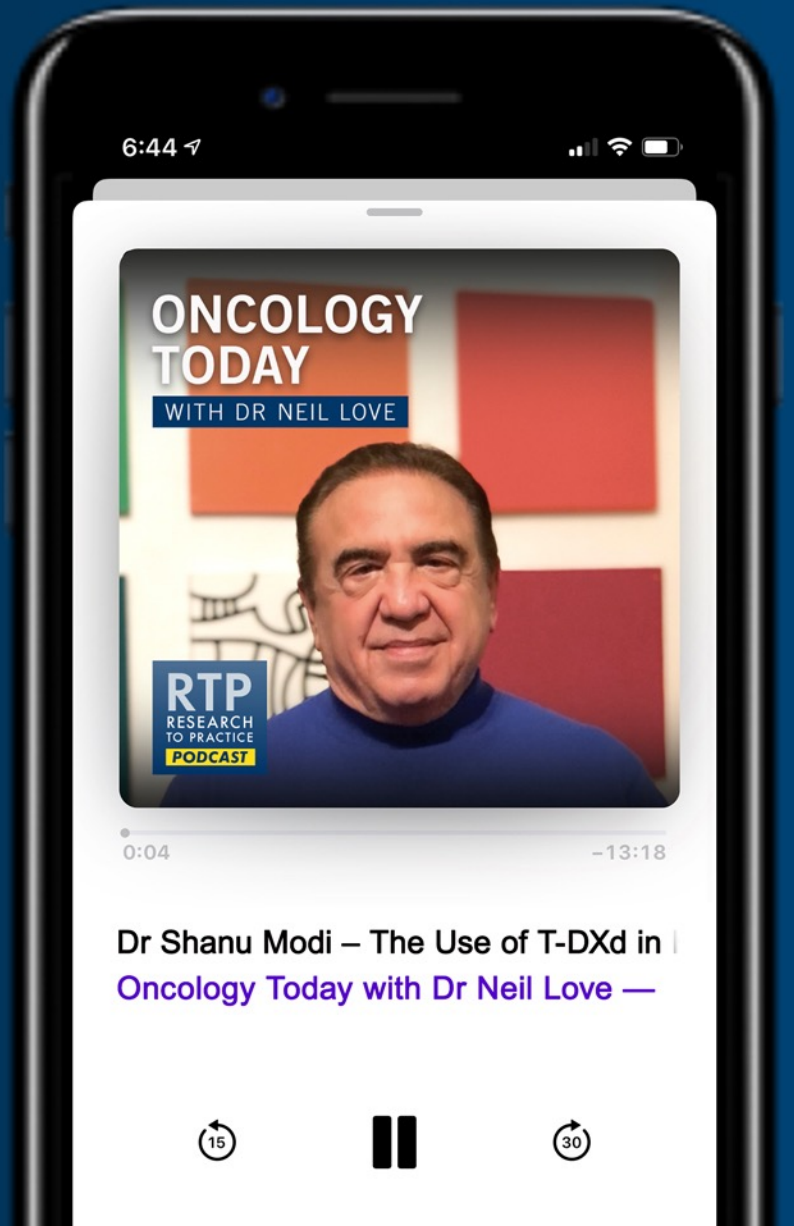

Meet The Professor

Optimizing the Management of Multiple Myeloma

Wednesday, October 5, 2022
5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD

Moderator

Neil Love, MD

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Meet The Professor

Current and Future Management of Non-Small Cell Lung Cancer with an EGFR Mutation

Monday, October 10, 2022
5:00 PM – 6:00 PM ET

Faculty

Pasi A Jänne, MD, PhD

Moderator

Neil Love, MD

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Challenging Cases from Junior Investigators — The Application of Available and Emerging Clinical Research in the Care of Patients with Chronic Lymphocytic Leukemia

Wednesday, October 12, 2022
5:00 PM – 6:30 PM ET

Faculty

Danielle Brander, MD
Matthew S Davids, MD, MMSc
Anthony R Mato, MD, MSCE
William G Wierda, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

Saturday, October 22, 2022

7:30 AM – 5:30 PM ET

JW Marriott Orlando| Orlando, Florida

Faculty

Ghassan Abou-Alfa, MD, MBA
Matthew P Goetz, MD
Ian E Krop, MD, PhD
Ann S LaCasce, MD, MMSc
Corey J Langer, MD
Prof Georgina Long, AO, BSc, PhD, MBBS
Christine M Lovly, MD, PhD
Wells A Messersmith, MD
Alicia K Morgans, MD, MPH
David M O'Malley, MD
Thomas Powles, MBBS, MRCP, MD
Mitchell R Smith, MD, PhD
John Strickler, MD
Shannon N Westin, MD, MPH
Evan Y Yu, MD
Saad Zafar Usmani, MD, MBA

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Melanoma

5:10 PM – 5:30 PM ET

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Prof Georgina Long, AO, BSc, PhD, MBBS

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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

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

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

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

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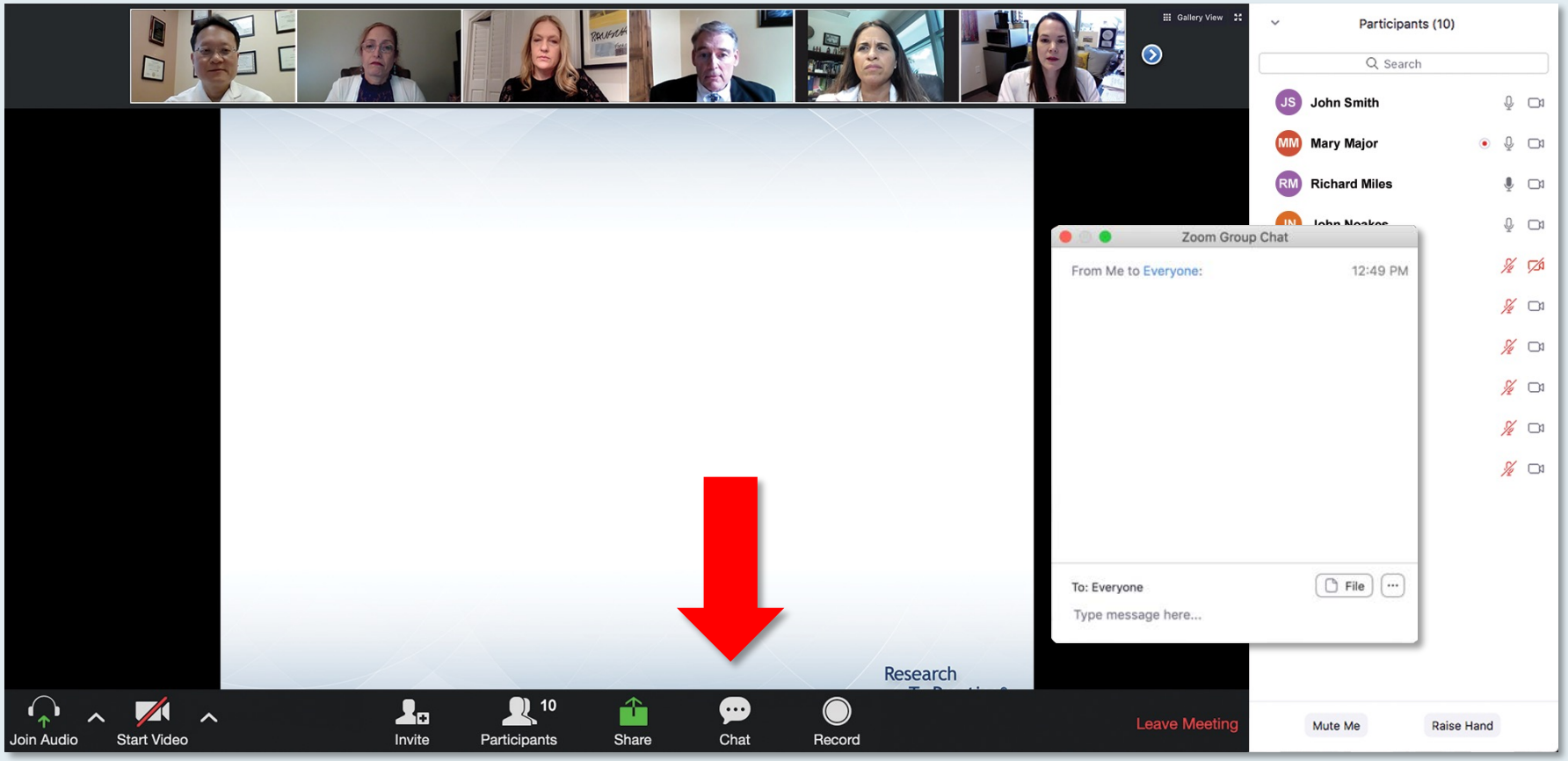

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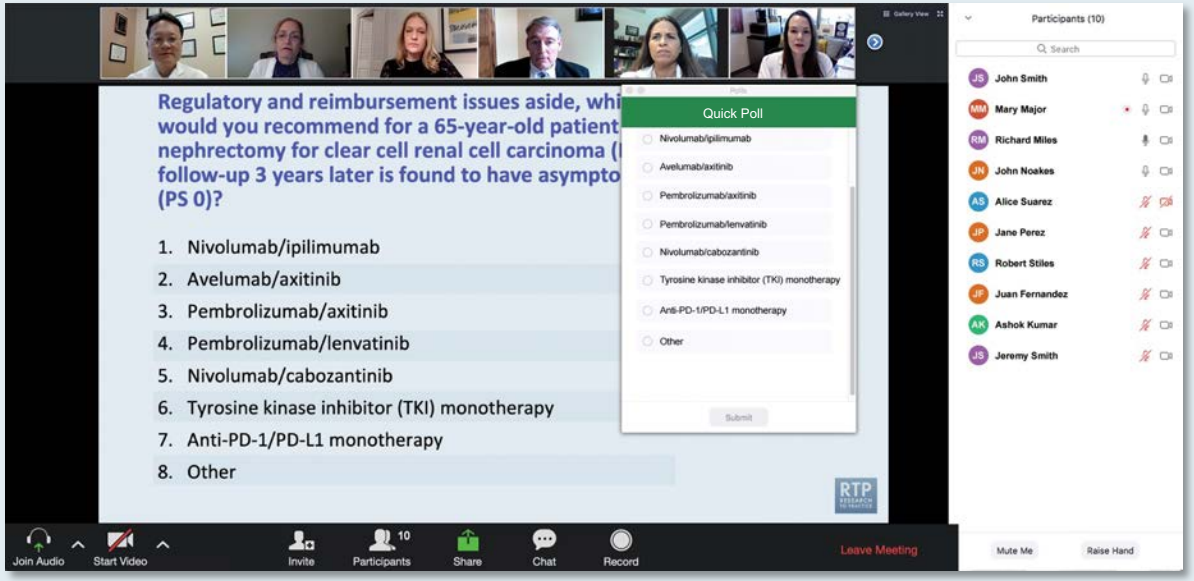

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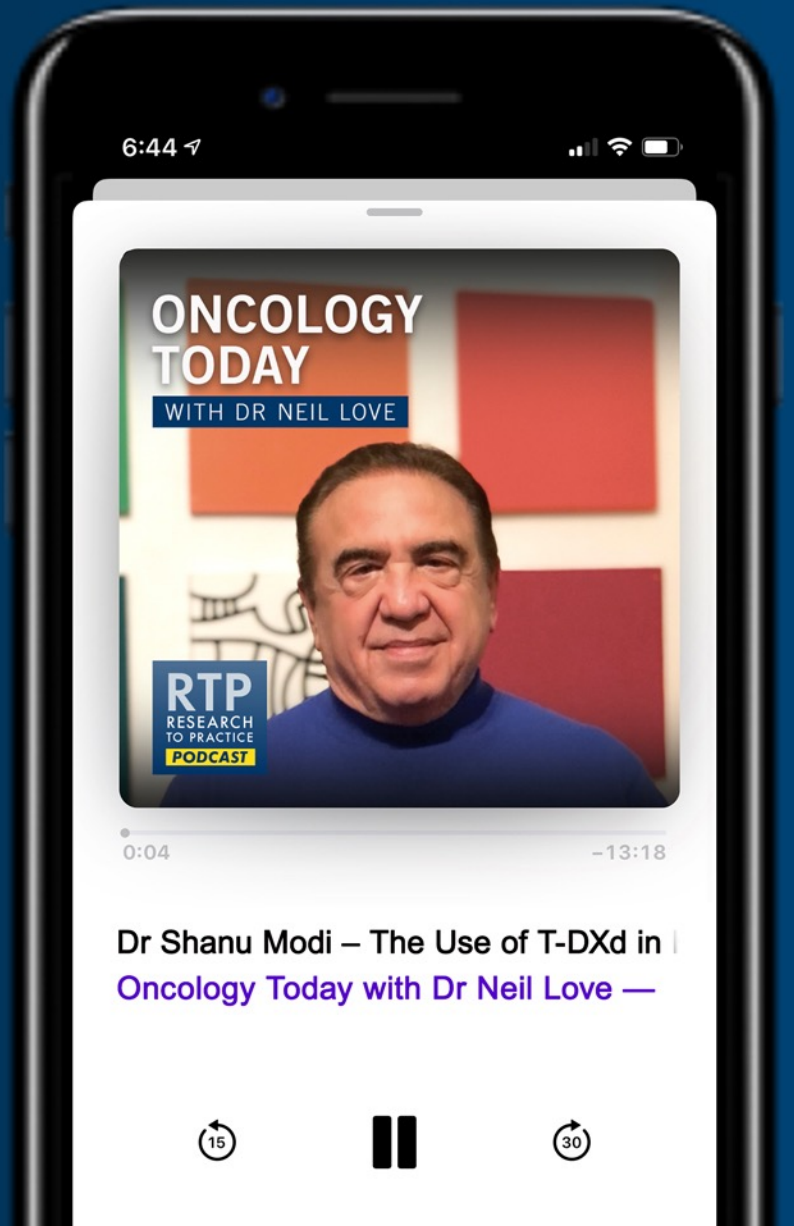

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Susmitha Apuri, MD
Florida Cancer Specialists
Lutz, Florida

Joseph Martins, MD
UT Health Science Center
Tyler, Texas

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

Laurie Matt-Amaral, MD, MPH
Cleveland Clinic Akron General
Akron, Ohio

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

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

Zanetta S Lamar, MD
Florida Cancer Specialists
Naples, Florida

Namrata I Peswani, MD
UT Southwestern Medical Center
Harold C Simmons
Comprehensive Cancer Center
Richardson, Texas

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Meet The Professor with Dr Lin

Introduction: Journal Club with Dr Lin – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Lin – Part 2

MODULE 4: Appendix

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Meet The Professor with Dr Lin

Introduction: Journal Club with Dr Lin – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Dr Lin – Part 2

MODULE 4: Appendix

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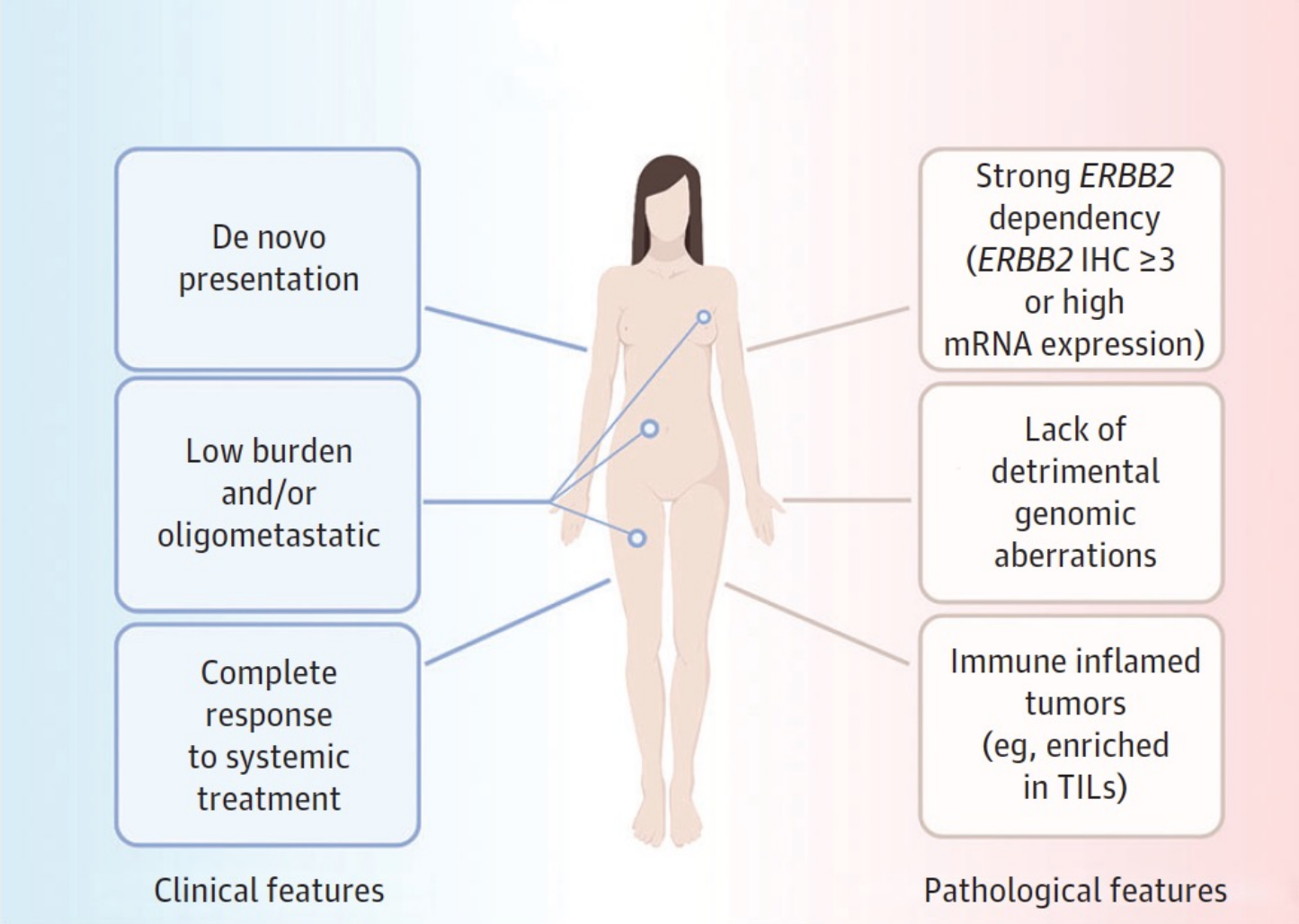
JAMA Oncology | Review

Aiming at a Tailored Cure for *ERBB2*-Positive Metastatic Breast Cancer
A Review

Paolo Tarantino, MD; Giuseppe Curigliano, MD, PhD; Heather A. Parsons, MD, MPH; Nancy U. Lin, MD; Ian Krop, MD, PhD; Elizabeth A. Mittendorf, MD, PhD; Adrienne Waks, MD; Eric P. Winer, MD; Sara M. Tolaney, MD, MPH

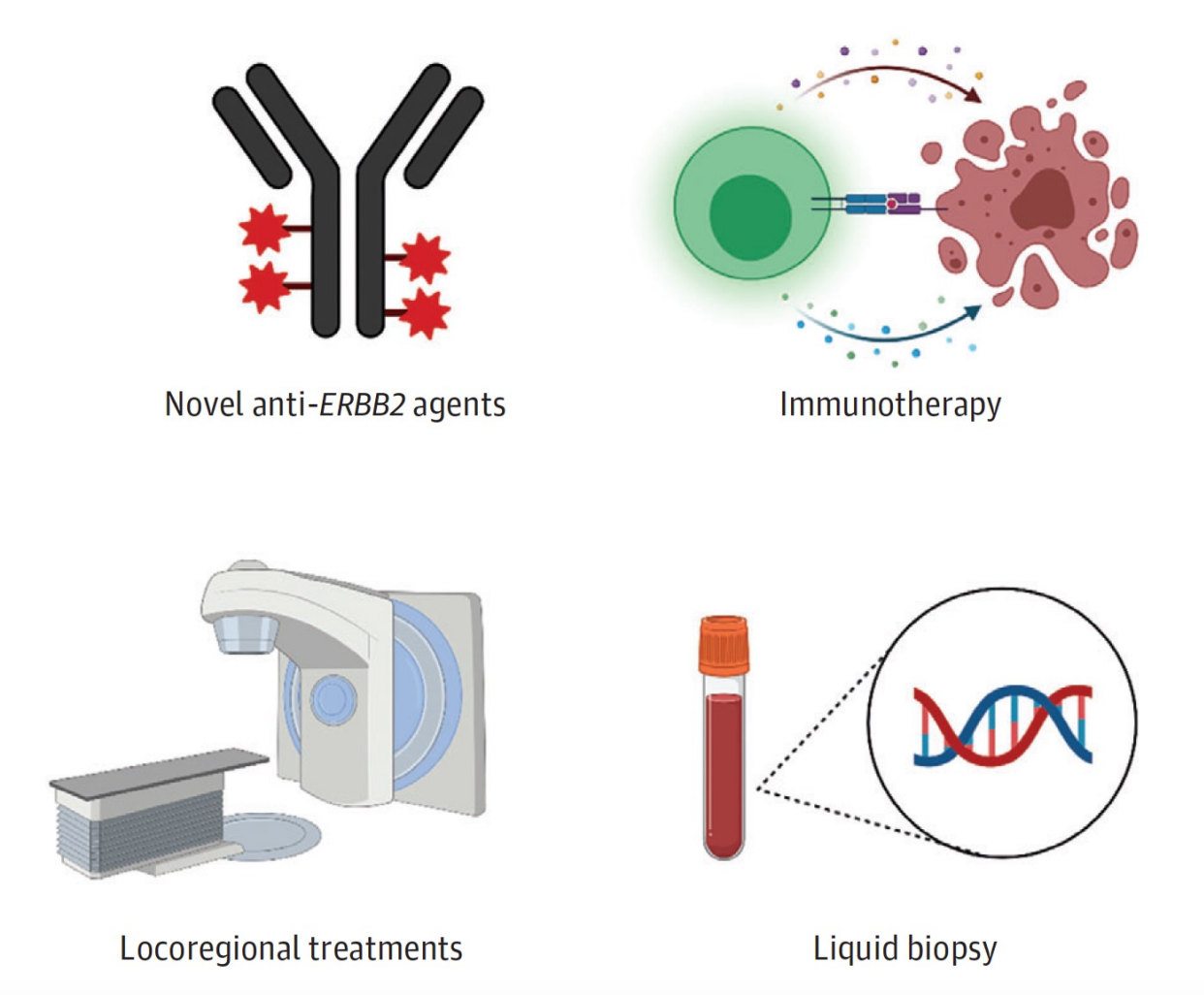
***JAMA Oncol* 2022 April 1;8(4):629-35.**

Features Associated with Favorable Long-Term Outcomes in Patients with ERBB2-Positive mBC Treated with Anti-ERBB2 Agents



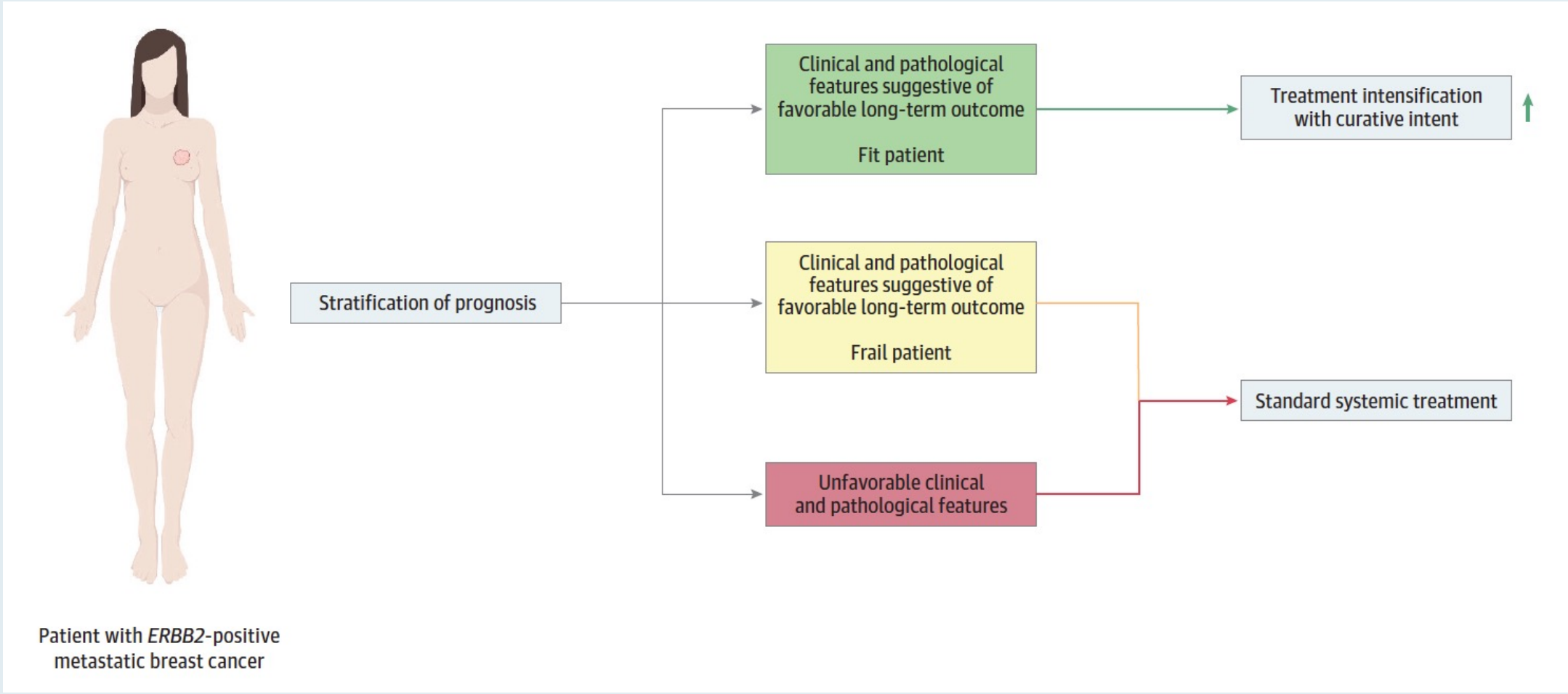
Tarantino P et al. *JAMA Oncol* 2022;8(4):629-35.

Toolkit of Established and Experimental Strategies to Cure ERBB2-Positive mBC



Tarantino P et al. *JAMA Oncol* 2022;8(4):629-35.

Potential Research Strategy to Tailor Treatment Intensity for ERBB2-Positive mBC According to Tumor and Patient Characteristics



Tarantino P et al. *JAMA Oncol* 2022;8(4):629-35.

ASCO 2022 Education Session

BREAST CANCER

Systemic Therapy for HER2-Positive Metastatic Breast Cancer: Moving Into a New Era

Maria Gion, MD[1,2]; Dario Trapani, MD[3,4]; Alfonso Cortés, MD[1,2]; Carmine Valenza, MD[3,4]; Nancy Lin, MD, PhD[5,6]; Javier Cortés, PhD, MD[7,8,9]; and Giuseppe Curigliano, MD, PhD[3,4]

JC JOURNAL CLUB

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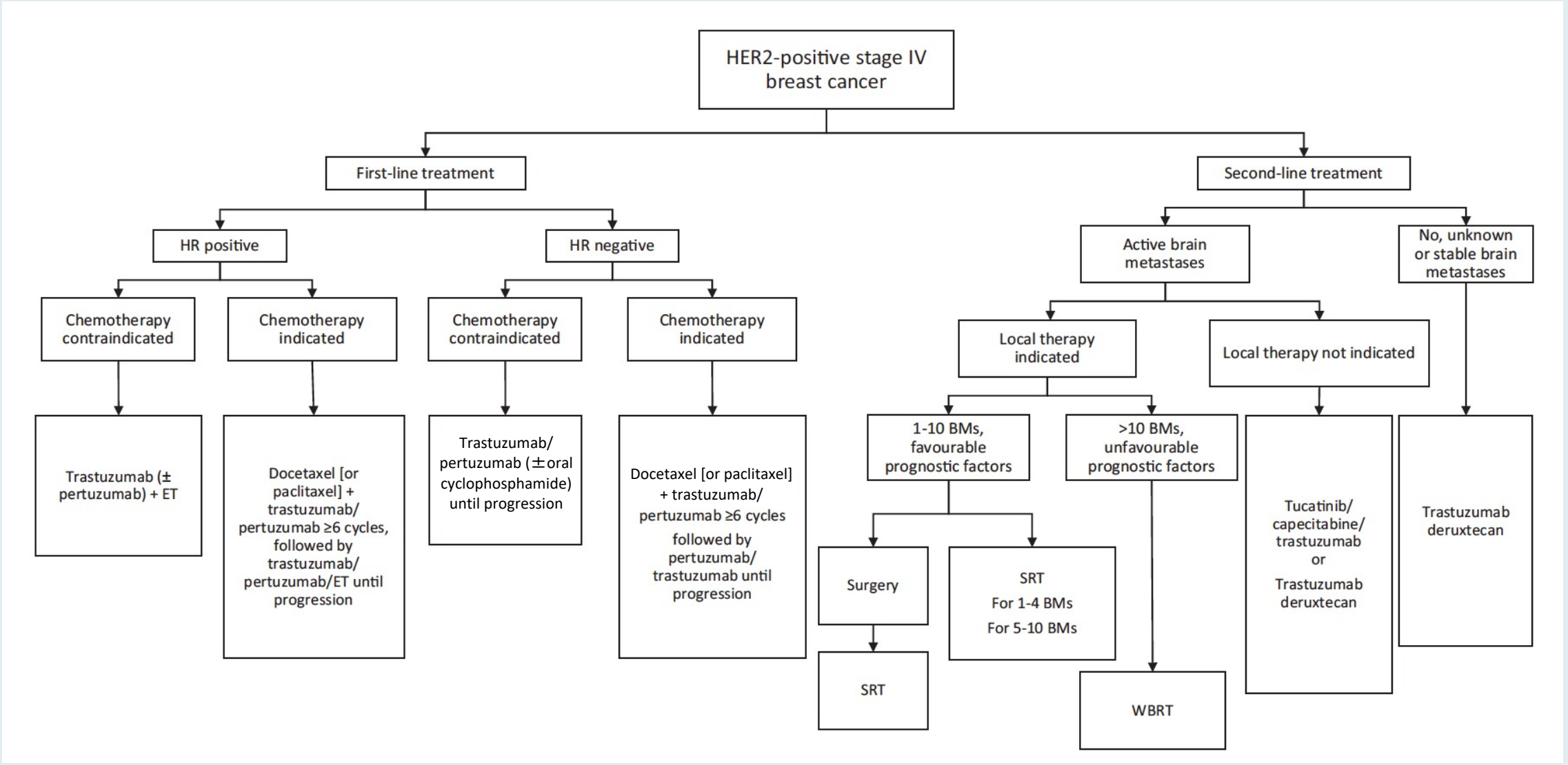
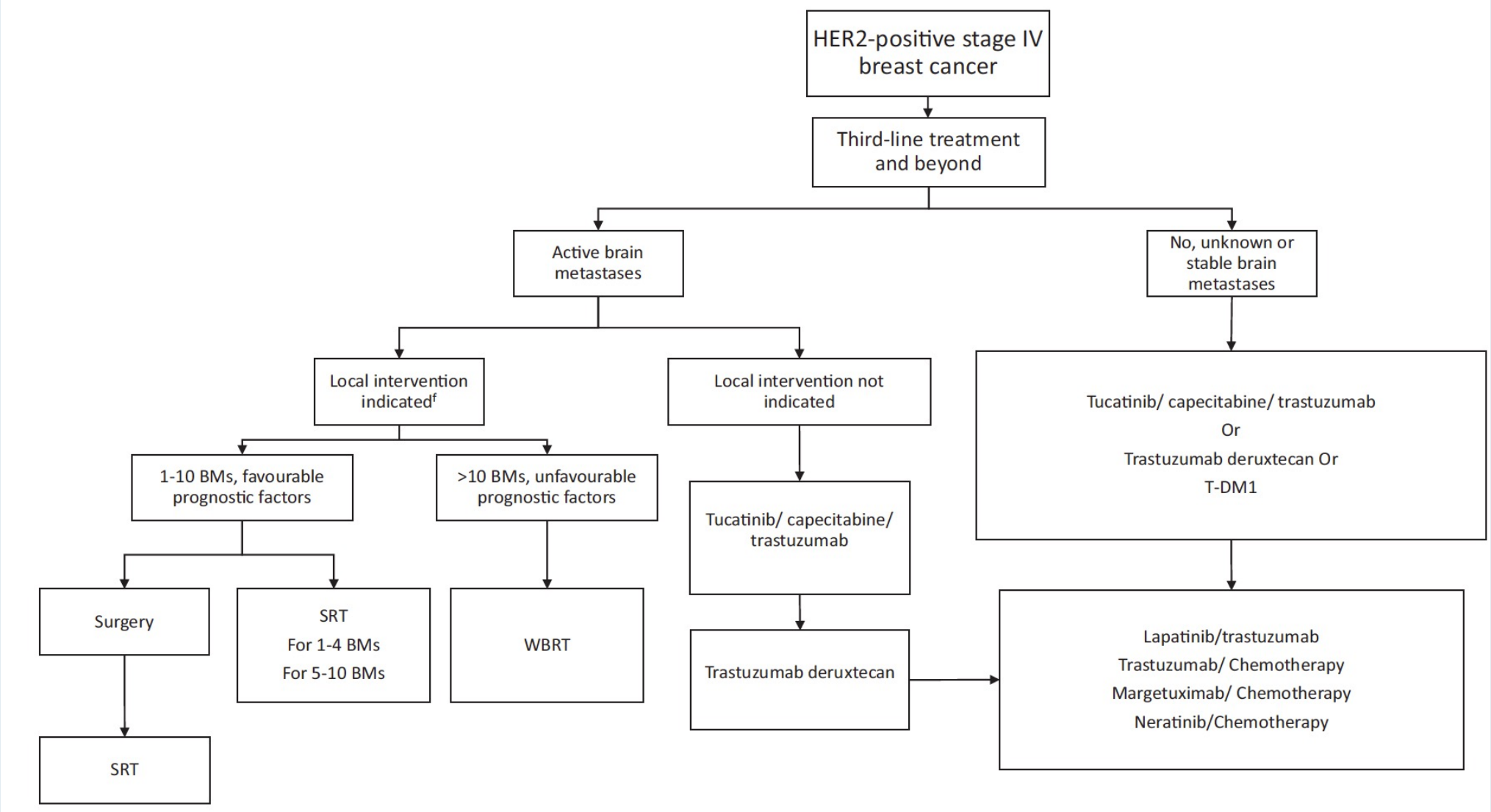
First- and Second-Line Treatments for HER2-Positive mBC



Gion M et al. *Am Soc Clin Oncol Educ Book* 2022.

Third-Line Treatment and Beyond for HER2-Positive mBC



Gion M et al. *Am Soc Clin Oncol Educ Book* 2022.

J Clin Oncol 2022 August 10;40(23):2612-35.

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]

Factors Associated with Short- and Long-Term Survival in Metastatic HER2+ Breast Cancer

Leone JP et al.

ASCO 2022;Abstract 1047.

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 • *If pCR* → postoperative trastuzumab/pertuzumab • *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) • T-DM1	2027
DESTINY-Breast11 (NCT05113251)	III (N = 624)	Neoadjuvant, high risk	• T-DXd • T-DXd → THP • AC → THP	2024

THP = paclitaxel, trastuzumab and pertuzumab

www.clinicaltrials.gov. Accessed August 2022.

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Meet The Professor with Dr Lin

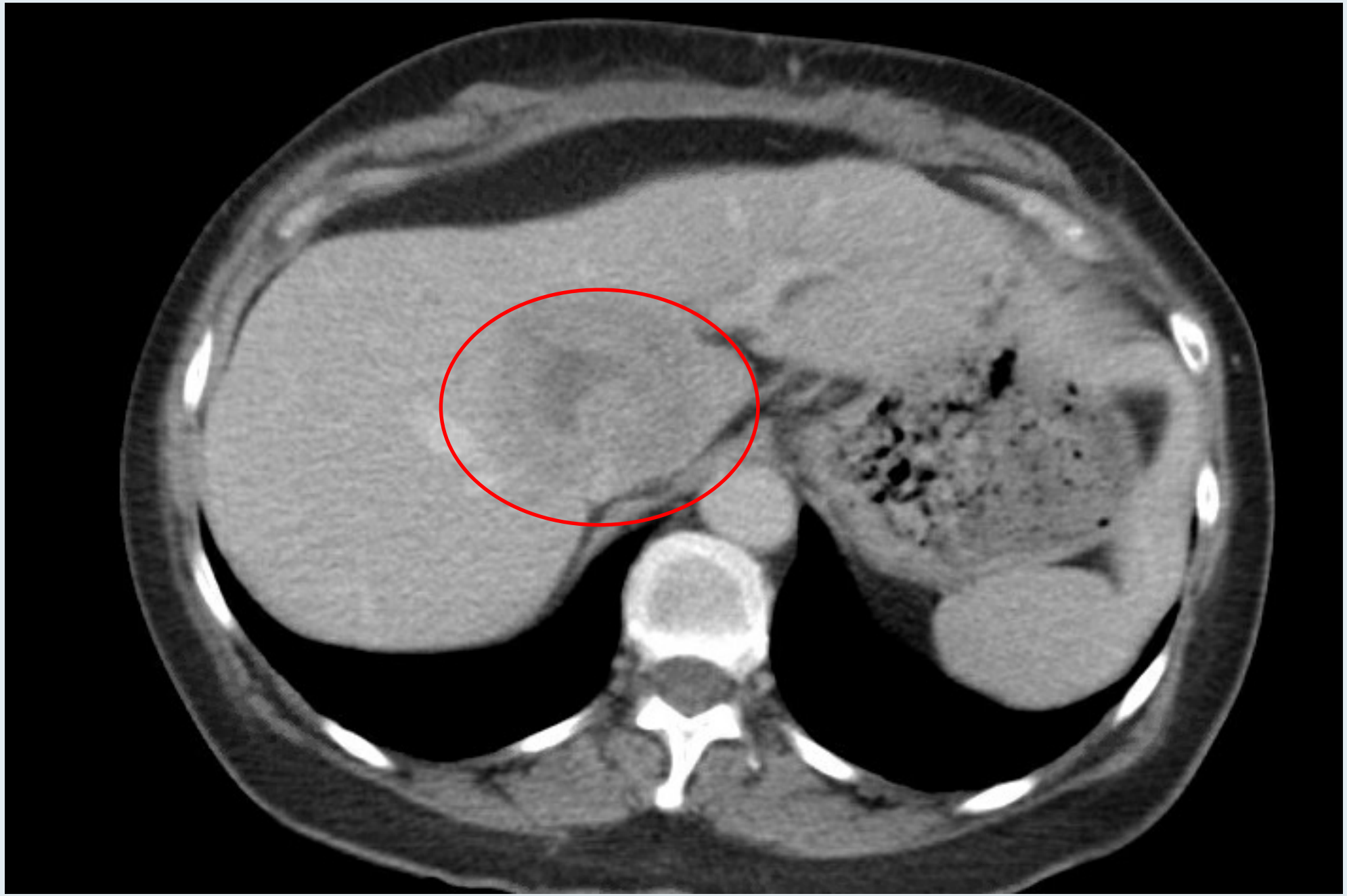
MODULE 1: Case Presentations

- Dr Matt-Amaral: 69-year-old woman with ER-positive, HER2-positive breast cancer s/p adjuvant TCH, with significant neuropathy, who develops liver metastases
- Dr Lamar: 88-year-old woman with weakly ER-positive, PR-negative, HER2-positive, gBRCA2 mutation-positive T2N1M0 breast cancer s/p neoadjuvant paclitaxel/trastuzumab
- Dr Favaro: 52-year-old woman with ER/PR-negative, HER2-positive mBC with progressive brain metastases s/p T-DM1 and WBRT
- Dr Gupta: 47-year-old woman with triple-positive breast cancer, s/p resection of brain metastasis
- Dr Narayanan: 65-year-old woman with ER/PR-positive, HER2-low mBC s/p ET-based therapies, capecitabine
- Dr Peswani: 50-year-old woman with triple-positive, BRCA2-mutant breast cancer, s/p bilateral mastectomies and adjuvant TH, now with locally recurrent ER/PR-positive, HER2-negative disease
- Dr Apuri: 72-year-old woman with triple-positive mBC who has CKD and significant neuropathy s/p 3 prior lines of therapy
- Dr Martins: 60-year-old woman with progressive triple-positive mBC receiving T-DXd

Case Presentation: 69-year-old woman with ER-positive, HER2-positive breast cancer s/p adjuvant TCH, with significant neuropathy, who develops liver metastases

Dr Laurie Matt-Amaral (Akron, Ohio)

RTP
RESEARCH
TO PRACTICE



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Case Presentation: 88-year-old woman with weakly ER-positive, PR-negative, HER2-positive, gBRCA2 mutation-positive T2N1M0 breast cancer s/p neoadjuvant paclitaxel/trastuzumab

Dr Zanetta Lamar (Naples, Florida)

RTP RESEARCH TO PRACTICE

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.

Case Presentation: 52-year-old woman with ER/PR-negative, HER2-positive mBC with progressive brain metastases s/p T-DM1 and WBRT

Dr Justin Favaro (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 47-year-old woman with triple-positive breast cancer, s/p resection of brain metastasis

Dr Shaachi Gupta (Lake Worth, Florida)

RTP
RESEARCH
TO PRACTICE

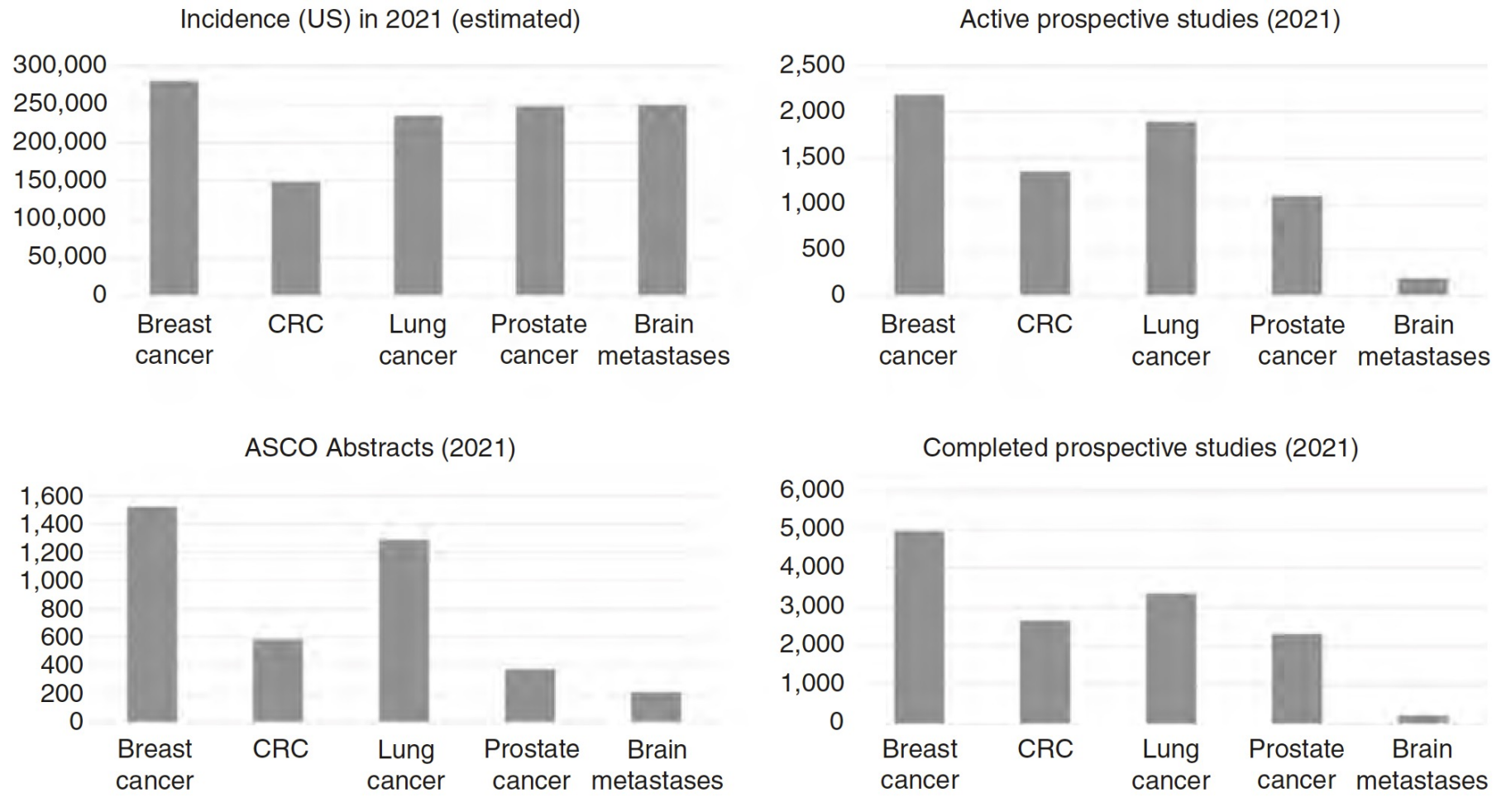
Neuro Oncol 2022 June 28;[Online ahead of print].

Neuro-Oncology

Brain metastases: A Society for Neuro-Oncology (SNO) consensus review on current management and future directions

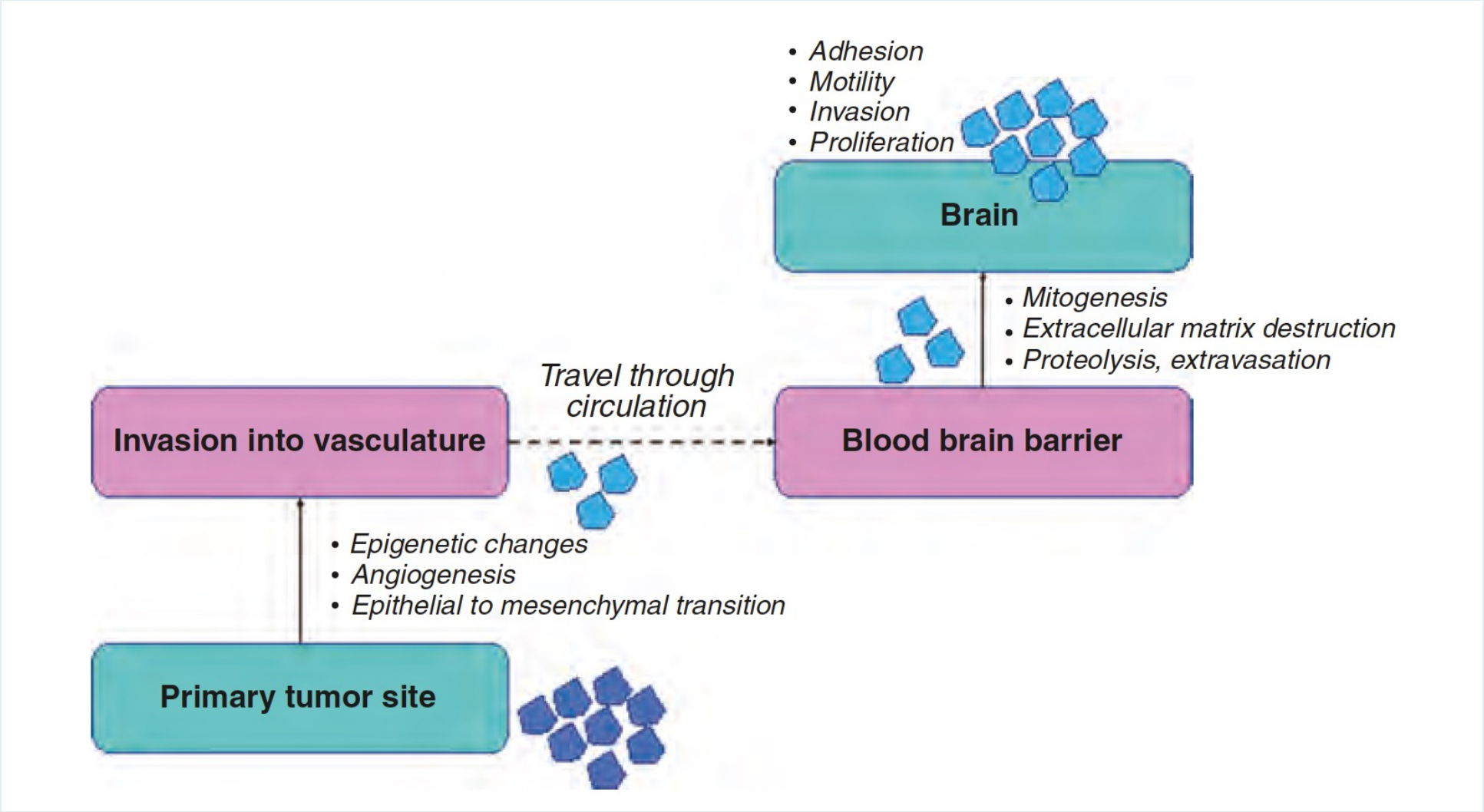
Ayal A. Aizer[†], Nayan Lamba[†], Manmeet S. Ahluwalia, Kenneth Aldape, Adrienne Boire, Priscilla K. Brastianos, Paul D. Brown, D. Ross Camidge, Veronica L. Chiang, Michael A. Davies, Leland S. Hu, Raymond Y. Huang, Timothy Kaufmann, Priya Kumthekar, Keng Lam, Eudocia Q. Lee, Nancy U. Lin, Minesh Mehta, Michael Parsons, David A. Reardon, Jason Sheehan, Riccardo Soffietti, Hussein Tawbi, Michael Weller, and Patrick Y. Wen

Incidence of Brain Metastases versus Other Oncologic Entities of Similar Incidence and Research Output Measured by ASCO Abstracts and Active or Completed Prospective Trials



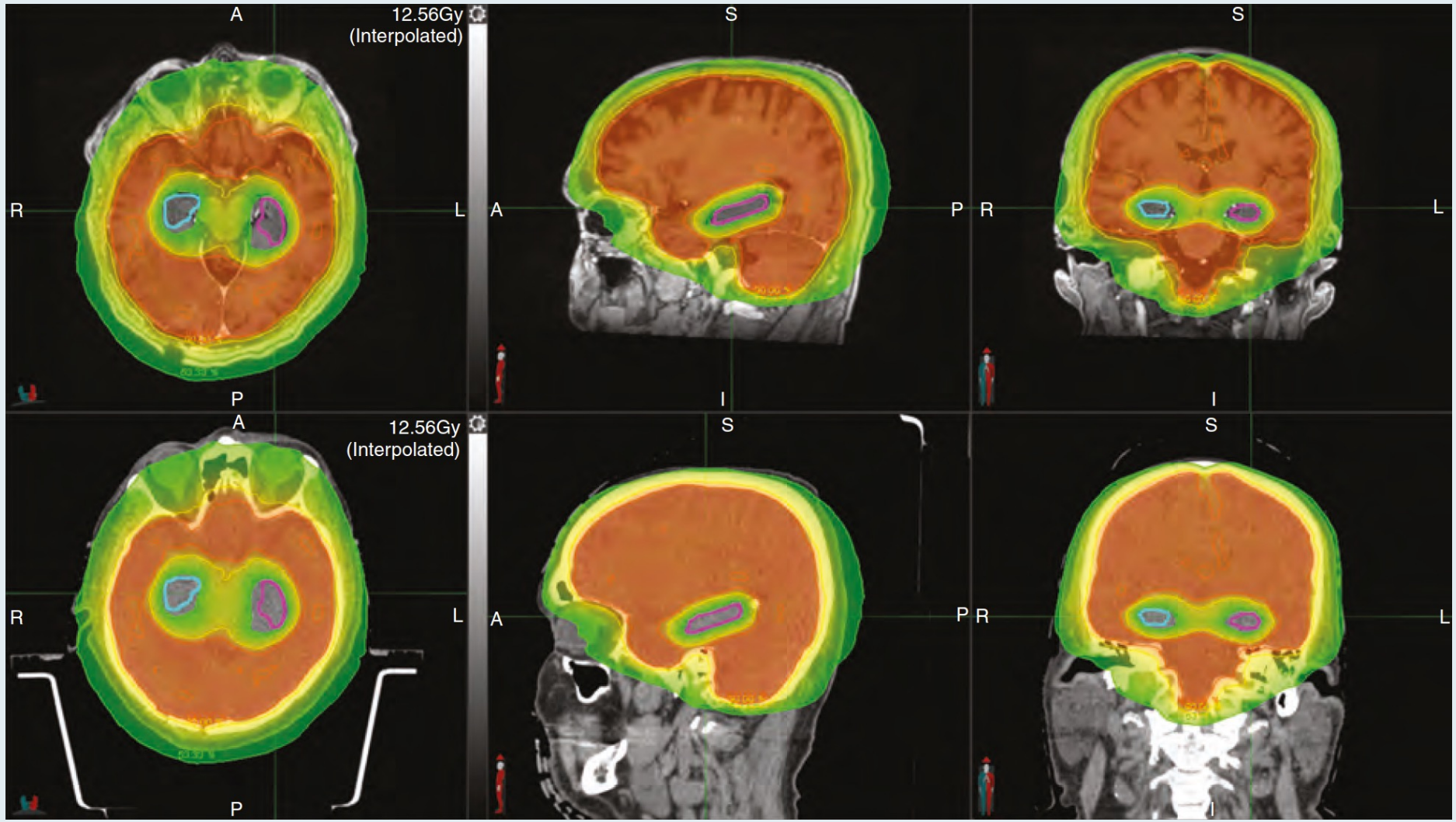
Aizer AA et al. *Neuro Oncol* 2022 Jun 28;[Online ahead of print].

Pathogenesis of Brain Metastases



Aizer AA et al. *Neuro Oncol* 2022 Jun 28;[Online ahead of print].

Hippocampal-Sparing Whole-Brain Radiation in a Patient with Brain Metastases



Aizer AA et al. *Neuro Oncol* 2022 Jun 28;[Online ahead of print].

Incidence Proportion of Brain Metastases in the United States at Diagnosis of Breast Cancer

Sub-Site	Incidence Proportion Among Entire Cohort[a]	Incidence Proportion Among Subset with Metastatic Disease[b]
HR+/HER2-	0.22	5.46
HR+/HER2+	0.61	7.98
HR-/HER2+	1.09	11.45
Triple negative	0.68	11.37

Aizer AA et al. *Neuro Oncol* 2022 Jun 28;[Online ahead of print].

Prognosis of Brain Metastases Associated with Breast Cancer in the United States as Derived from SEER, SEER-Medicare and GPA-based Data

Sub-Site	Median Survival (Months) Based on SEER data	Median Survival (Months) in Older Patients Based on SEER-Medicare Data[c]	Median Survival (Months) Based on GPA Data
		2.1-4.5	16
HR+/HER2–	14.0	2.0–4.9	
HR+/HER2+	21.0	2.5–6.4	
HR–/HER2+	10.0		
Triple negative	6.0	2.3–3.4	

GPA = graded prognostic assessment

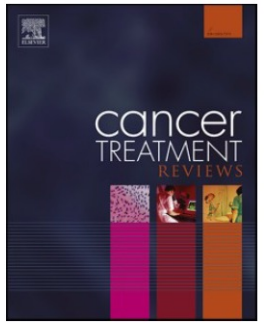
Aizer AA et al. *Neuro Oncol* 2022 Jun 28;[Online ahead of print].

Cancer Treatment Reviews 103 (2022) 102324

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

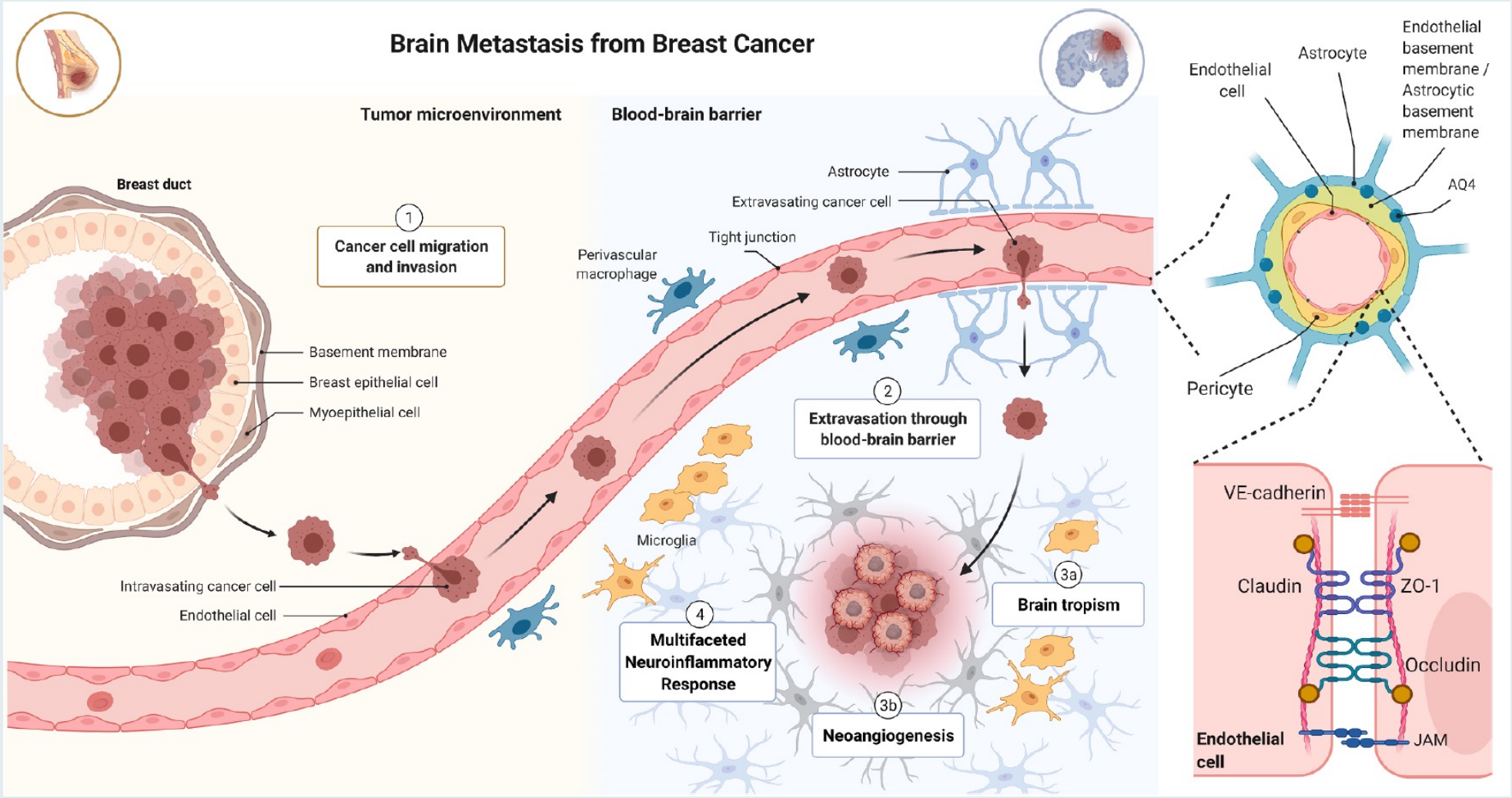


Anti-tumour Treatment

Targeting brain metastases in breast cancer

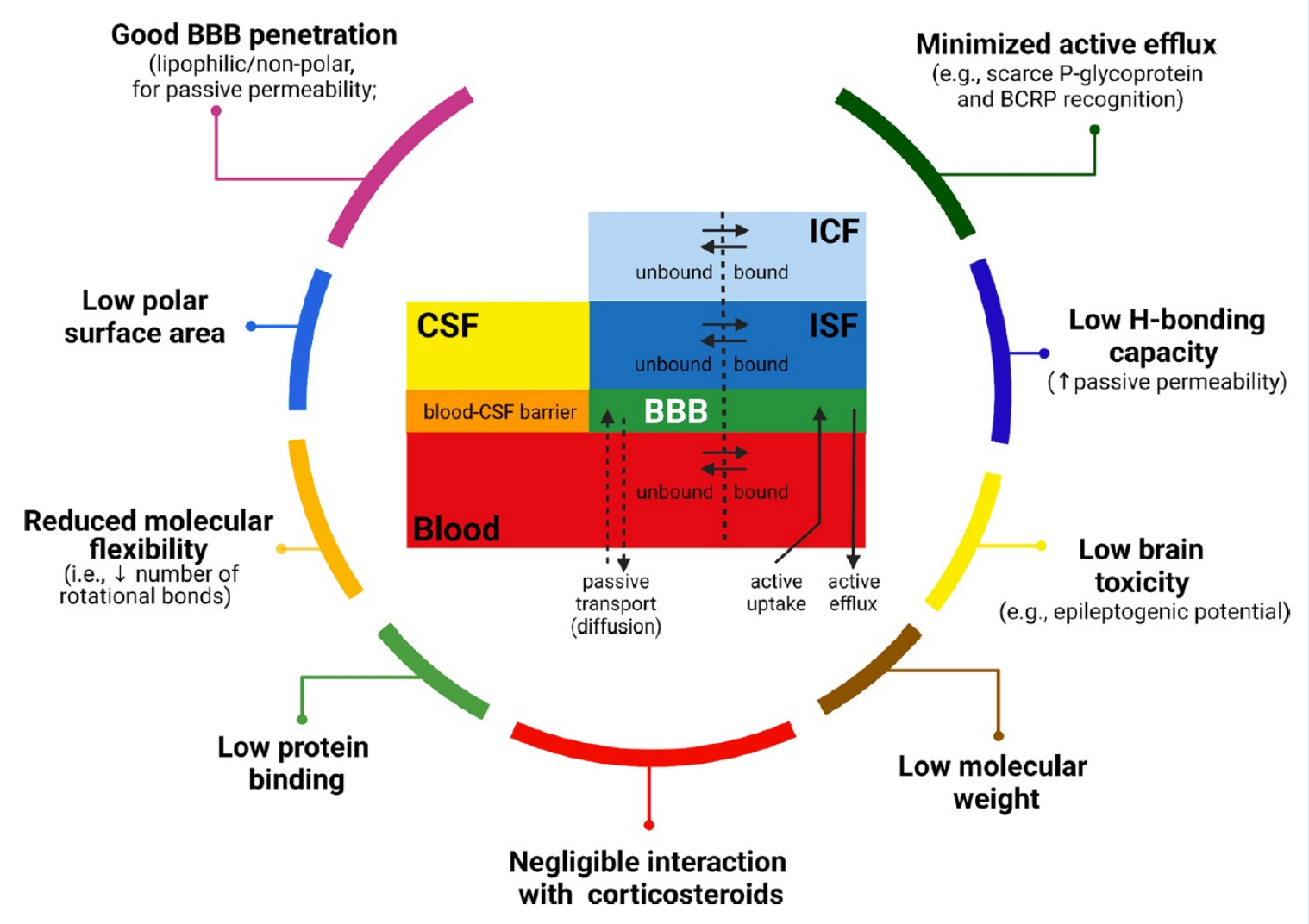
Chiara Corti [a,b,*], Gabriele Antonarelli [a,b], Carmen Criscitiello [a,b], Nancy U. Lin [c], Lisa A. Carey [d], Javier Cortés [e,f,g,h,i], Philip Poortmans [j], Giuseppe Curigliano [a,b]

Hypothesized Mechanism of Spread of Breast Cancer Cells to the Central Nervous System



Corti C et al. *Cancer Treat Rev* 2022;103:102324.

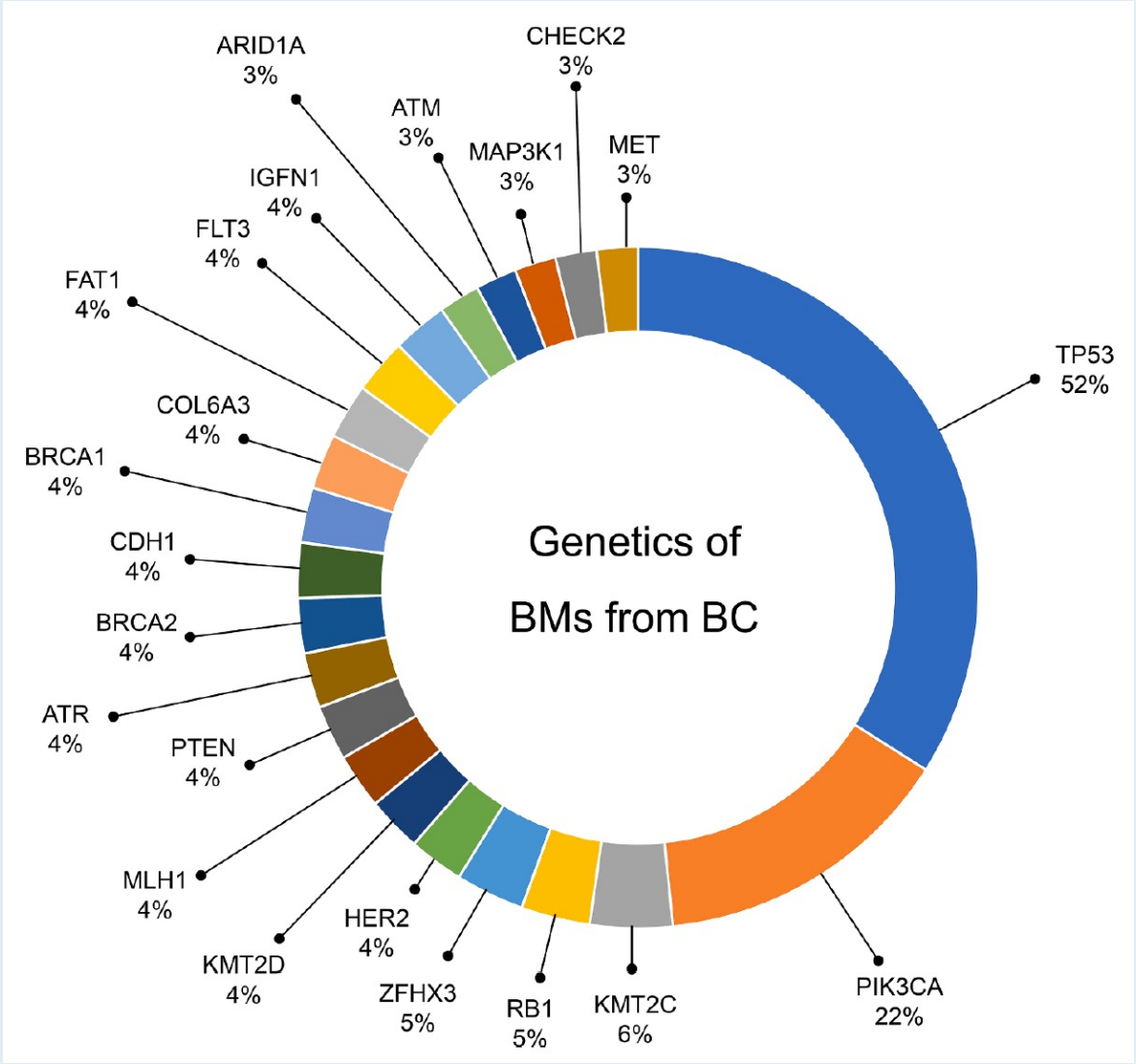
Pharmacological Aspects to Consider in Drug Design for Targeting Brain Metastases



BBB = blood-brain barrier; ICF = intracellular fluid; CSF = cerebrospinal fluid; ISF = interstitial fluid

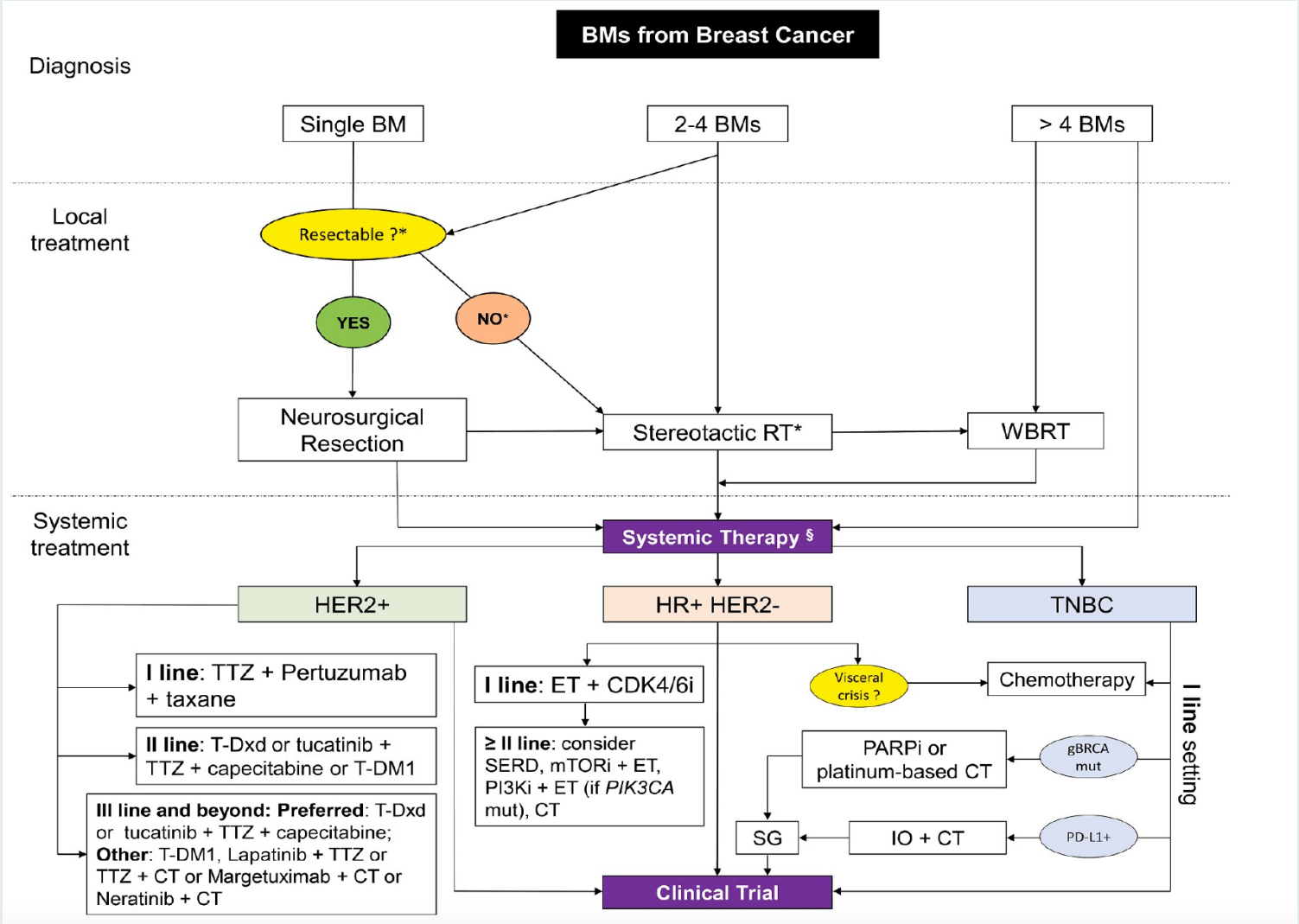
Corti C et al. *Cancer Treat Rev* 2022;103:102324.

Commonly Mutated Genes in Brain Metastases (BMs) from Breast Cancer



Corti C et al. *Cancer Treat Rev* 2022;103:102324.

Treatment Algorithm for Patients with Brain Metastases from Brain Cancer



Corti C et al. *Cancer Treat Rev* 2022;103:102324.

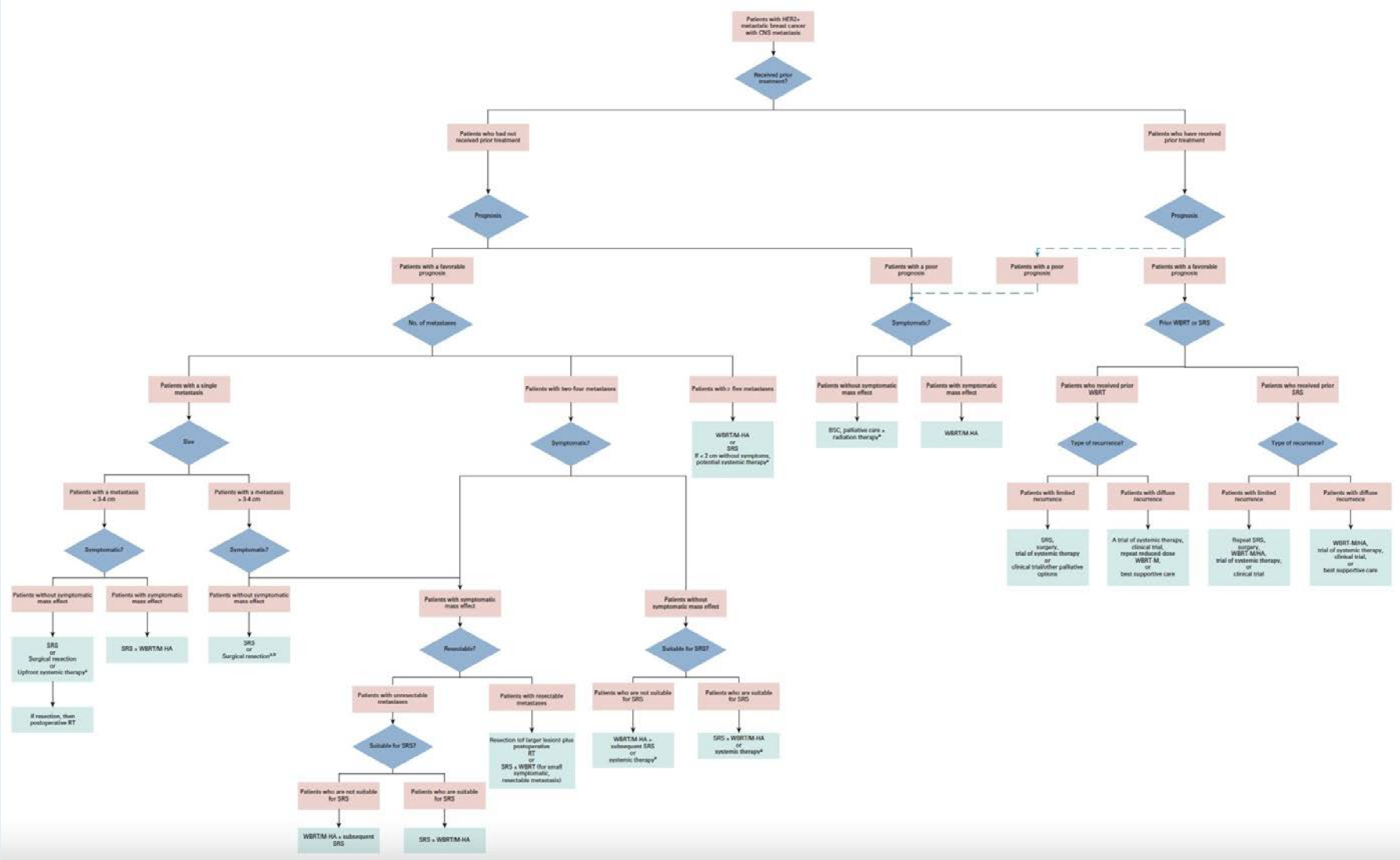
J Clin Oncol 2022 August 10;40(23):2636-55.

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]

Treatment Algorithm for Patients with Brain Metastases from Brain Cancer



Ramakrishna N et al. *J Clin Oncol* 2022;40(23):2636-55.

Clin Cancer Res 2022 September 8:CCR-22-1138.

Preclinical and clinical efficacy of trastuzumab deruxtecan in breast cancer brain metastases

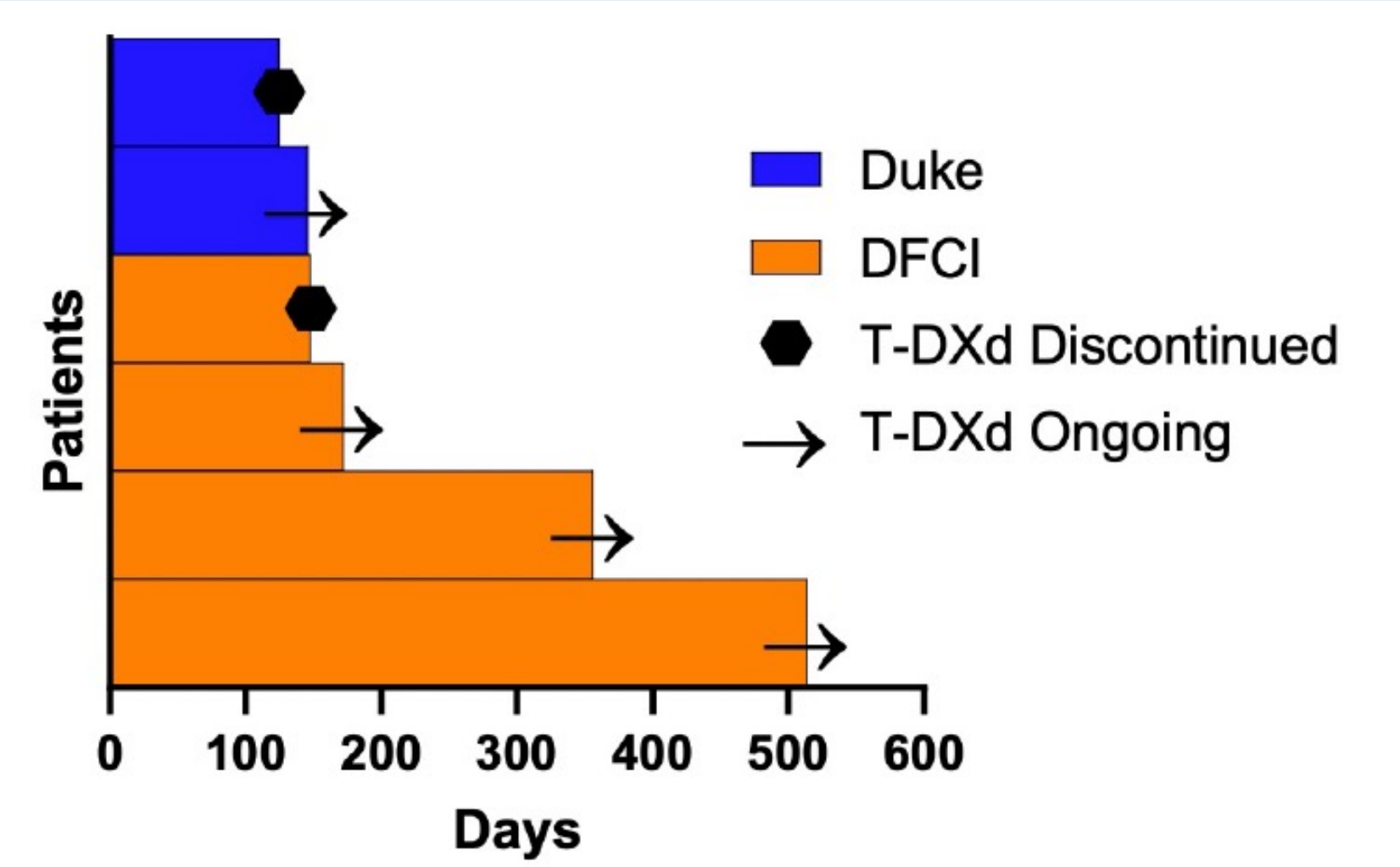
Sheheryar Kabraji*[1], Jing Ni*[1], Sarah Sammons[2], Tianyu Li[1], Amanda E.D. Van Swearingen[2], Yanzhi Wang[1], Alyssa Pereslete[1], Liangge Hsu[3], Pamela J. DiPiro[3], Chris Lascola[2], Heather Moore[2], Melissa Hughes[1], Akshara S. Raghavendra[4], Maria Gule-Monroe[4], Rashmi K. Murthy[4], Eric P. Winer[1], Carey K. Anders[2], Jean J. Zhao[1*], Nancy U. Lin[1*]

Durable Clinical and Radiographic Responses in a Series of Patients with HER2+ Breast Cancer (BC) Leptomeningeal Disease (LMD) Treated with Trastuzumab Deruxtecan (T-DXd)

Alder L et al.

AACR 2022;Abstract 5257.

Duration of T-DXd



Alder L et al. AACR 2022;Abstract 5257.

Clinical Outcomes

Clinical Outcomes	# (%) or median (range)
Response on first MRI post-C1D1 T-DXd	
Yes	5 (83.3%)
No	1 (16.6%)
Clinical Benefit	
Yes	6 (100%)
Alive	5 (83.3%)
Remains on T-DXd	4 (66.7%)
Median # cycles T-DXd	6.5 (5-23)
Median duration T-DXd (days)	160 (125 - 514)
Median Survival since C1D1 T-DXd (days)	264 (146 - 514)
Median survival since LMD diagnosis (days)	379 (208 – 626)

Alder L et al. AACR 2022;Abstract 5257.

nature COMMUNICATIONS

Nat Commun 2021 October 12;12(1):5954.

ARTICLE

https://doi.org/10.1038/s41467-021-25859-y OPEN

Phase II study of ipilimumab and nivolumab in leptomeningeal carcinomatosis

Priscilla K. Brastianos[1,3]✉, Matthew R. Strickland[1,2,3], Eudocia Quant Lee[2], Nancy Wang[1], Justine V. Cohen[1], Ugonma Chukwueke[2], Deborah Anne Forst[1], April Eichler[1], Beth Overmoyer[2], Nancy U. Lin[2], Wendy Y. Chen[2], Aditya Bardia[1], Dejan Juric[1], Ibiayi Dagogo-Jack[1], Michael D. White[1], Jorg Dietrich[1], Naema Nayyar[1], Albert E. Kim[1], Christopher Alvarez-Breckenridge[1], Maura Mahar[1], Joana L. Mora[1], Brian V. Nahed[1], Pamela S. Jones[1], Helen A. Shih[1], Elizabeth R. Gerstner[1], Anita Giobbie-Hurder[2], Scott L. Carter[2], Kevin Oh[1], Daniel P. Cahill[1,4] & Ryan J. Sullivan[1,4]

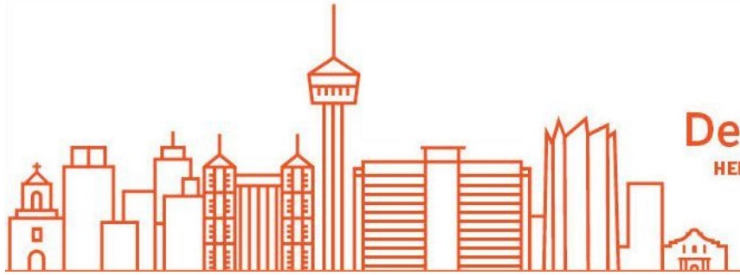
Neuro Oncol 2022 August 10;[Online ahead of print].

Neuro-Oncology

XX(XX), 1–9, 2022 | https://doi.org/10.1093/neuonc/noac195 | Advance Access date 10 August 2022

A phase I/II study of intrathecal trastuzumab in human epidermal growth factor receptor 2-positive (HER2-positive) cancer with leptomeningeal metastases: Safety, efficacy, and cerebrospinal fluid pharmacokinetics

Priya U. Kumthekar, Michael J. Avram, Andrew B. Lassman, Nancy U. Lin, Eudocia Lee, Sean A. Grimm, Margaret Schwartz, Kirsten L. Bell Burdett, Rimas V. Lukas, Karan Dixit, Isabella Perron, Hui Zhang, William J. Gradishar, Elena I. Pentsova, Suriya Jeyapalan, Morris D. Groves, Michelle Melisko, and Jeffrey J. Raizer



December 7-10, 2021
HENRY B. GONZALEZ CONVENTION CENTER
SAN ANTONIO, TEXAS

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AACR American Association for Cancer Research

(https://www.sabcs.org/2021-SABCS)

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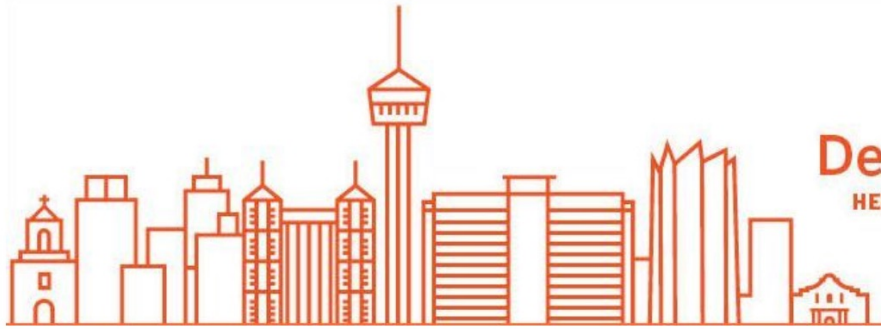
Session PD4 - Brain Metastases: Managing LMD / Targeting HER2

PD4-02. Safety and efficacy of a tucatinib-trastuzumab-capecitabine regimen for treatment of leptomeningeal metastasis (LM) in HER2-positive breast cancer: Results from TBCRC049, a phase 2 non-randomized study

December 8, 2021, 5:00 PM - 6:30 PM | Stars at Night 3/4

Author

Rashmi K Murthy[1], Barbara O'Brien[1], Donald A Berry[1], Akshara Singareeka-Raghavendra[1], Maria Gule Monroe[1], Jason Johnson[1], Jason White[1], Jennifer Childress[1], Justin Sanford[1], Jill Schwartz-Gomez[1], Michelle Melisko[2], Aki Morikawa[3], Sherise Ferguson[1], John F de Groot[1], Ian Krop[4], Vicente Valero[1], Mothaffar Rimawi[5], Antonio Wolff[6], Debu Tripathy[1], Nancy U Lin[7] and Erica Stringer-Reasor[8]. [1]University of Texas MD Anderson Cancer Center, Houston, TX;[2]University of California San Francisco, San Francisco, CA;[3]University of Michigan, Ann Arbor, MI;[4]Dana-Farber Cancer Center, Boston, MA;[5]Baylor College of Medicine, Houston, TX;[6]Johns Hopkins University, Baltimore, MD;[7]Dana-Farber Cancer Institute, Boston, MA;[8]University of Alabama at Birmingham O'Neal Comprehensive Cancer Center, Birmingham, AL



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Session P2 - Poster Session 2

P2-13-05. Central nervous system metastases as a site of first recurrence in adjuvant therapy trials of HER2+ early breast cancer (EBC)

December 8, 2021, 5:00 PM - 5:00 PM | Hall 1

Author

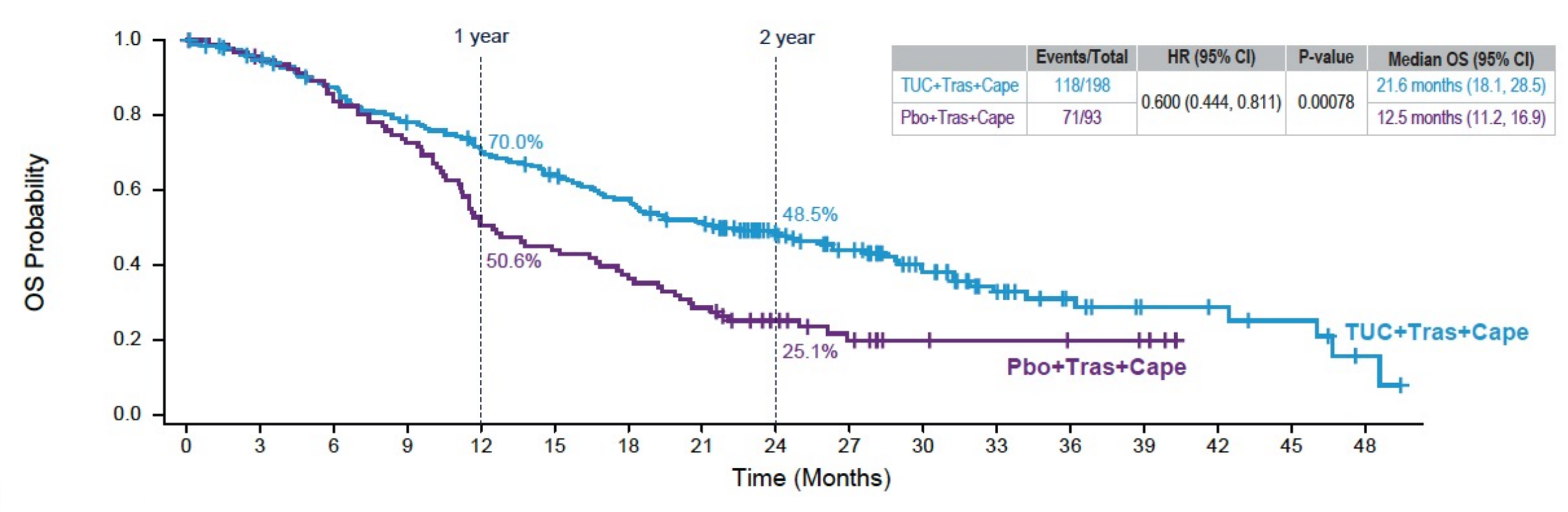
Nancy U Lin[1], Diana Lueftner[2], Adam M Brufsky[3], Sara M Tolaney[1], Michelle E Melisko[4], Frankie Ann Holmes[5] and Ahmad Awada[6]. [1]Dana-Farber Cancer Institute, Boston, MA;[2]University Hospital Charité, Berlin, Germany[3]Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA;[4]University of California San Francisco, San Francisco, CA;[5]Texas Oncology, US Oncology, Houston, TX;[6]Jules Bordet Institute, Brussels, Belgium

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.

ASCO 2021;Abstract PD4-04.

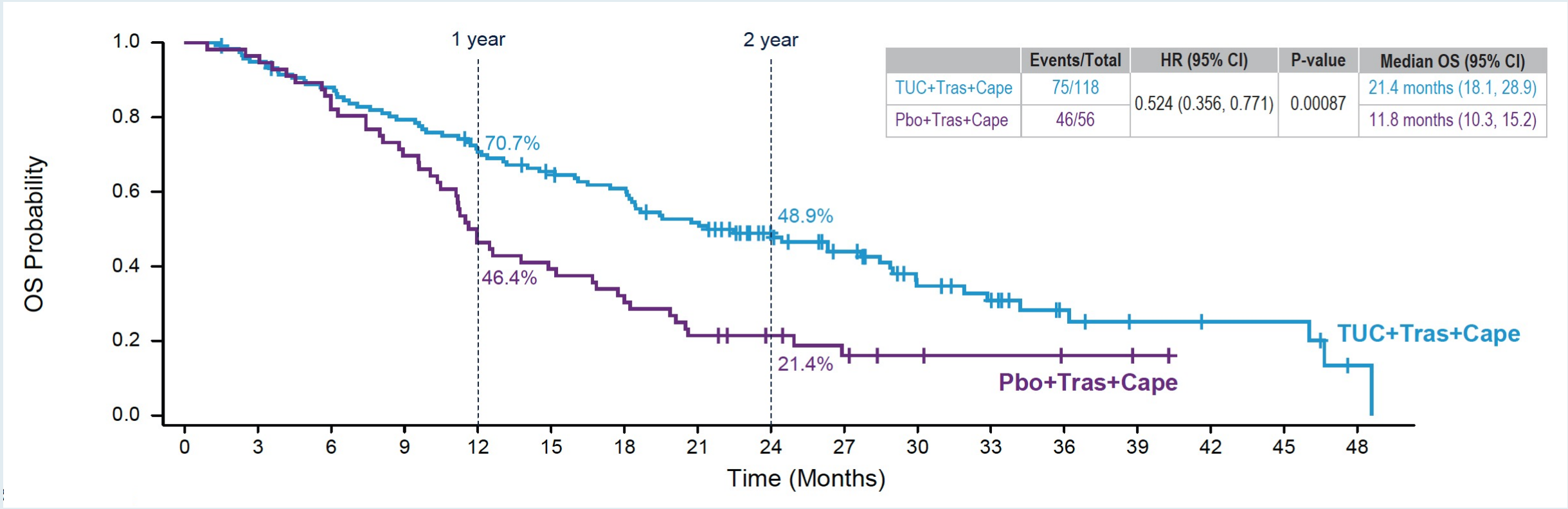
HER2CLIMB: Overall Survival (OS) for All Patients with Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

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

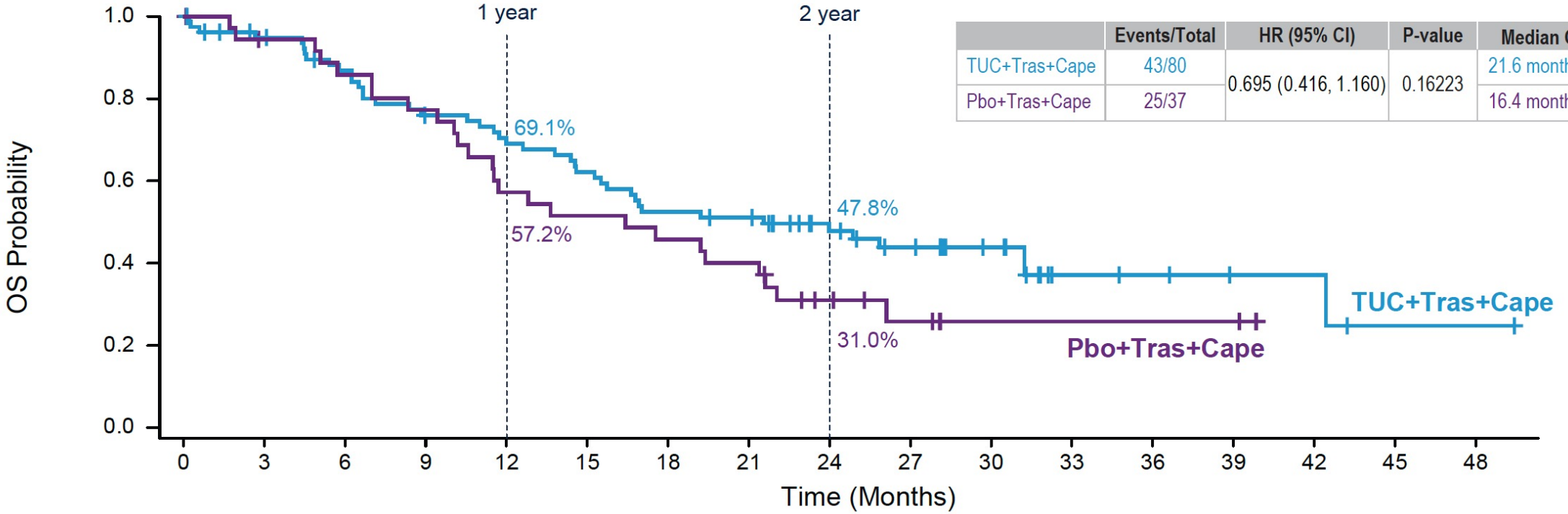
HER2CLIMB: OS for Patients with Active Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

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

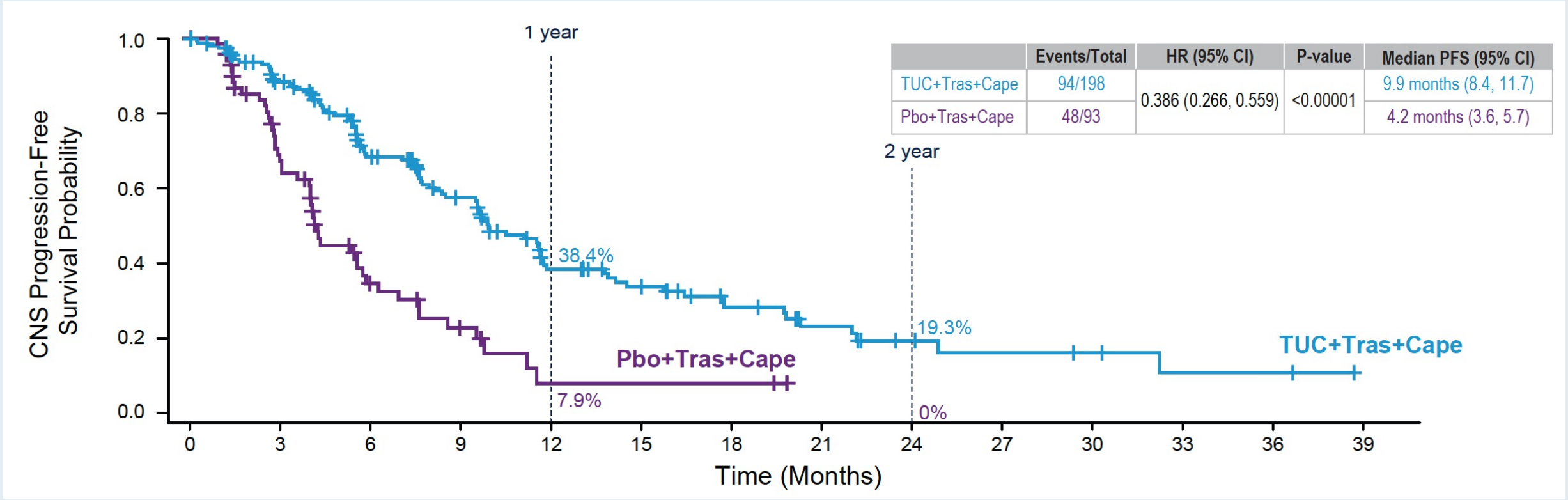
HER2CLIMB: OS for Patients with Treated Stable Brain Metastases



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	43/80	0.695 (0.416, 1.160)	0.16223	21.6 months (15.3, 42.4)
Pbo+Tras+Cape	25/37			16.4 months (10.6, 21.6)

Lin NU et al. ASCO 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)

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

Case Presentation: 65-year-old woman with ER/PR-positive, HER2-low mBC s/p ET-based therapies, capecitabine

Dr Vignesh Narayanan (Lone Tree, Colorado)

RTP
RESEARCH
TO PRACTICE

Research

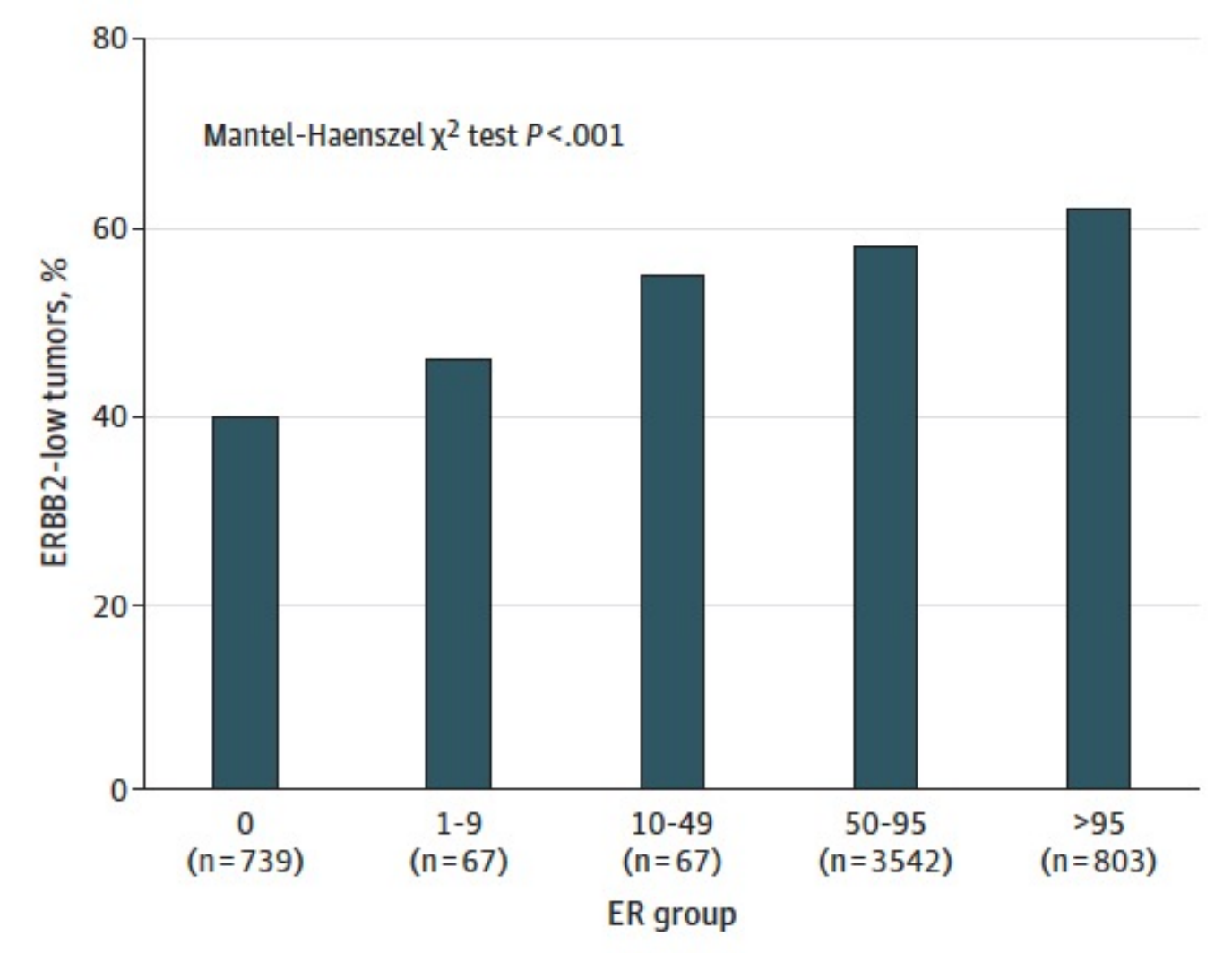
JAMA Oncology | Original Investigation

Prognostic and Biologic Significance of ERBB2-Low Expression in Early-Stage Breast Cancer

Paolo Tarantino, MD; Qingchun Jin, MPH; Nabihah Tayob, PhD; Rinath M. Jeselsohn, MD; Stuart J. Schnitt, MD; Julie Vincuilla, BS; Tonia Parker, BS; Svitlana Tyekucheva, PhD; Tianyu Li, MS; Nancy U. Lin, MD; Melissa E. Hughes, MSc; Anna C. Weiss, MD; Tari A. King, MD; Elizabeth A. Mittendorf, MD, PhD; Giuseppe Curigliano, MD, PhD; Sara M. Tolaney, MD, MPH

JAMA Oncol 2022 August 1;8(8):1177-83.

Proportion of ERBB2-Low Tumors by Estrogen Receptor (ER) Expression Threshold



Tarantino P et al. *JAMA Oncol* 2022 August 1;8(8):1177-83.

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

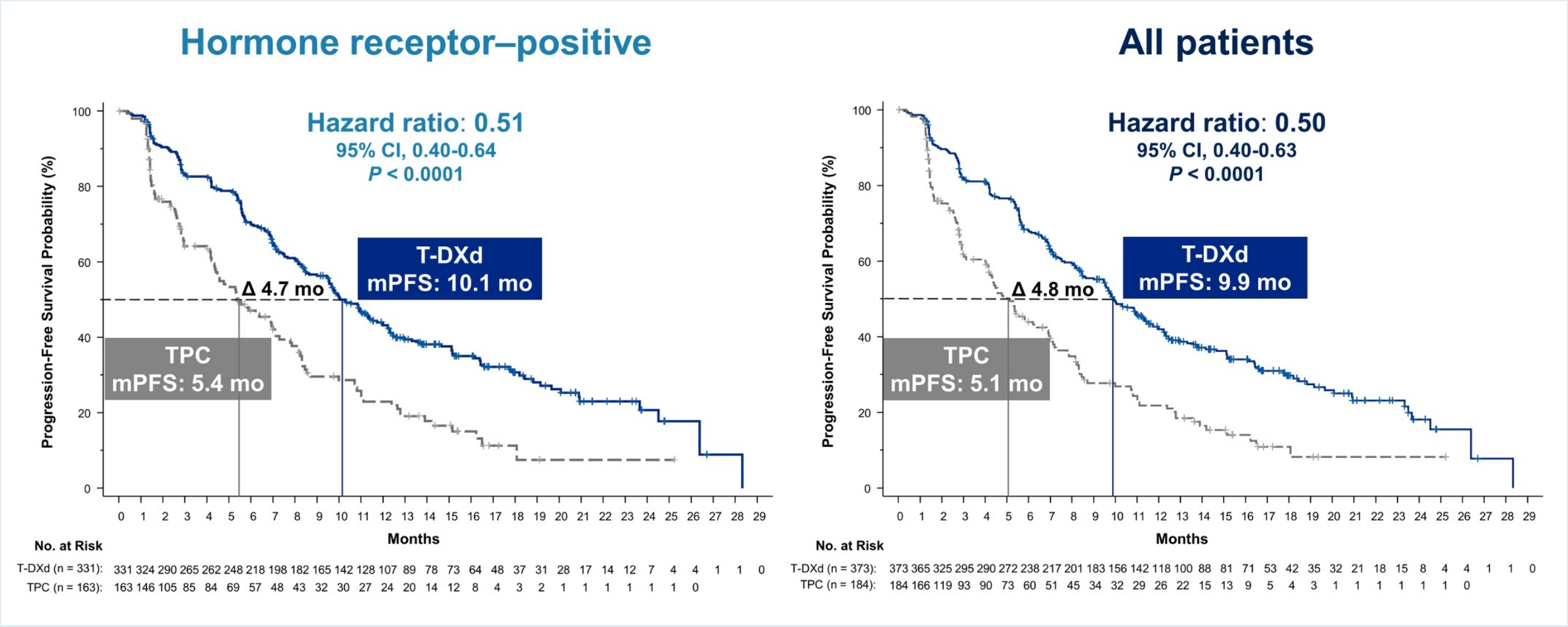
The NEW ENGLAND JOURNAL of MEDICINE

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*

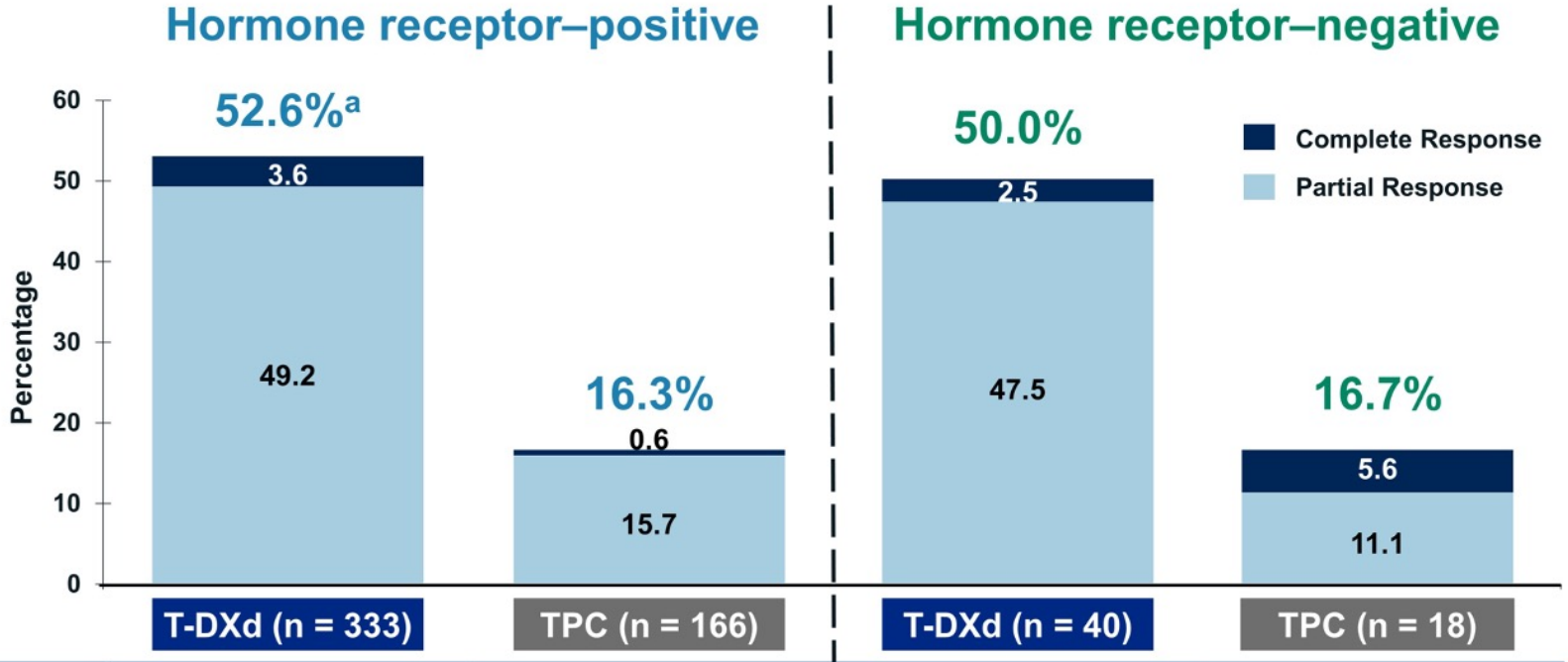
DESTINY-Breast04: PFS for HR-Positive (Primary Endpoint) and All Patients



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: Confirmed Objective Response Rate



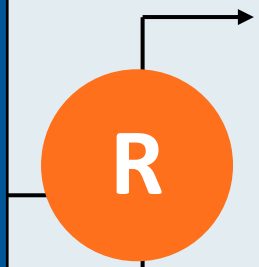
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

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

DESTINY-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



Trastuzumab deruxtecan

Physician's choice:

Capecitabine or paclitaxel or *nab* paclitaxel

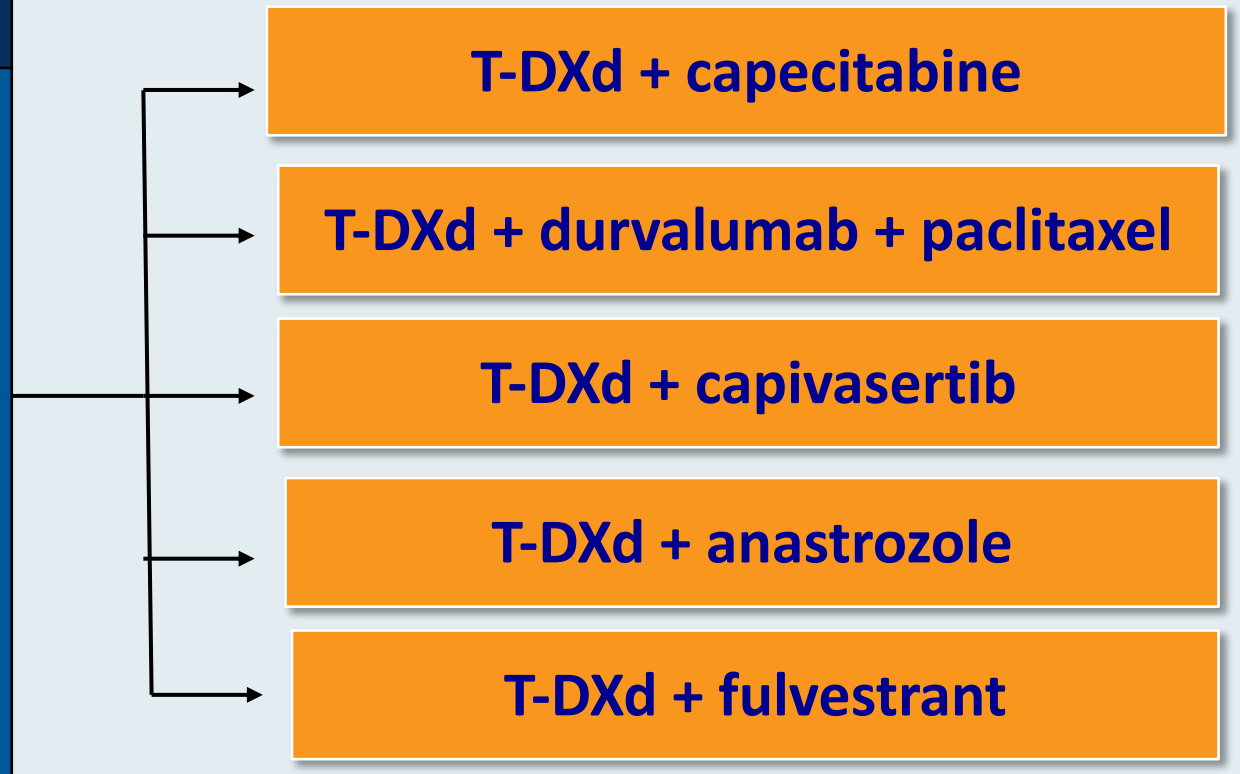
Primary endpoint: PFS in HR-positive, HER2-low population

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.

Case Presentation: 50-year-old woman with triple-positive, BRCA2-mutant breast cancer, s/p bilateral mastectomies and adjuvant TH, now with locally recurrent ER/PR-positive, HER2-negative disease

Dr Namrata Peswani (Richardson, Texas)

RTP
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Case Presentation: 72-year-old woman with triple-positive mBC who has CKD and significant neuropathy s/p 3 prior lines of therapy

Dr Susmitha Apuri (Lutz, Florida)

RTP RESEARCH TO PRACTICE

Case Presentation: 60-year-old woman with progressive triple-positive mBC receiving T-DXd

Dr Joseph Martins (Tyler, Texas)

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

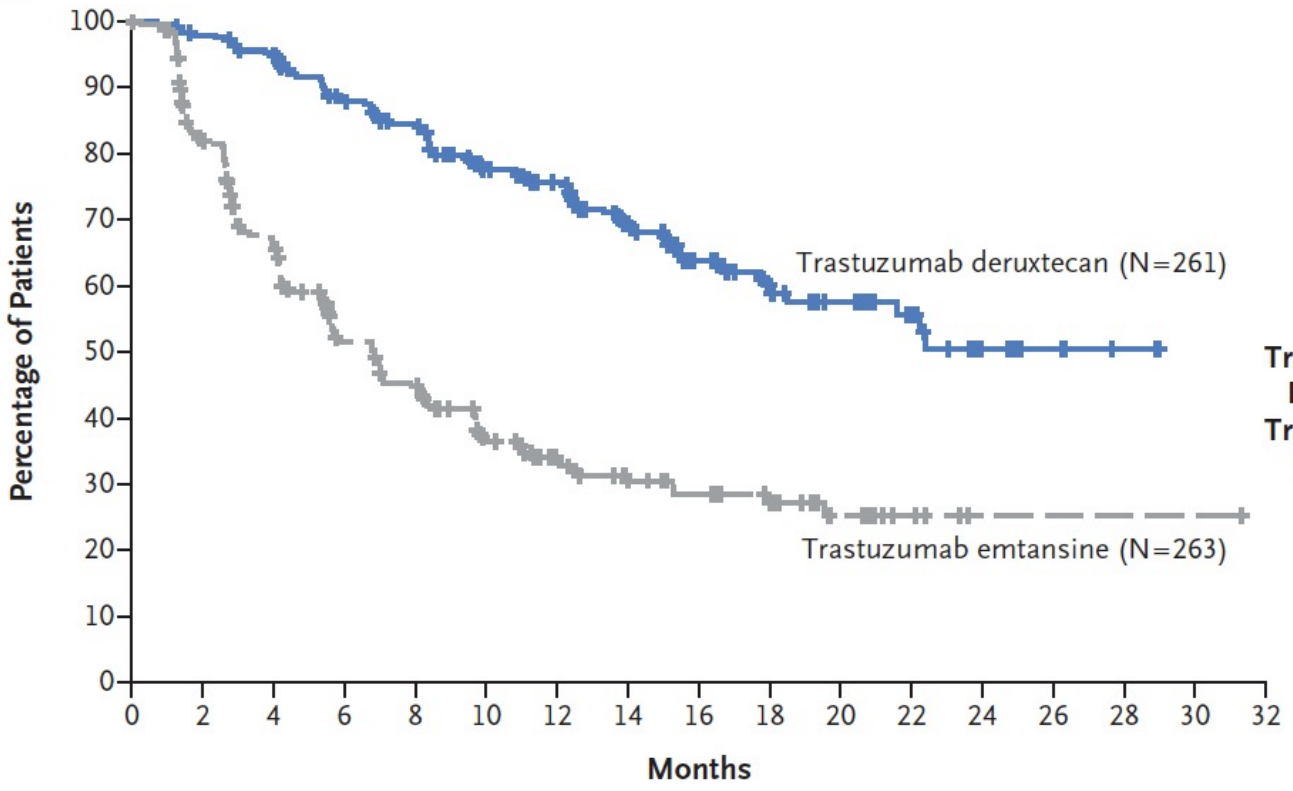
The NEW ENGLAND JOURNAL of MEDICINE

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)

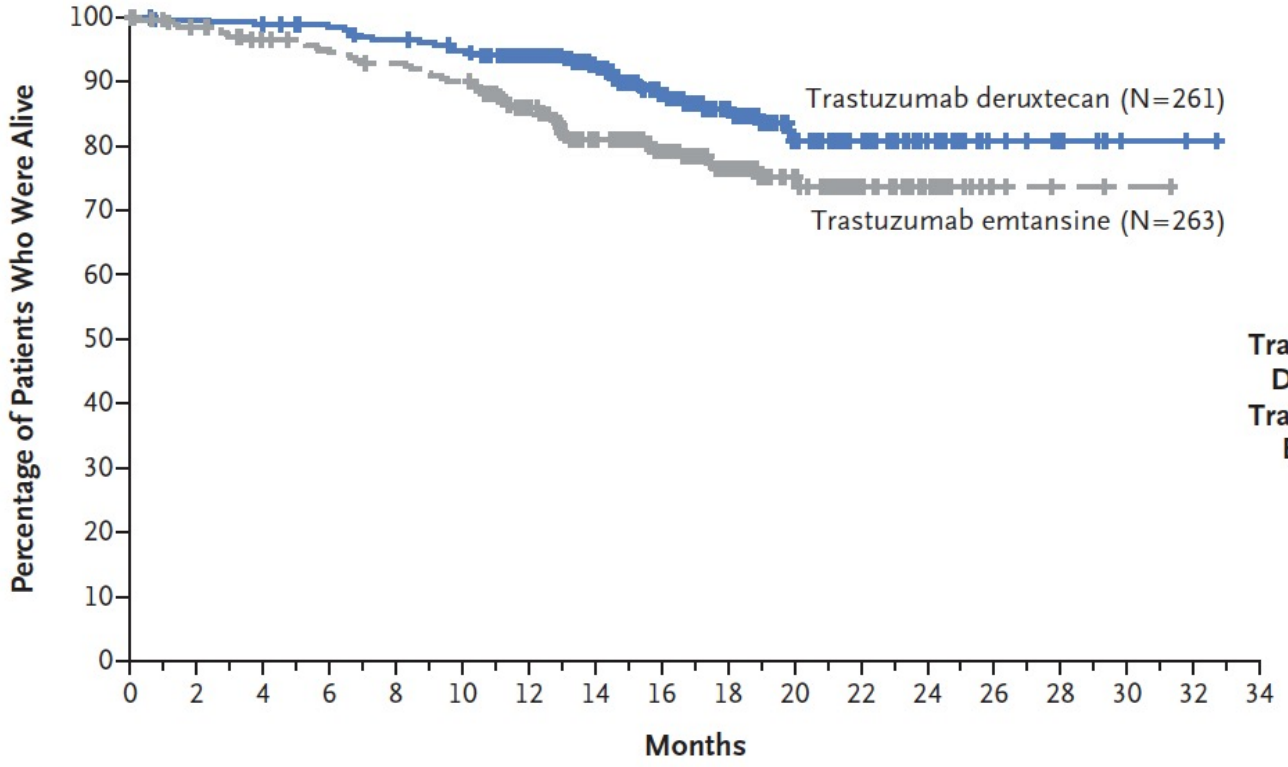
Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22–0.37)
P<0.001

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: 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

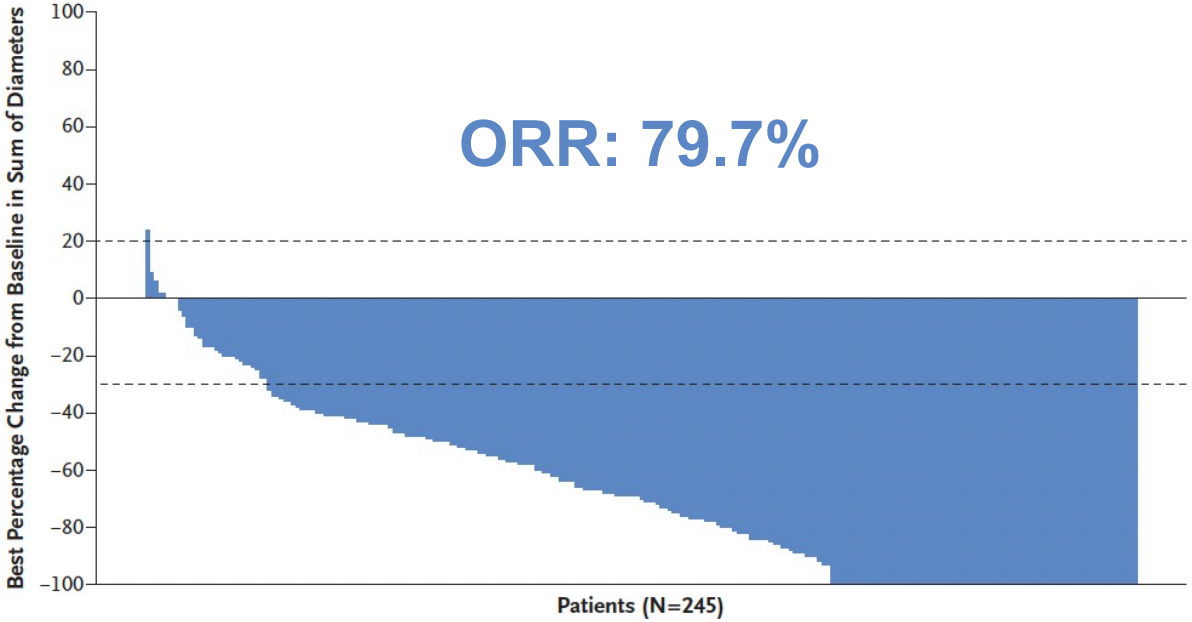
No. at Risk

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	

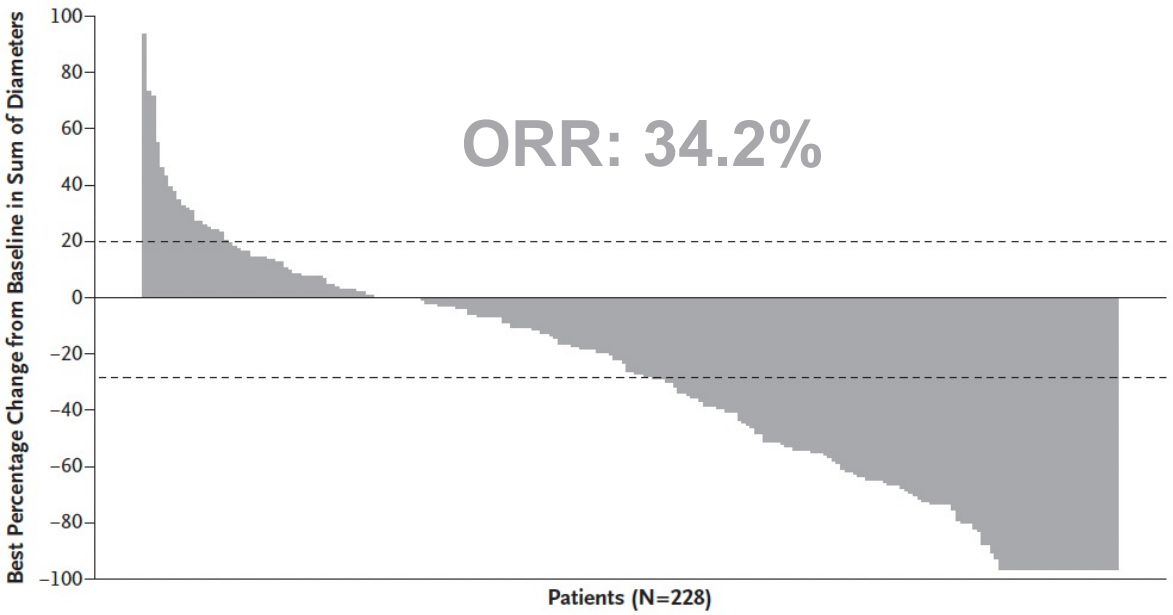
Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

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

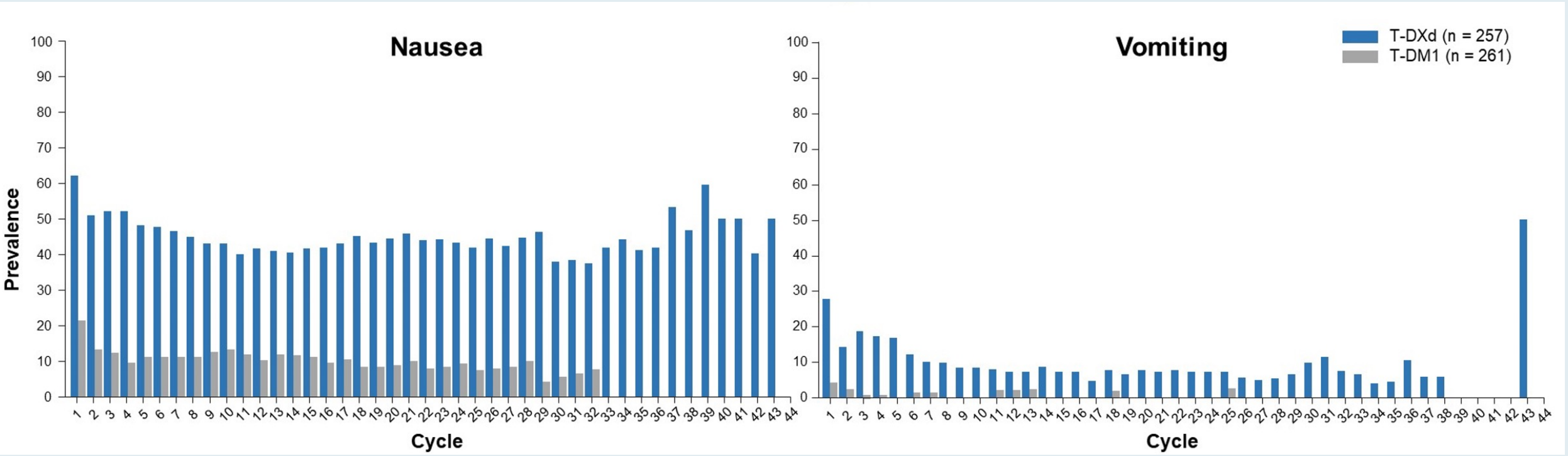
Abstract 1000

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

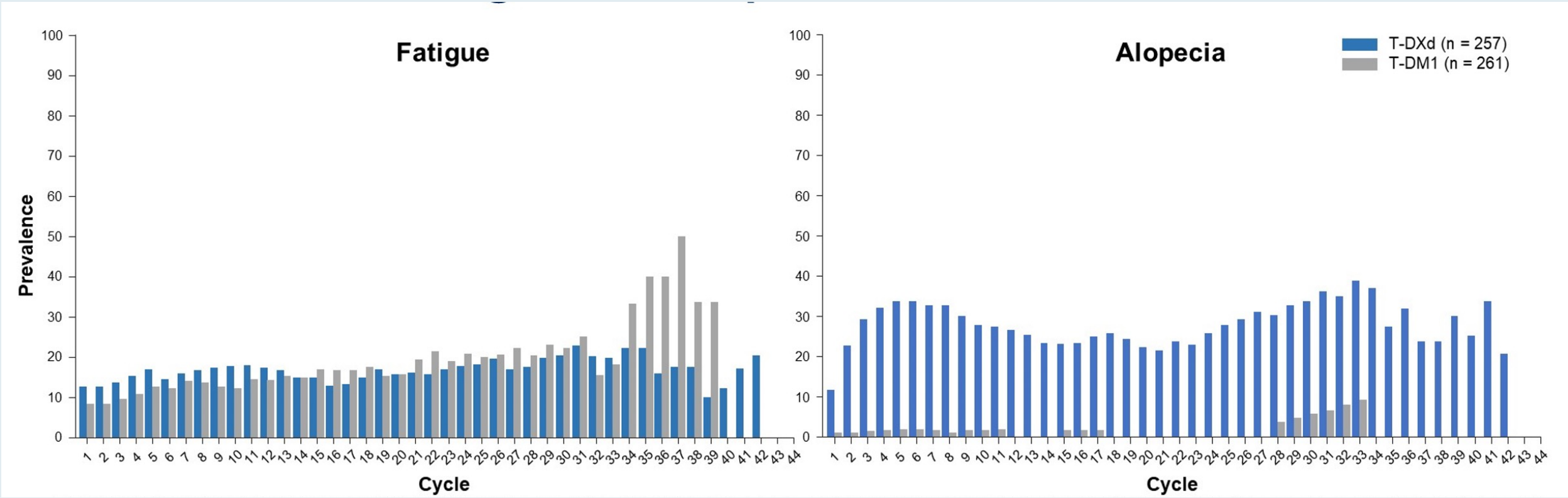
[a]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

DESTINY-Breast03: 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.

Meet The Professor with Dr Lin

Introduction: Journal Club with Dr Lin – Part 1

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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

RTP RESEARCH TO PRACTICE

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?

 Dr Brufsky	After 1 line of chemotherapy	 Dr Lin	After 1 line of chemotherapy
 Dr Carey	After 1 line of chemotherapy	 Dr O'Shaughnessy	After 1 line of endocrine therapy
 Prof Curigliano	After 1 line of endocrine therapy	 Dr Pegram	After 1 line of chemotherapy

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?

 Dr Brufsky	Similar to but less concerning than anthracycline/platinum agents	 Dr Lin	Similar to the profile of anthracycline/platinum agents
 Dr Carey	Similar to but less concerning than anthracycline/platinum agents	 Dr O’Shaughnessy	Similar to but less concerning than anthracycline/platinum agents
 Prof Curigliano	Similar to but less concerning than anthracycline/platinum agents	 Dr Pegram	Similar to the profile of anthracycline/platinum agents

RTP RESEARCH TO PRACTICE

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

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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

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RESEARCH
TO PRACTICE

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]

Breast Cancer Research and Treatment (2021) 188:561–569
https://doi.org/10.1007/s10549-021-06174-y

EPIDEMIOLOGY

Management and outcomes of men diagnosed with primary breast cancer

Andrew E. Johnson[1] · Suzanne B. Coopey[2] · Laura M. Spring[3] · Nora K. Horick[4] · Jose Pablo Leone[5] · Nancy U. Lin[5] · Laura S. Dominici[6] · Kevin S. Hughes[2] · Rachel B. Jimenez[1]

Cancer 2022 September 7;[Online ahead of print].

Original Article

Efficacy of neoadjuvant chemotherapy in male breast cancer compared with female breast cancer

José Pablo Leone, MD [1]; Michael J. Hassett, MD[1]; Julieta Leone, MD[2]; Sara M. Tolaney, MD, MPH[1]; Carlos T. Vallejo, MD[2]; Bernardo A. Leone, MD; Eric P. Winer, MD[1]; and Nancy U. Lin, MD[1]

Breast Cancer Research and Treatment (2021) 188:695–702
https://doi.org/10.1007/s10549-021-06182-y

EPIDEMIOLOGY

Tumor subtypes and survival in male breast cancer

Julieta Leone[1] · Rachel A. Freedman[2,3] · Nancy U. Lin[2,3] · Sara M. Tolaney[2,3] · Carlos T. Vallejo[1] · Bernardo A. Leone[1] · Eric P. Winer[2,3] · José Pablo Leone[2,3]

Meet The Professor with Dr Lin

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

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RESEARCH
TO PRACTICE

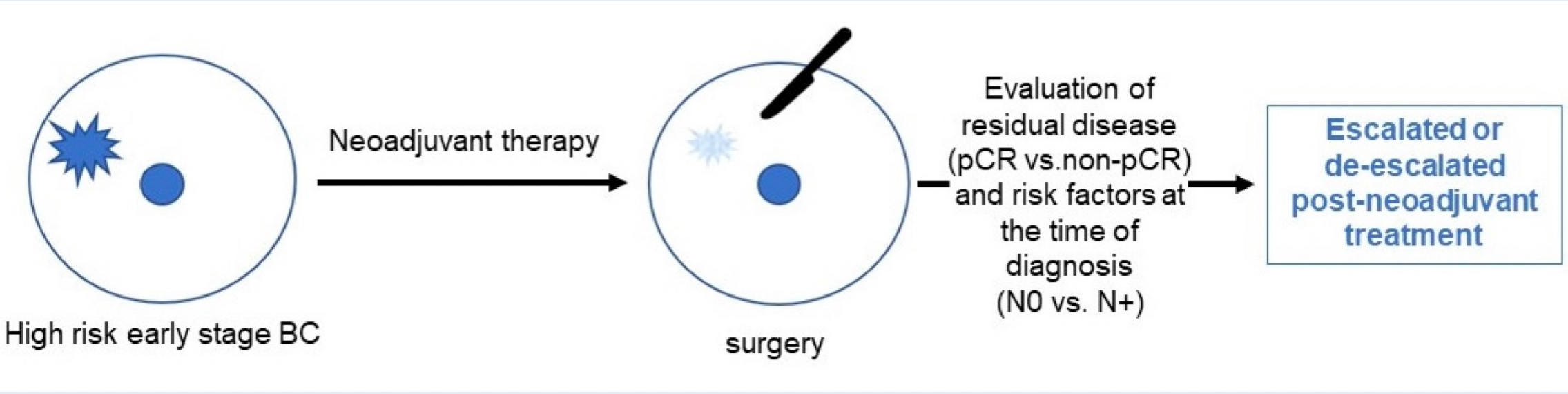
FDA-Approved Agents for HER2-Positive Localized Breast Cancer

Agent	Setting	Pivotal trial(s)	Regimens	Year approved
Trastuzumab	Adjuvant HER2+ LBC, first line	NSABP-31 N9831 BCIRG 006 HERA	AC-T-placebo vs AC-T-H AC-T vs AC-H vs AC-T-H AC-T vs ACT-H vs TC-H 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

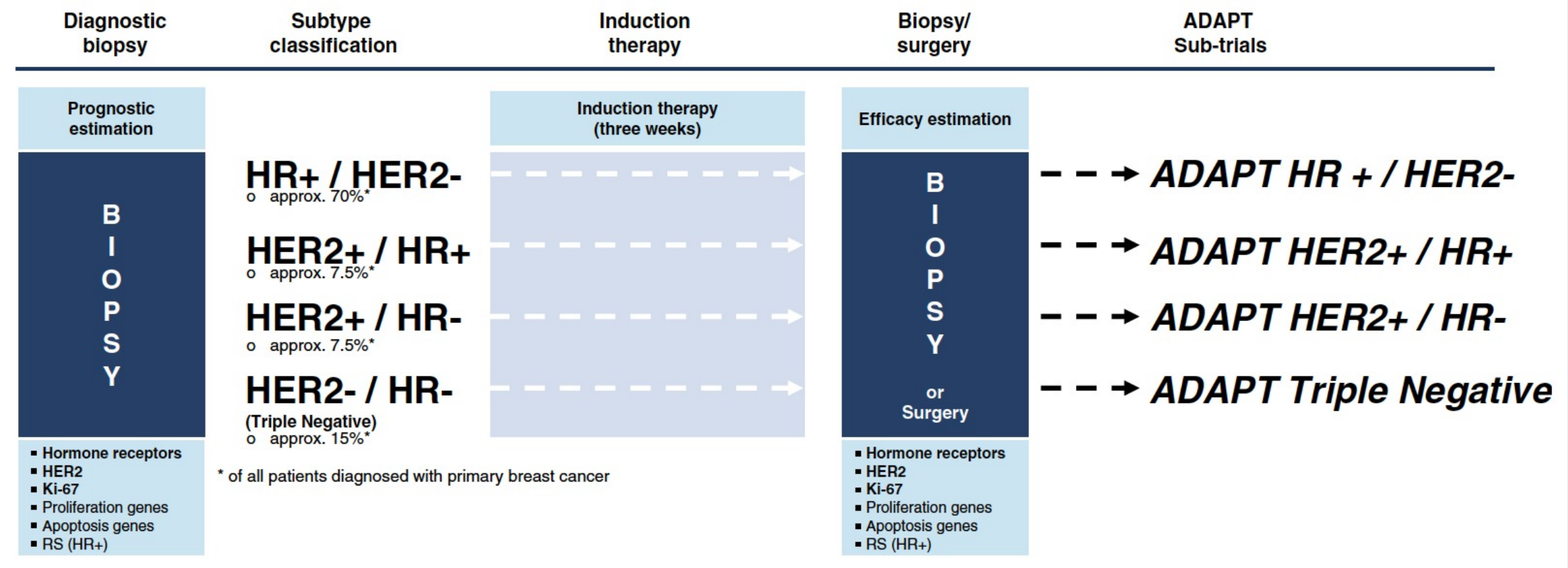
U. A. Nitz[1,2], O. Gluz[1,2,3*], M. Christgen[4], E.-M. Grischke[5], D. Augustin[6], S. Kuemmel[7], M. Braun[8], J. Potenberg[9], A. Kohls[10], K. Krauss[11], A. Stefek[12], C. Schumacher[13], H. Forstbauer[14], T. Reimer[15], H. Fischer[16], C. Liedtke[17,18], R. Wuerstlein[19], J. Schumacher[20], 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

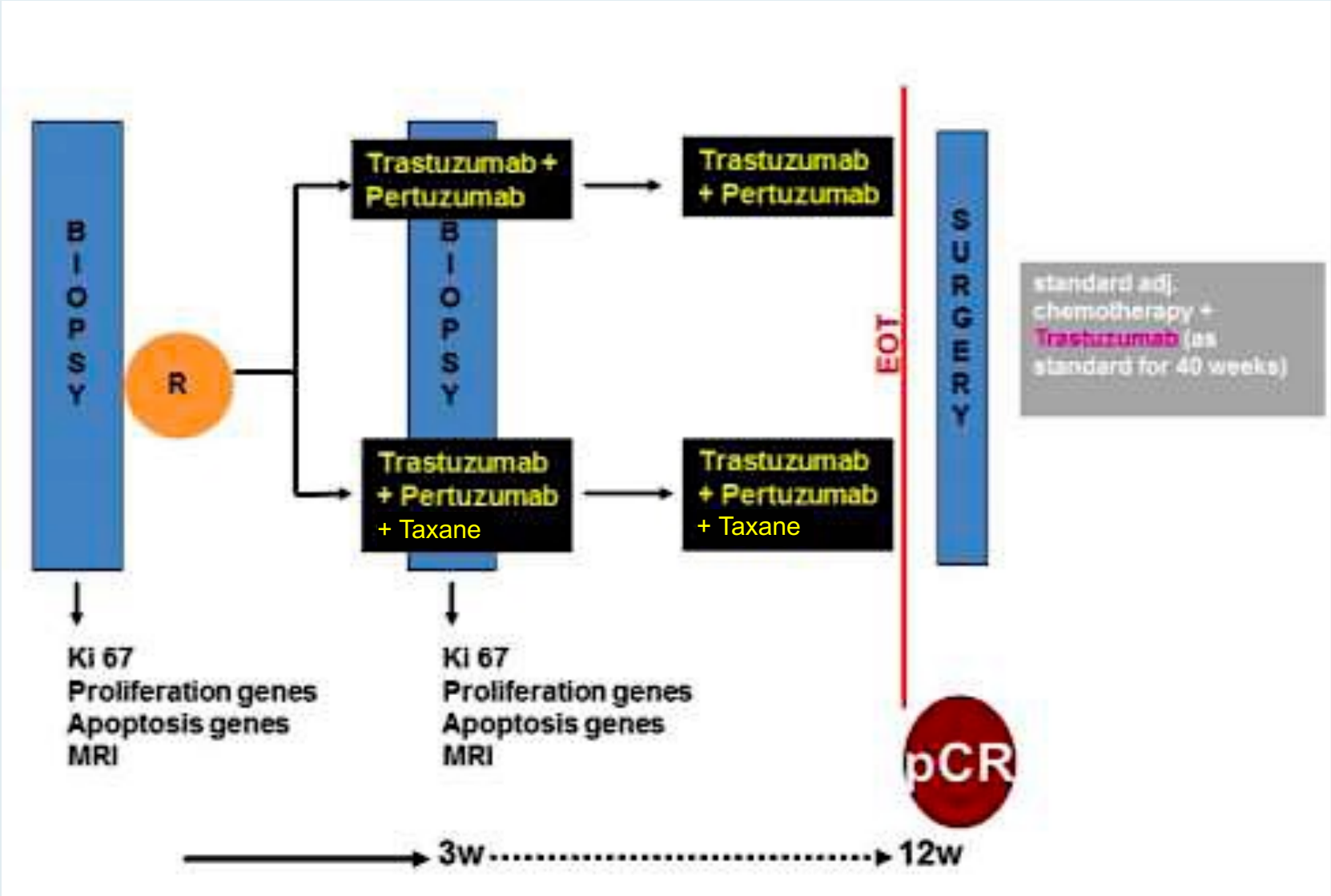
Ulrike Nitz, Oleg Gluz*, Monika Graeser, Matthias Christgen, Sherko Kuemmel, Eva-Maria Grischke, Michael Braun, Doris Augustin, Jochem Potenberg, Katja Krauss, Claudia Schumacher, Helmut Forstbauer, Toralf Reimer, Andrea Stefek, Hans Holger Fischer, Enrico Pelz, Christine zu Eulenburg, Ronald Kates, 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 ER/PR-negative cT1-4c	• Trastuzumab + pertuzumab • Trastuzumab + pertuzumab + paclitaxel	34.4% vs 90.5%	**5-year iDFS** 87% vs 98% **5-year dDFS** 92% vs 98% **5-year OS** 94% vs 98%
WSG-ADAPT-TP HER2+/HR+	375 ER and/or PR-positive cT1-4c	• T-DM1 • T-DM1 + ET • Trastuzumab + ET	41% vs 41.5% vs 15%	**5-year DFS** 88.9% vs 85.3% vs 84.6% **5-year OS** 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

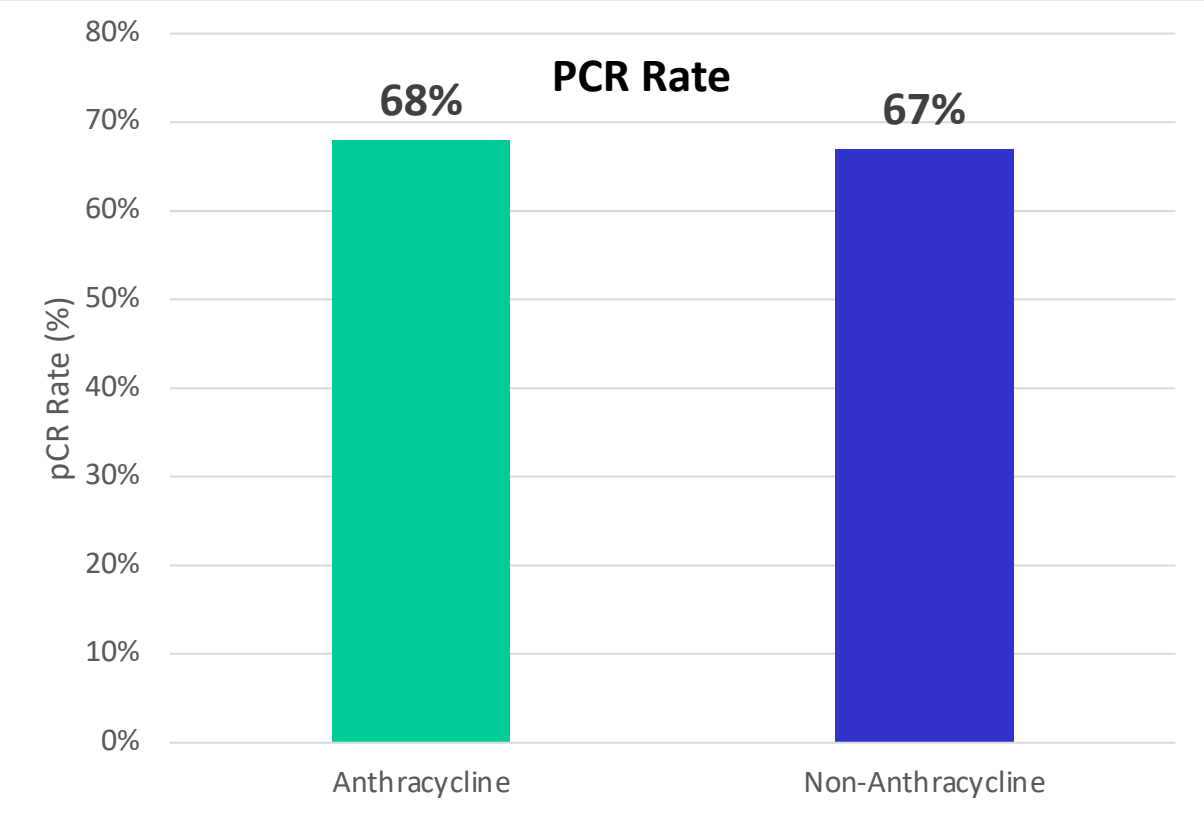
Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual *ERBB2* Blockade in Patients With *ERBB2*-Positive Breast Cancer

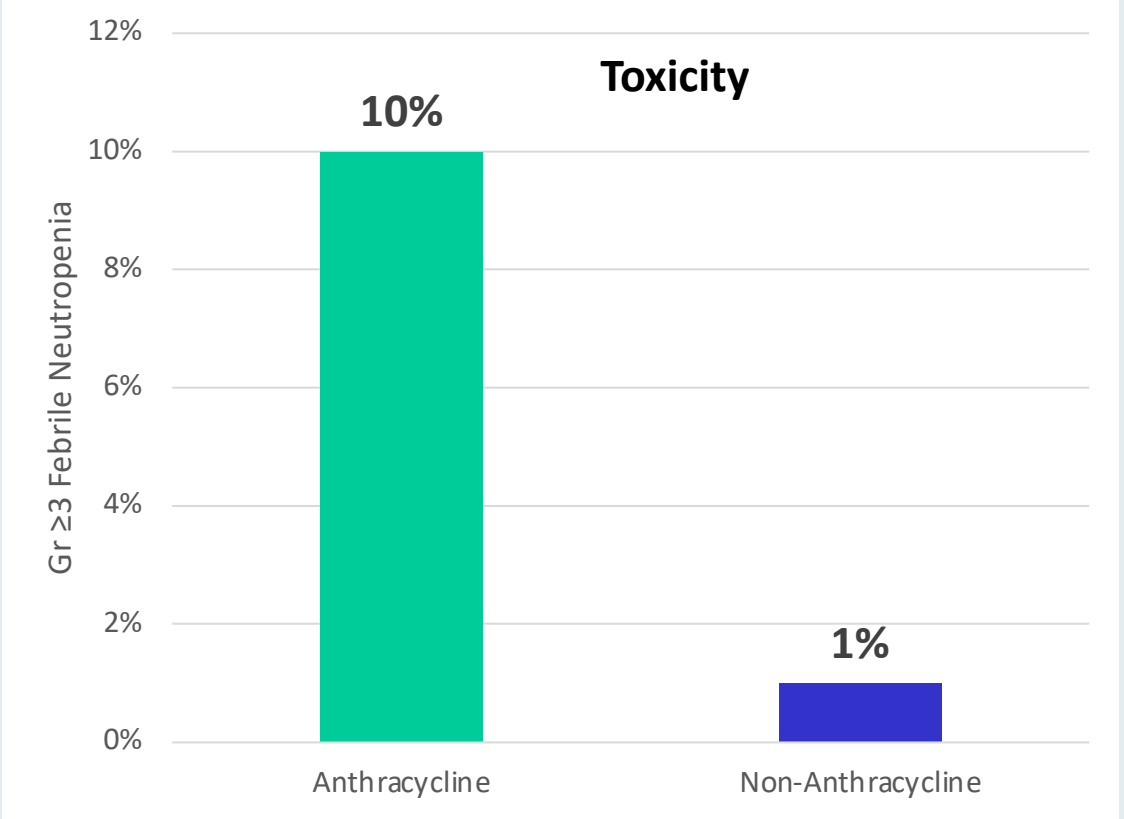
A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial

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

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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.

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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

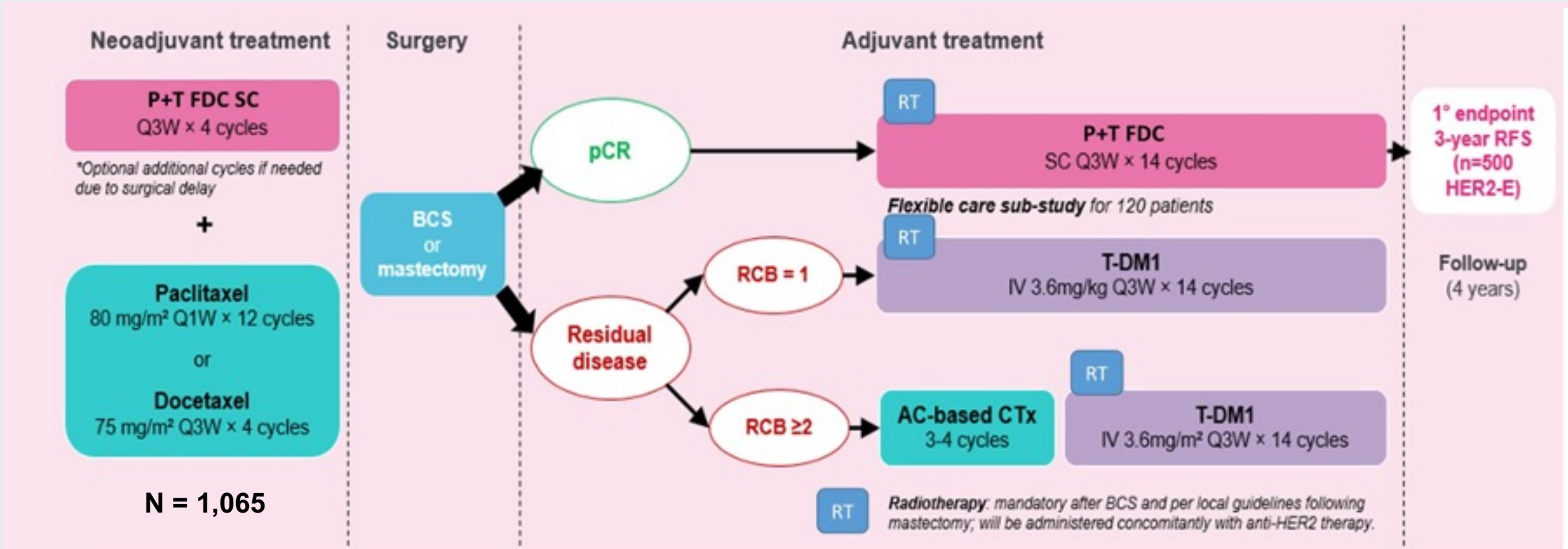
Trial identifier	Phase (N)	Setting	Regimens	Estimated completion date
CompassHER2 pCR (NCT04266249)	II (N = 2,156)	Neoadjuvant and adjuvant	• Preoperative chemotherapy + trastuzumab/pertuzumab • *If pCR* → postoperative trastuzumab/pertuzumab • *If residual disease* → postoperative T-DM1 or T-DM1 + tucatinib	2023
DESTINY-Breast05 (NCT04622319)	III (N = 1,600)	High risk, residual disease after neoadjuvant chemotherapy	• Trastuzumab deruxtecan (T-DXd) • T-DM1	2027
DESTINY-Breast11 (NCT05113251)	III (N = 624)	Neoadjuvant, high risk	• T-DXd • T-DXd → THP • 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 • Early HER2+ (IHC 3+ or FISH), HR- (ER<1% and PR<1%) per local assessment • Tumor size between 15 and 50mm • 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. • Short-and long-term safety of paclitaxel, docetaxel, P+T FDC SC, T-DM1.

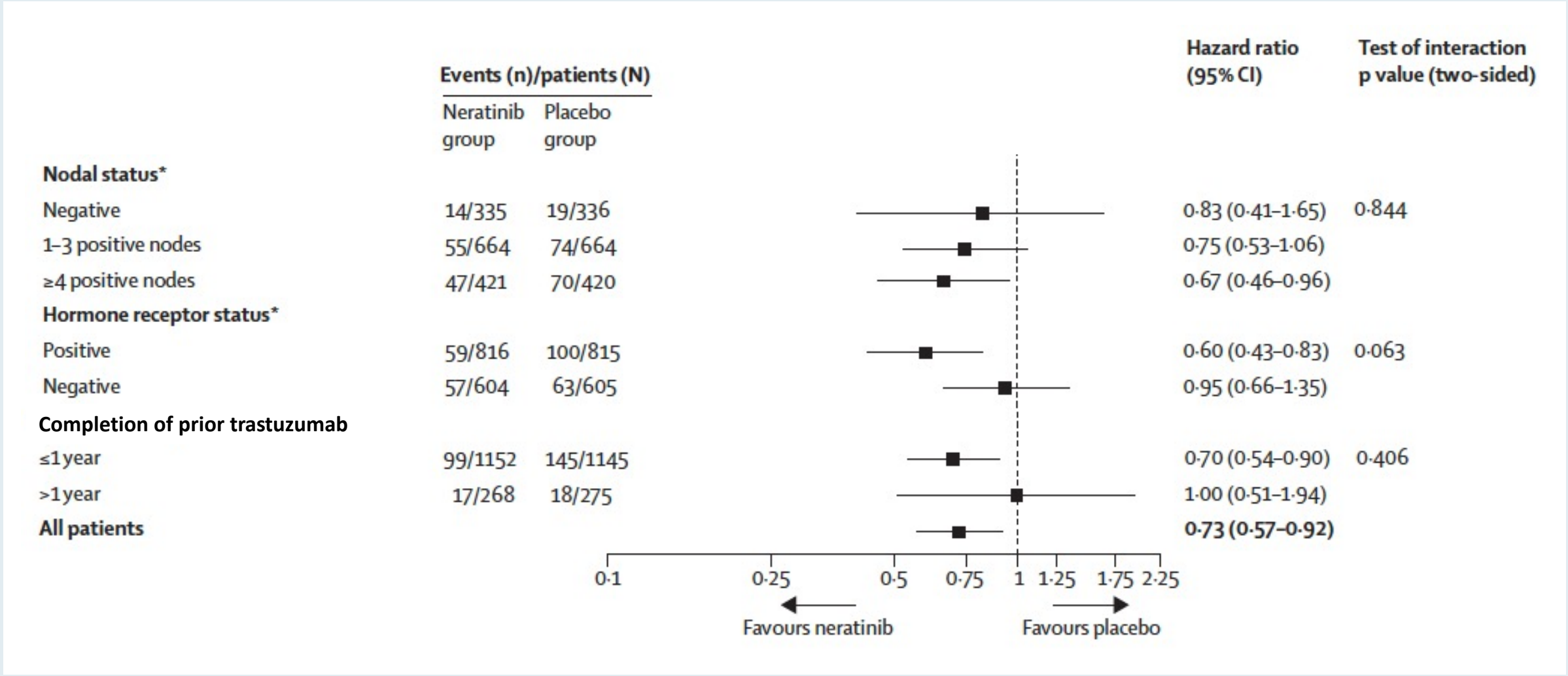
Debien V et al. ASCO 2022;Abstract TPS621.

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



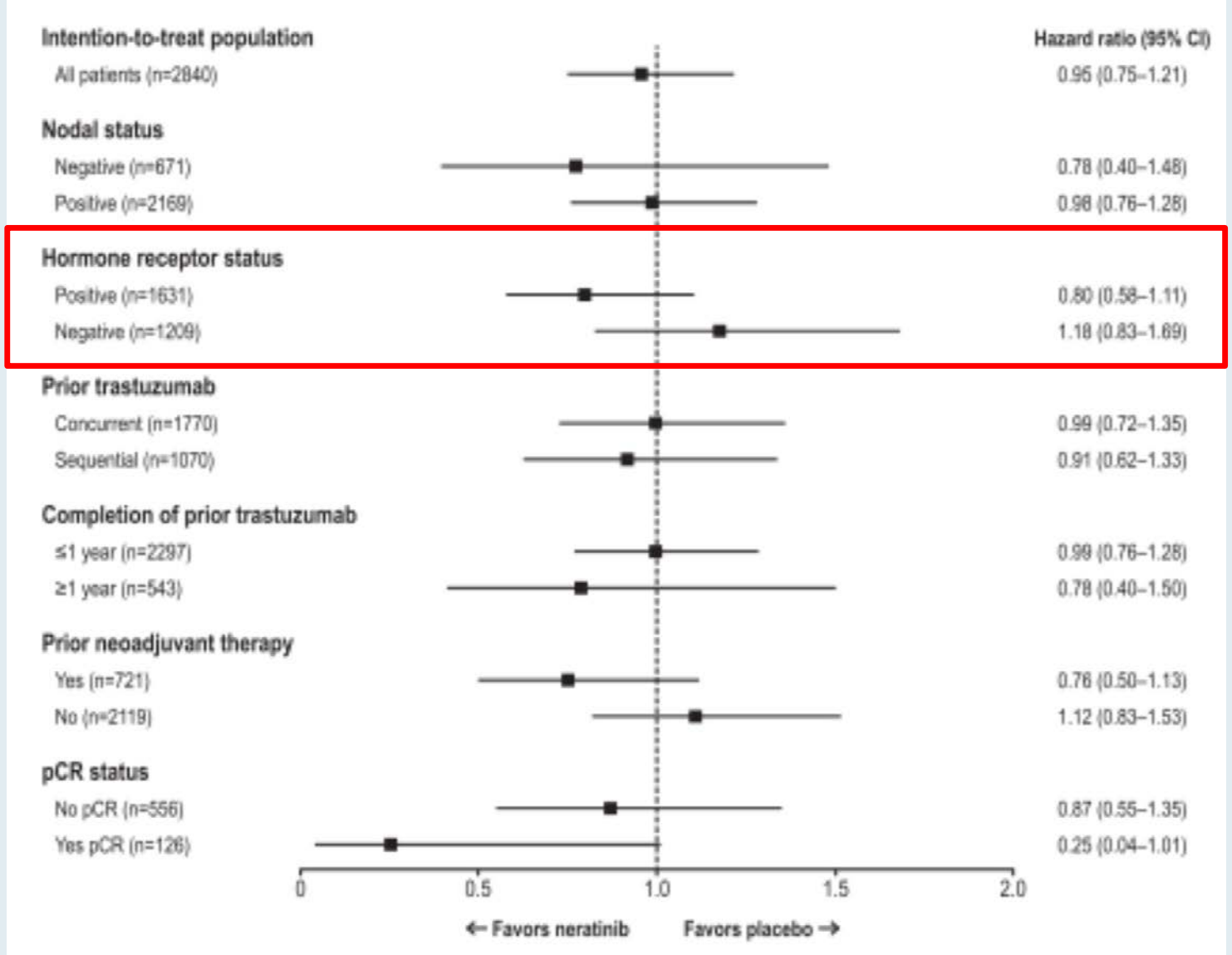
Martin M et al. *Lancet Oncol* 2017;18:1688-700.

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.

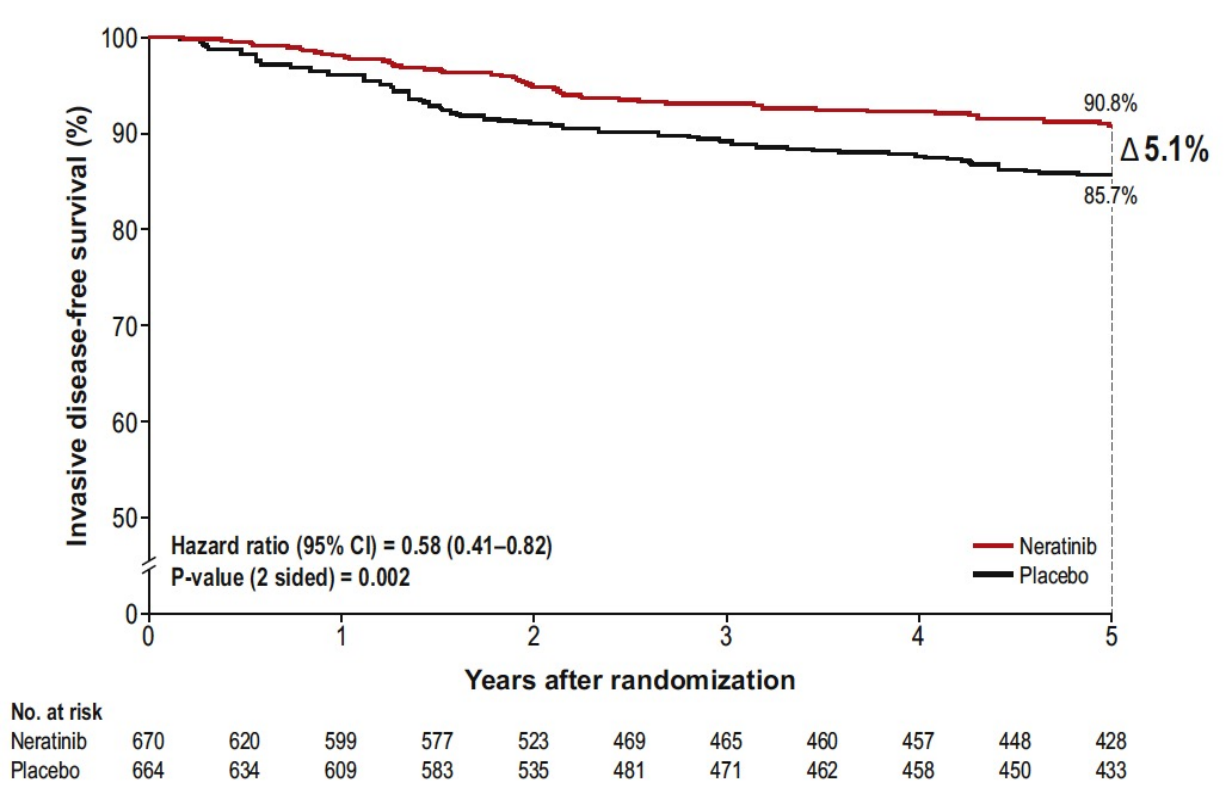
Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial

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

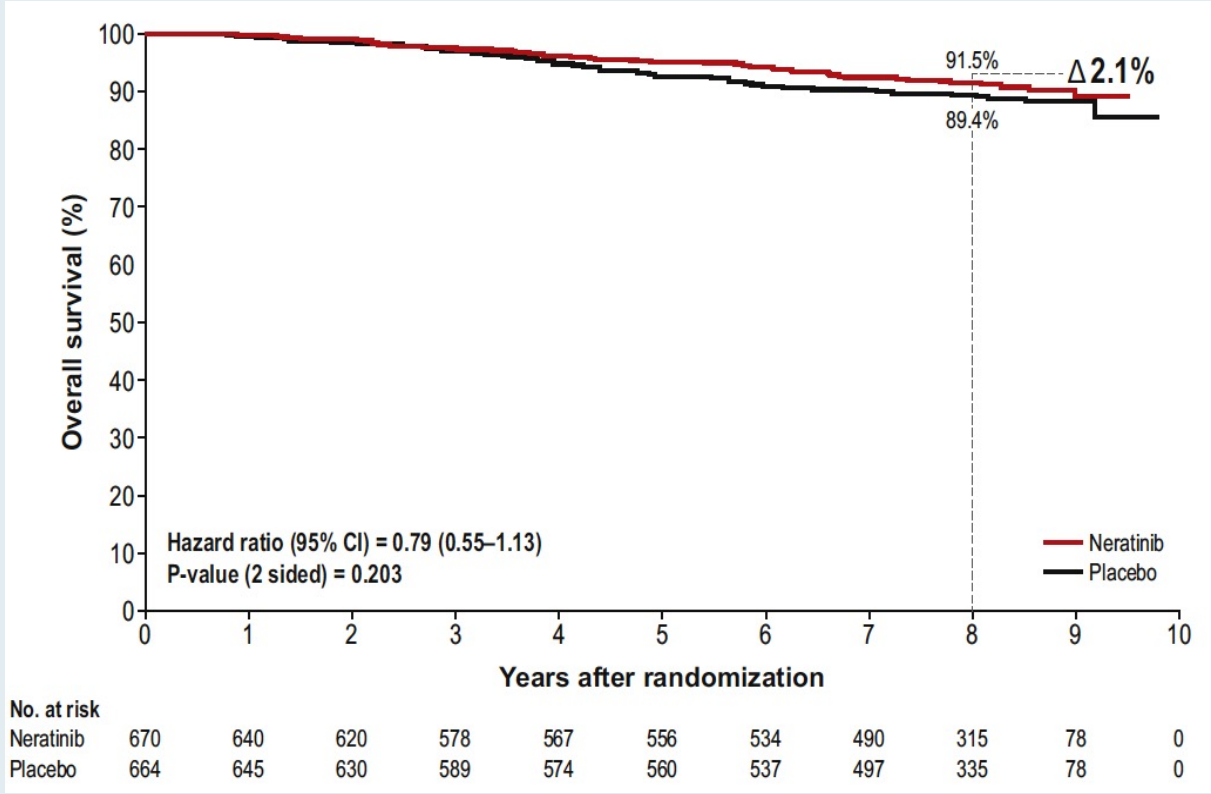
***Clin Breast Cancer* 2021;21(1):80-91.**

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

Invasive disease-free survival at 5 years



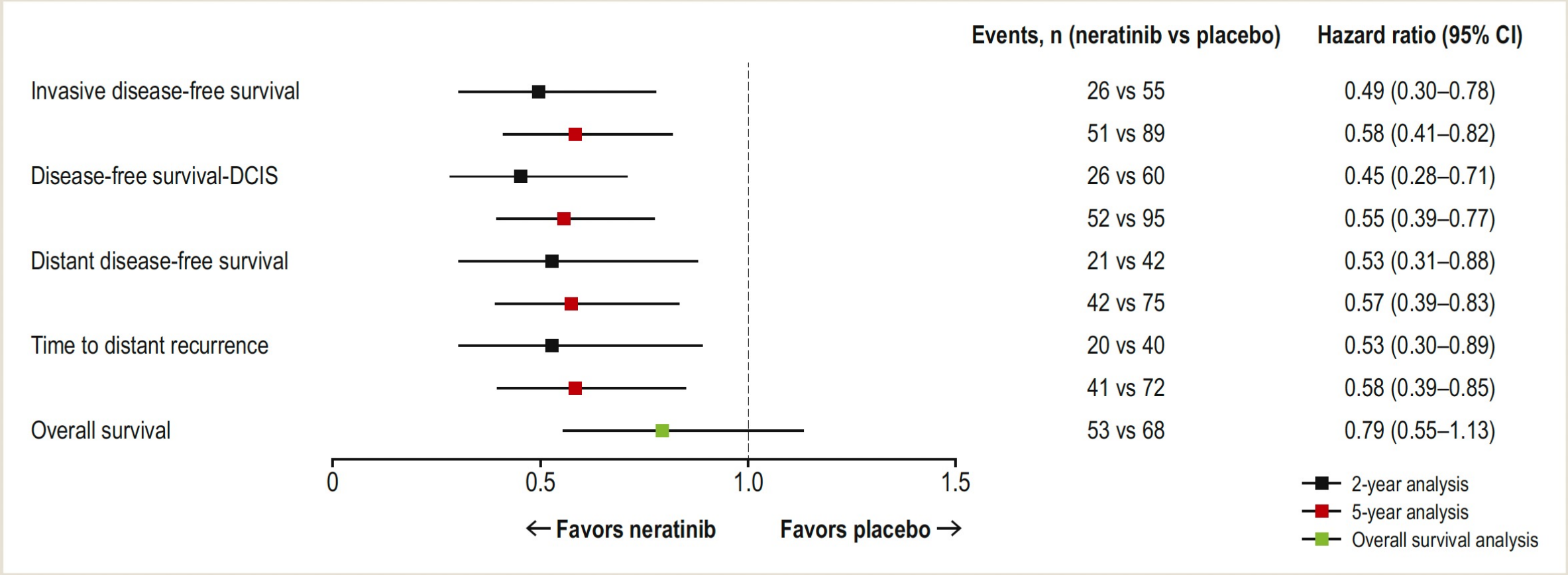
Overall survival at 8 years



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

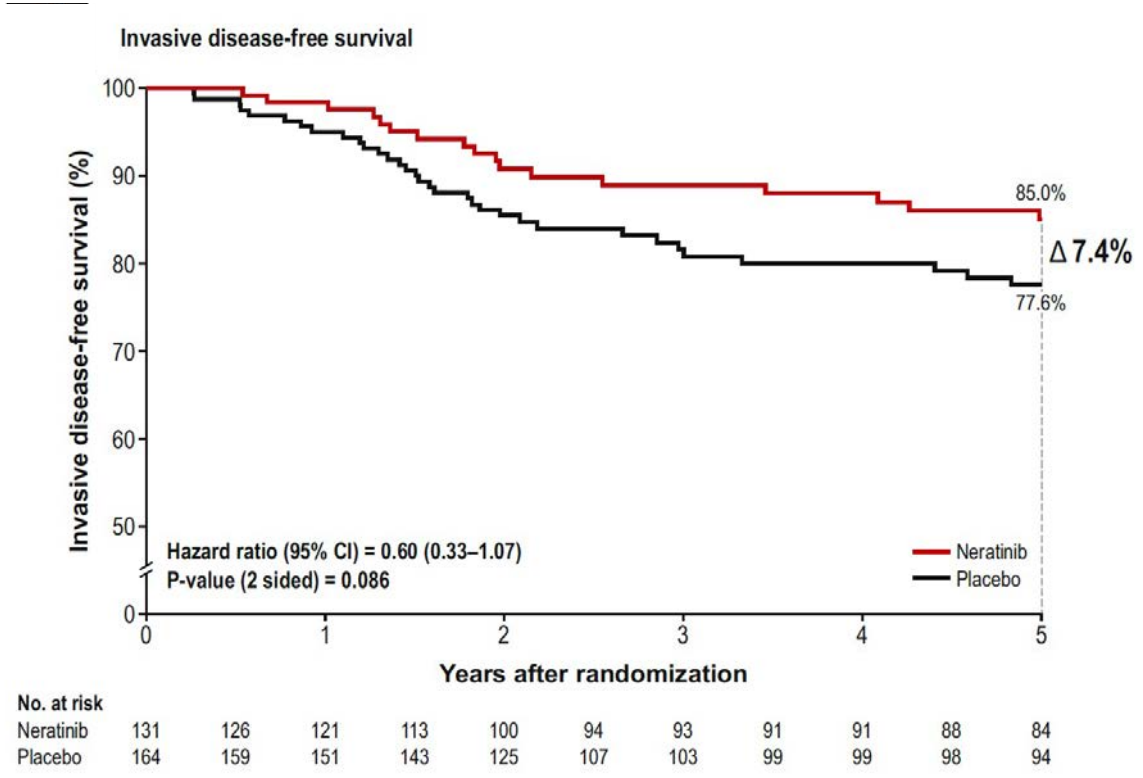
RTP RESEARCH TO PRACTICE

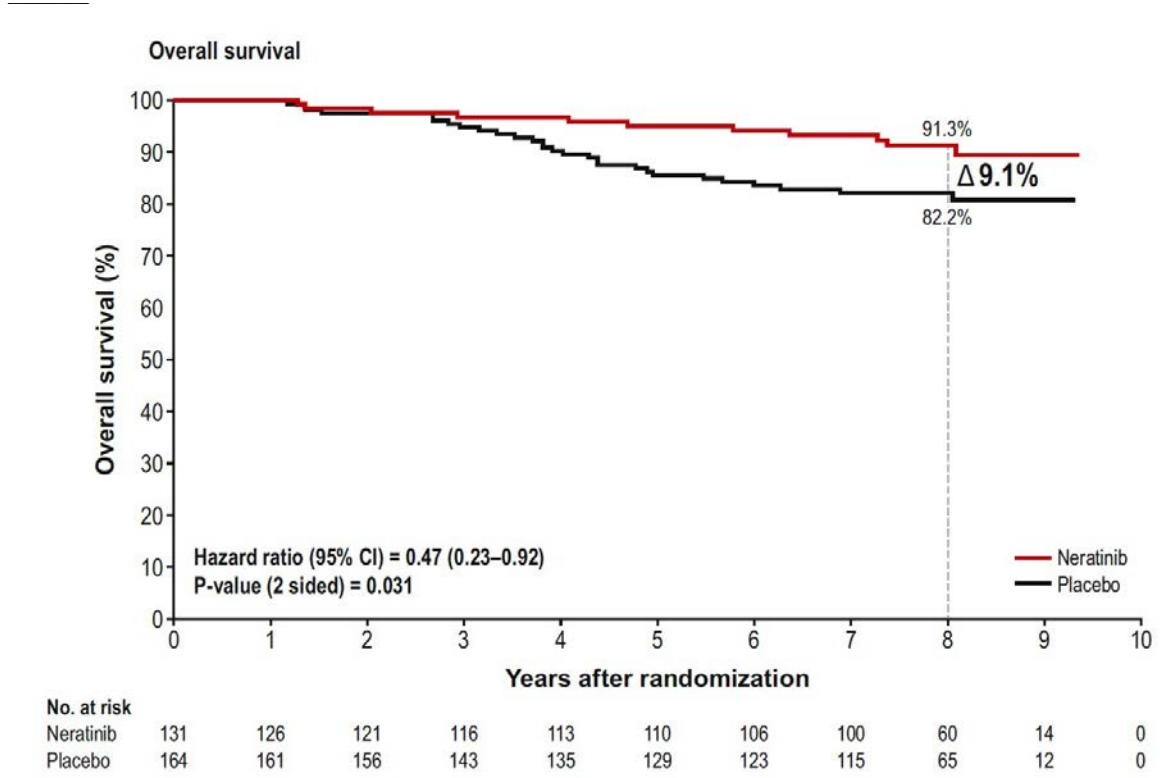
ExteNET: 2-Year, 5-Year and Overall Survival in HR+/≤1-Year Population (N = 1,334)



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.

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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)

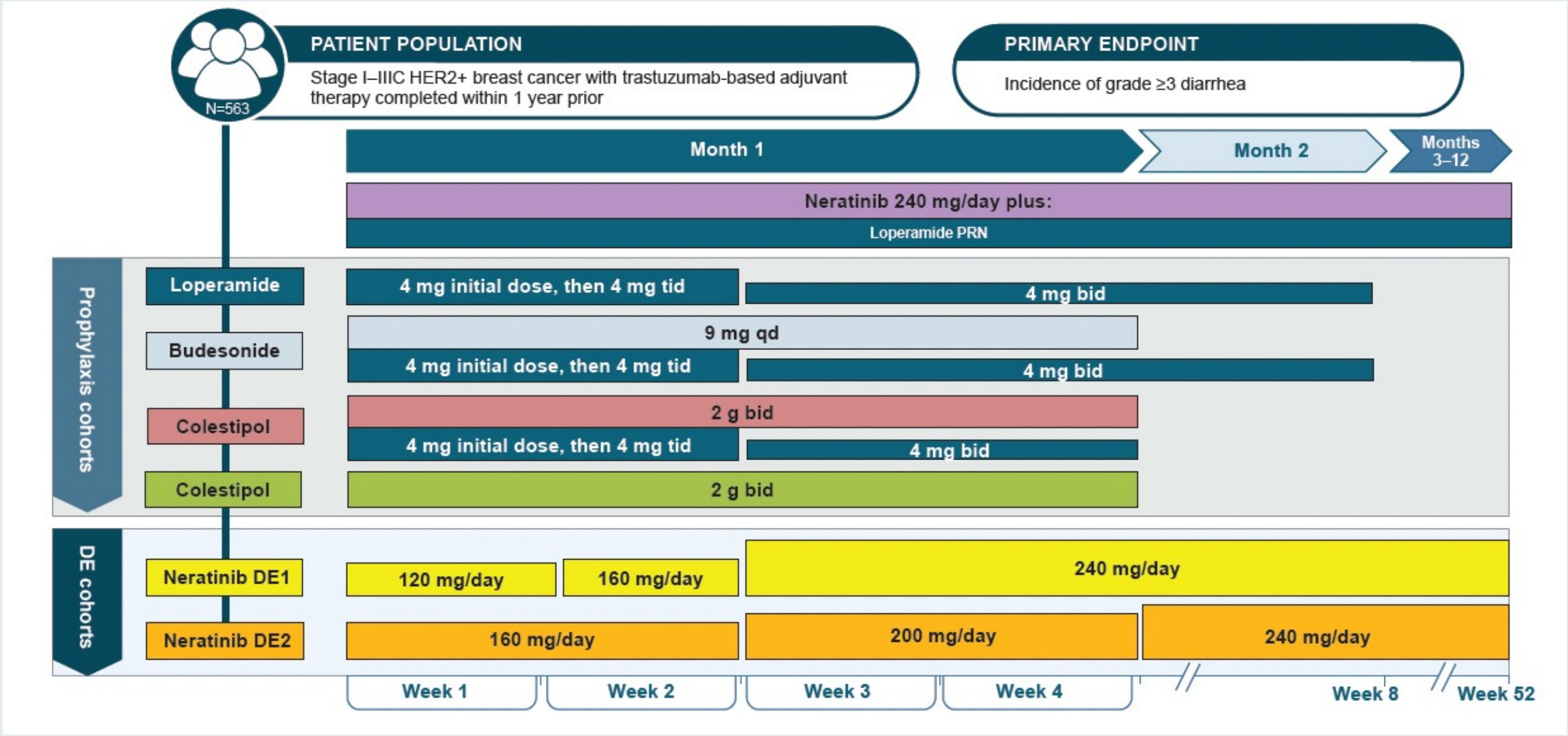
Moy B et al. ASCO 2021;Abstract 540.

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.

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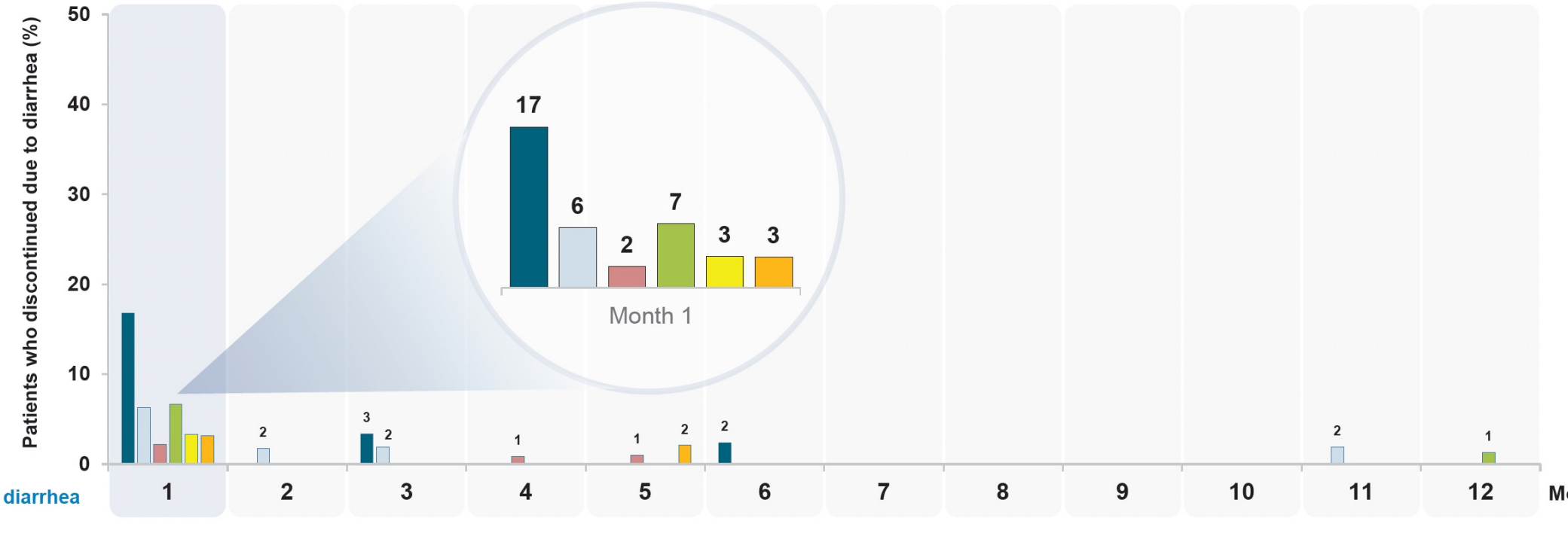
CONTROL: All Strategies Reduced the Rate of Discontinuation Due to Diarrhea



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.

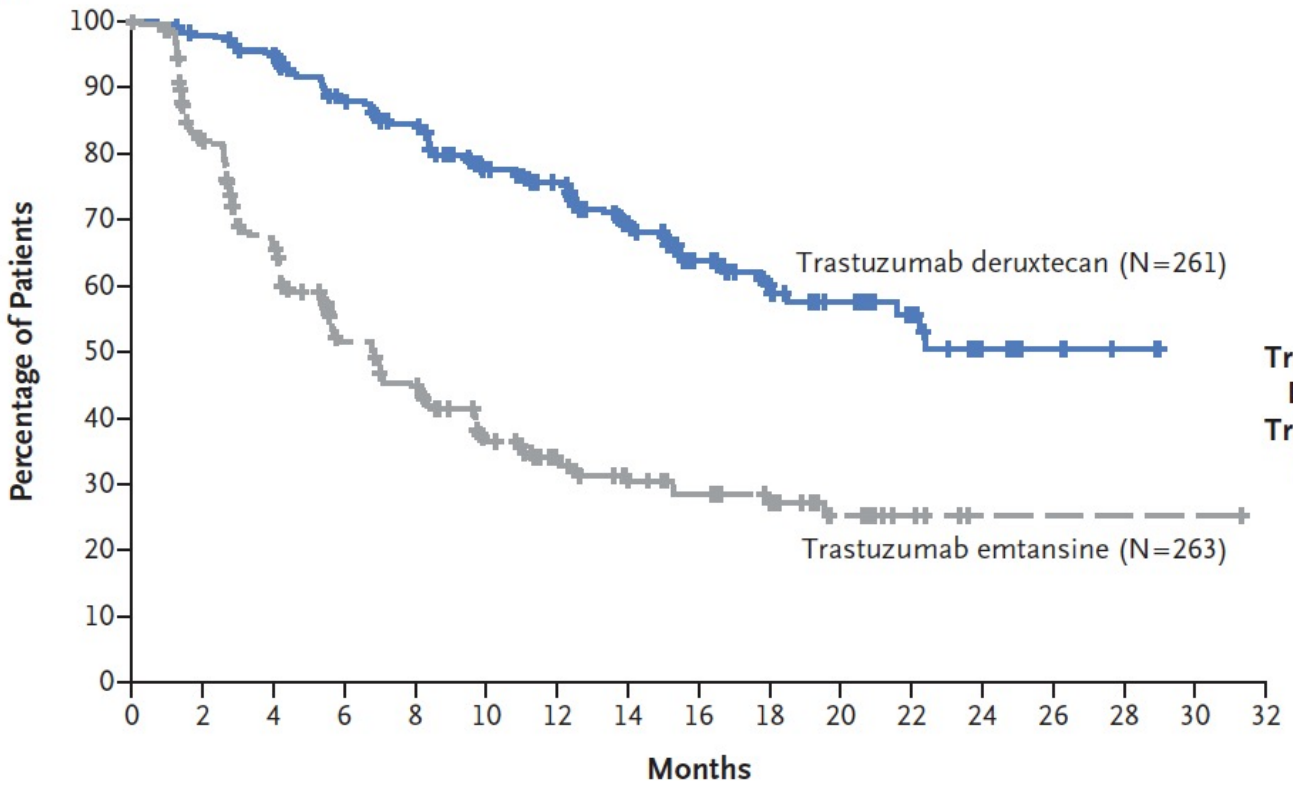
The NEW ENGLAND JOURNAL of MEDICINE

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

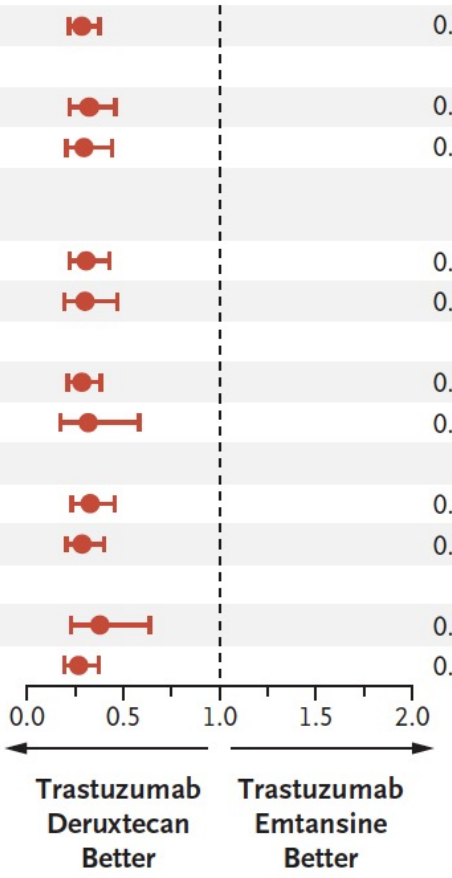
No. at Risk

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.

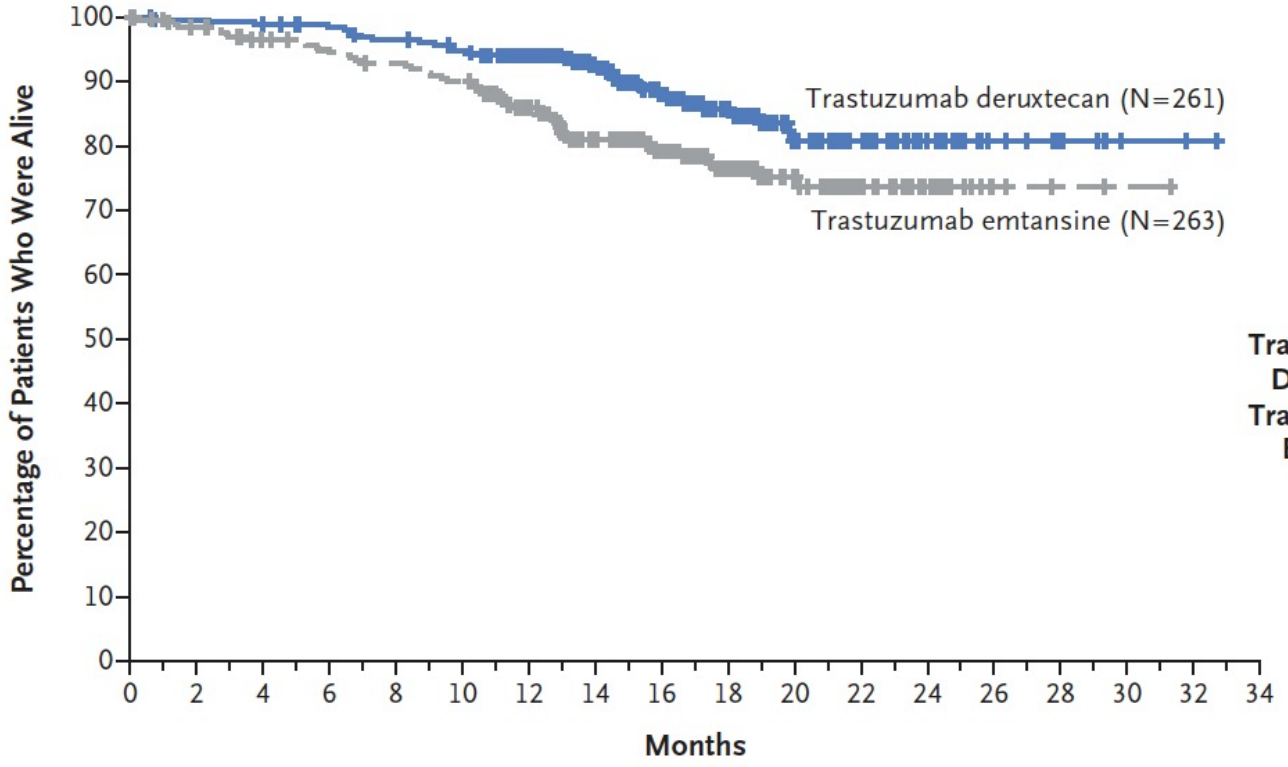
DESTINY-Breast03: Progression-Free Survival in Prespecified Subgroups

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

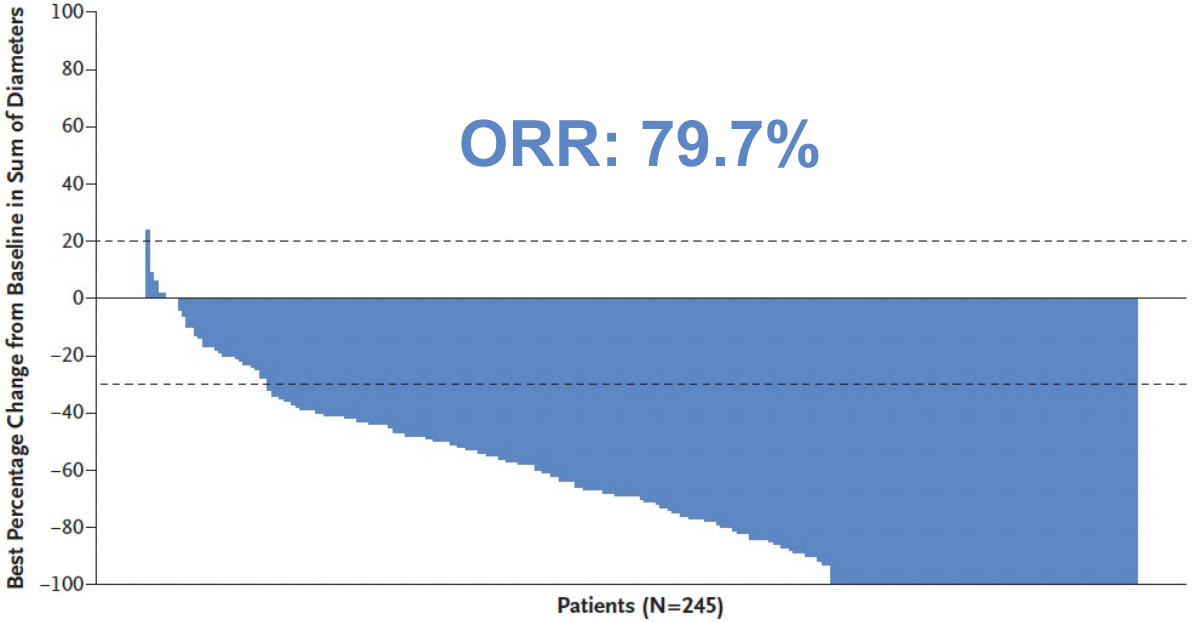
No. at Risk

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	

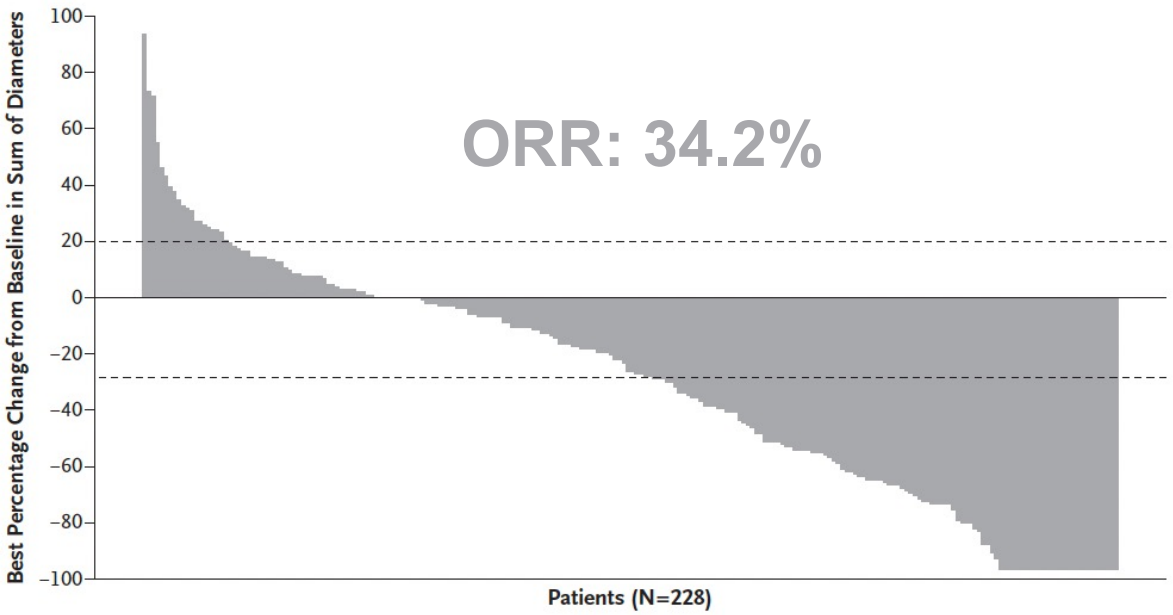
Cortés J et al. *N Engl J Med* 2022;386(12):1143-54.

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

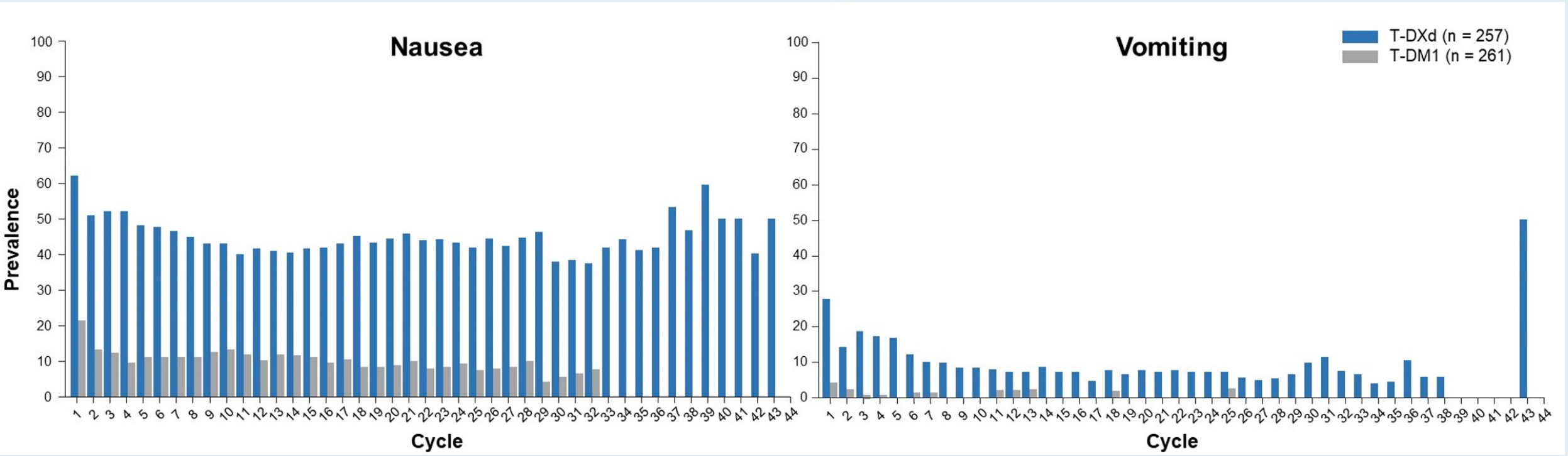
Median time to event, days	T-DXd n = 257	T-DM1 n = 261
TEAE associated with treatment discontinuation	224	147
TEAE associated with first dose reduction	96	19
Selected TEAEs		
Anemia	70.0	42.0
Lymphopenia	196.0	168.0
Thrombocytopenia	132.0	8.0
Fatigue	22.0	24.0
Leukopenia	74.5	92.0
Neutropenia[a]	64.0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

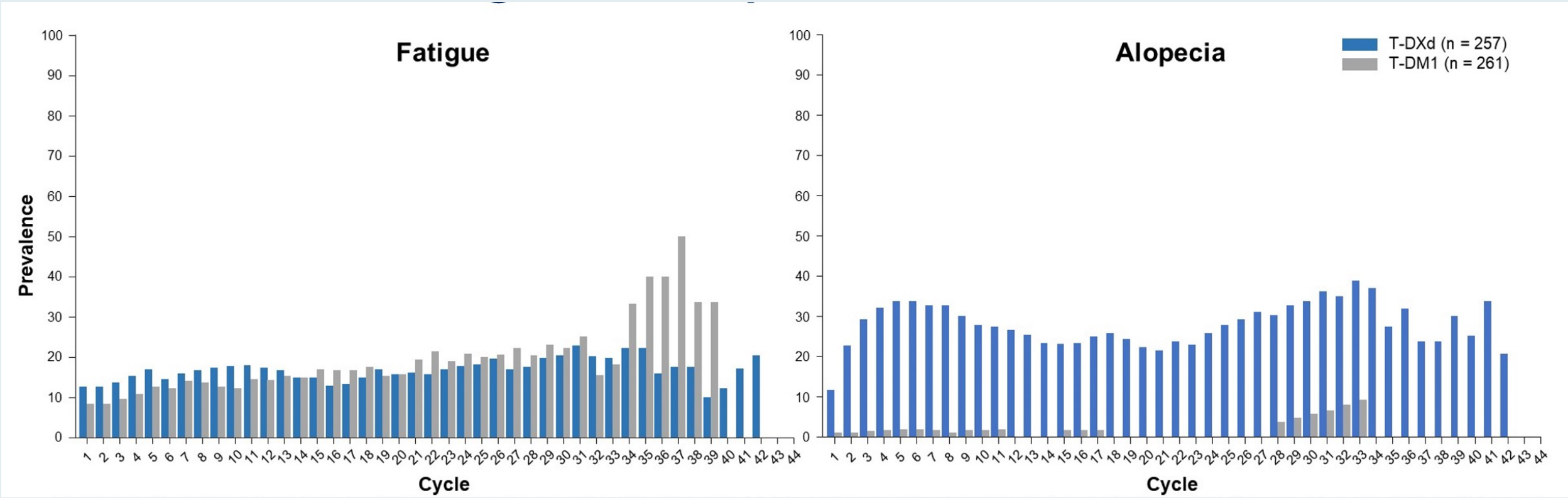
Hamilton E et al. ASCO 2022;Abstract 1000.

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

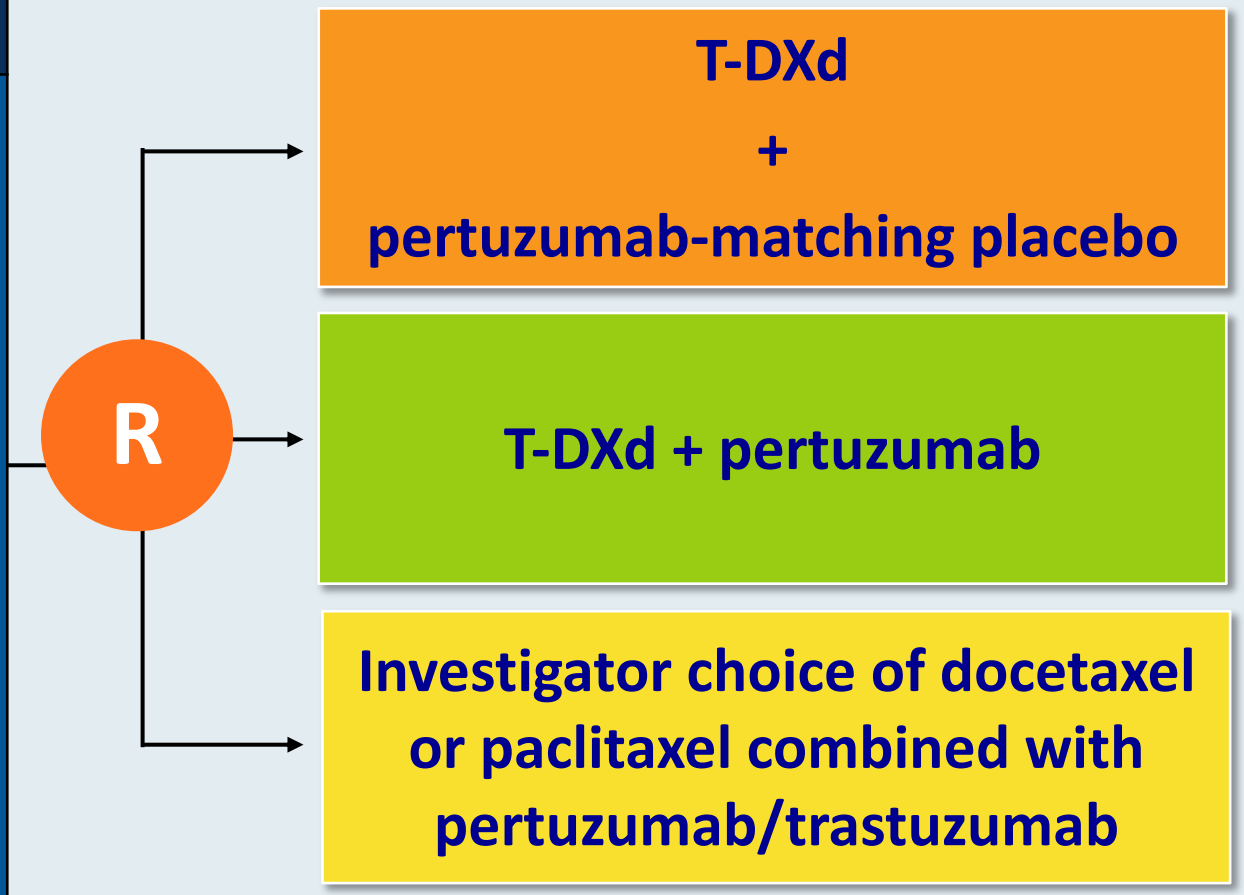
Estimated enrollment: N = 1,134

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.

HER2-Low Metastatic Breast Cancer

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

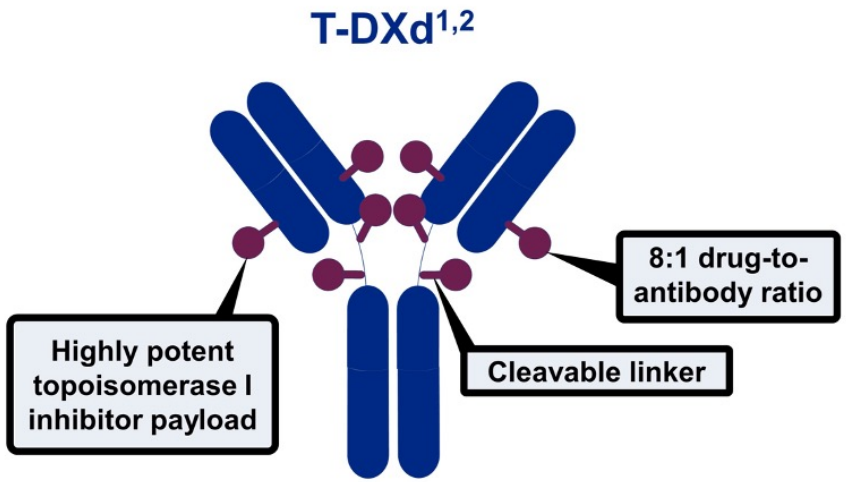
The NEW ENGLAND JOURNAL of MEDICINE

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

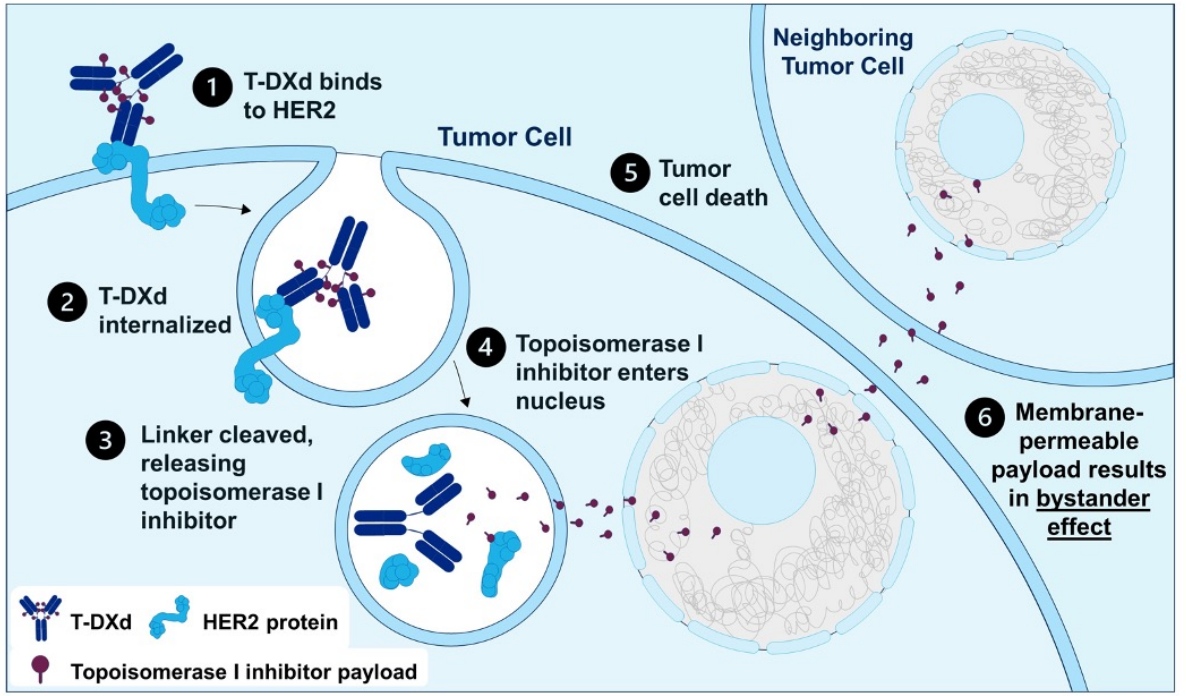
Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

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]

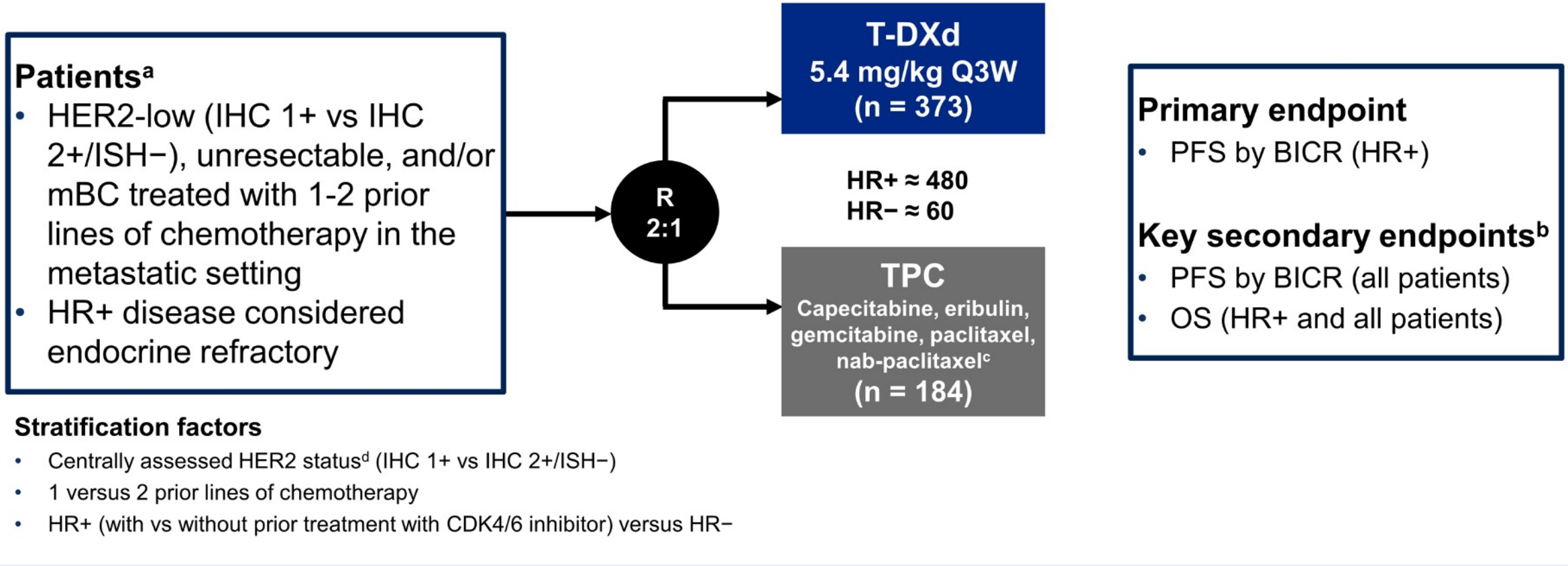


Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

- **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.

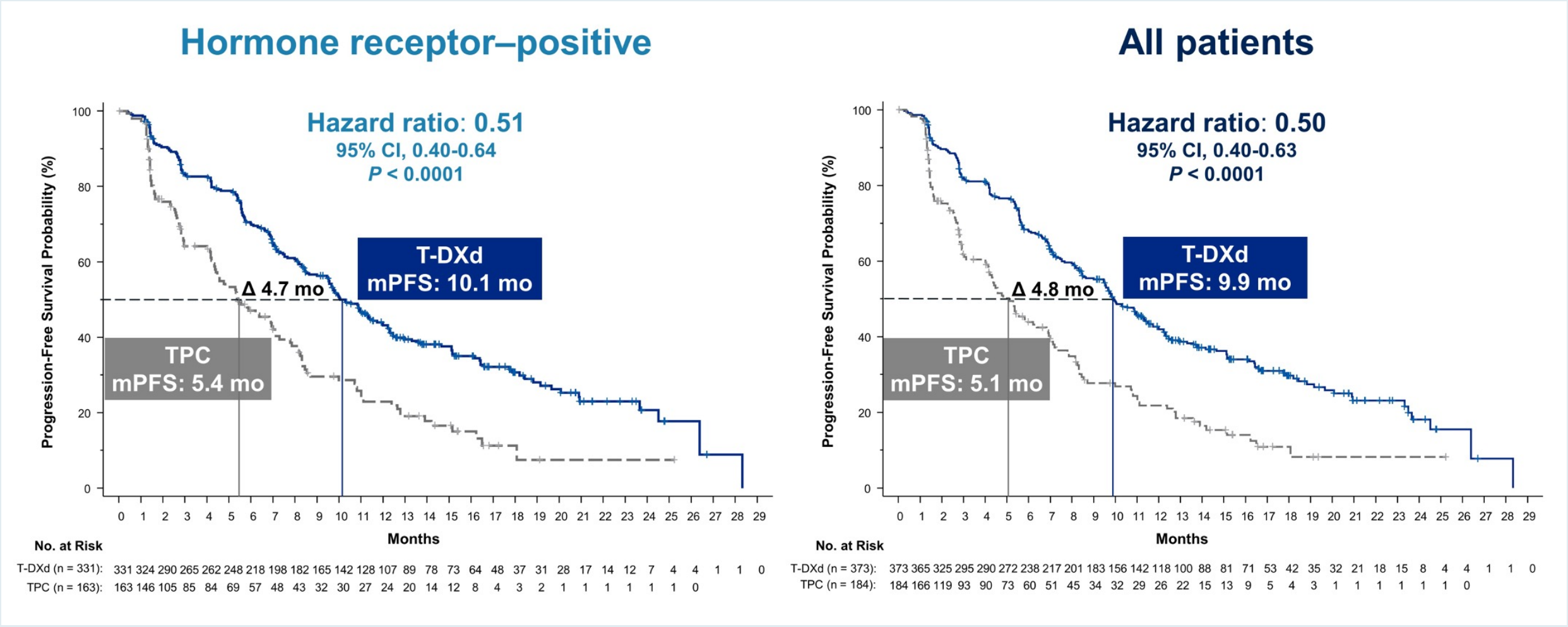
DESTINY-Breast04 Phase III Trial Schema



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.

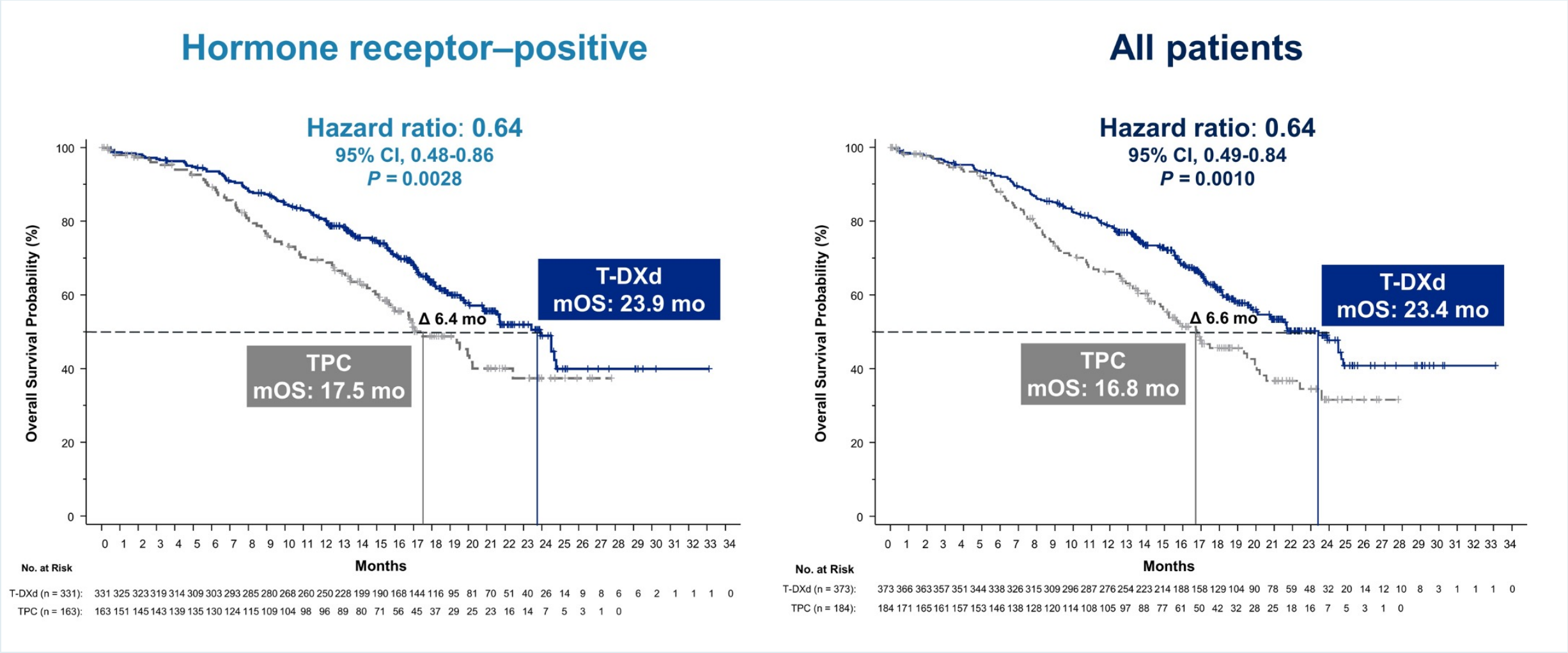
DESTINY-Breast04: PFS for HR-Positive (Primary Endpoint) and All Patients



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.

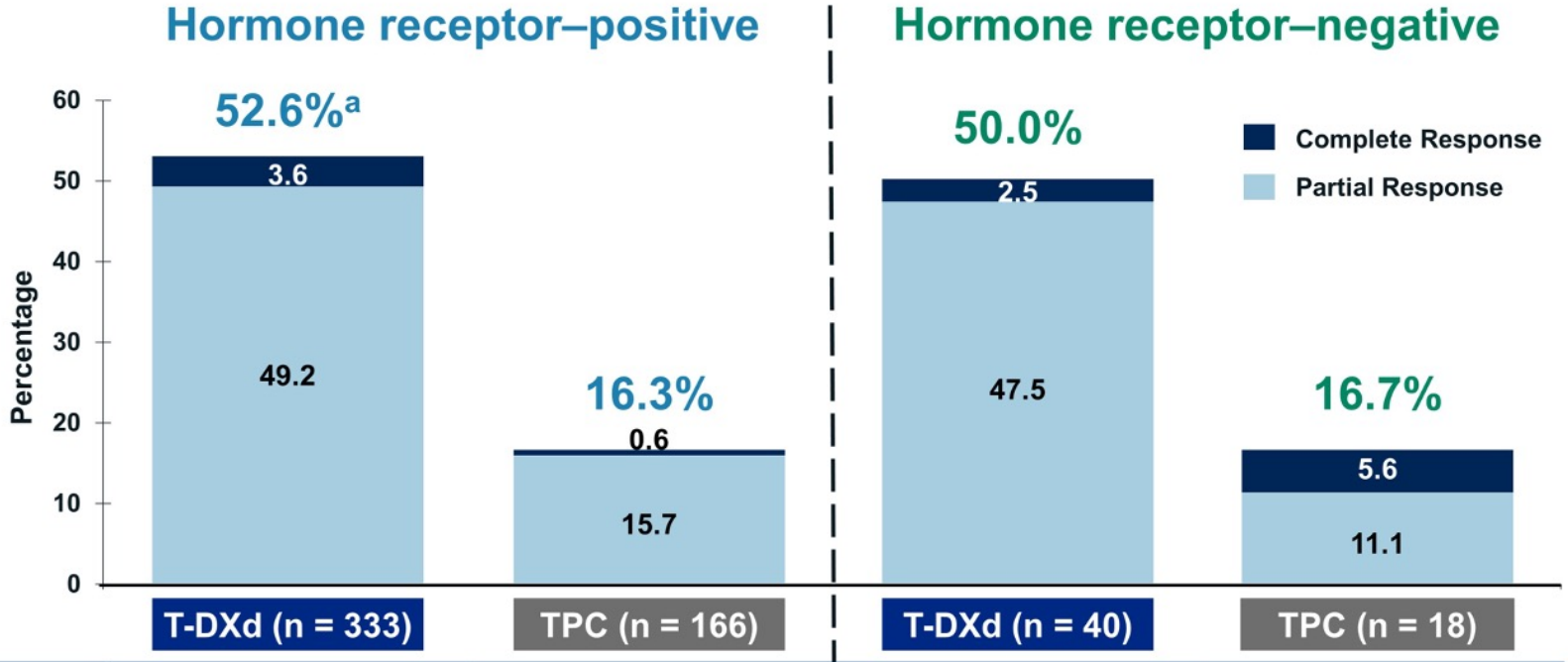
DESTINY-Breast04: OS for HR-Positive and All Patients



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.

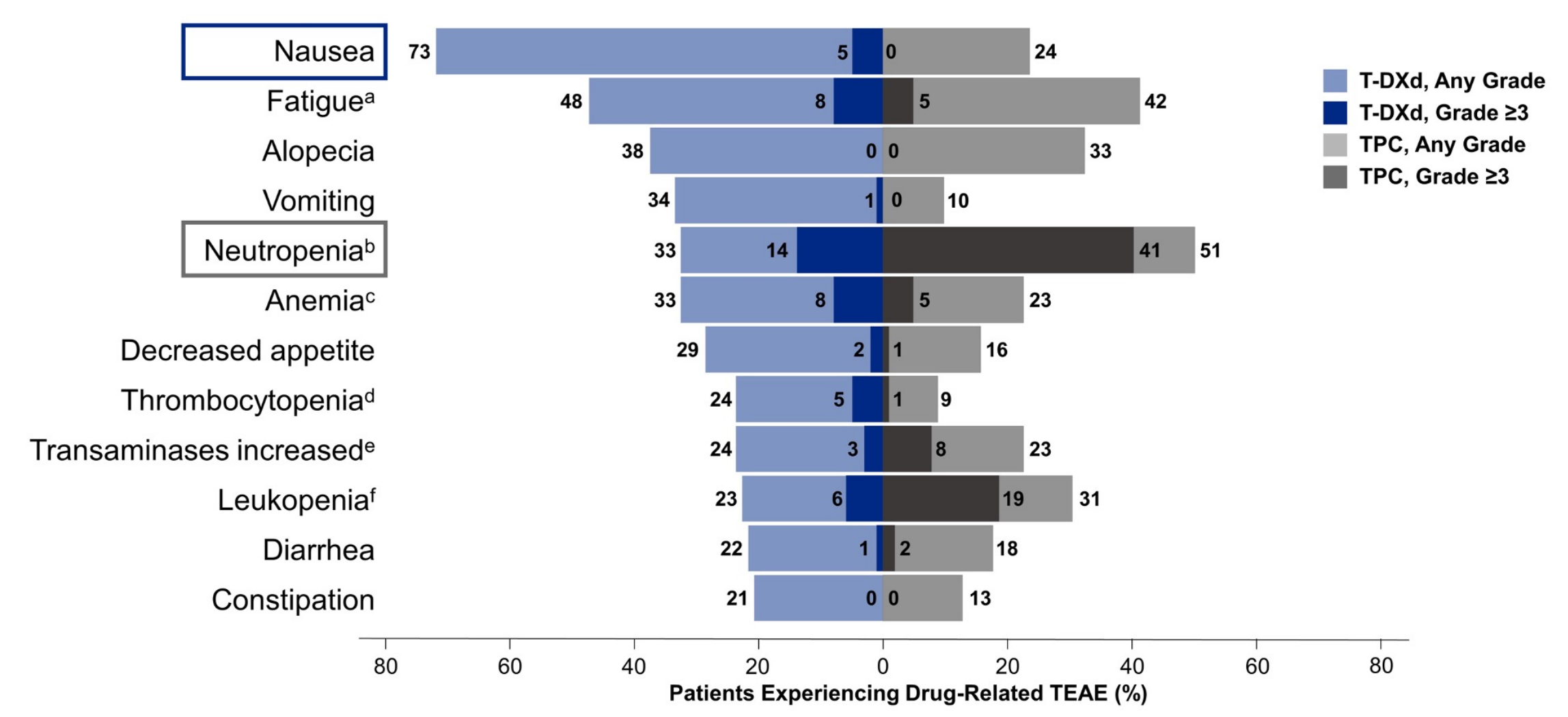
DESTINY-Breast04: Confirmed Objective Response Rate



	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

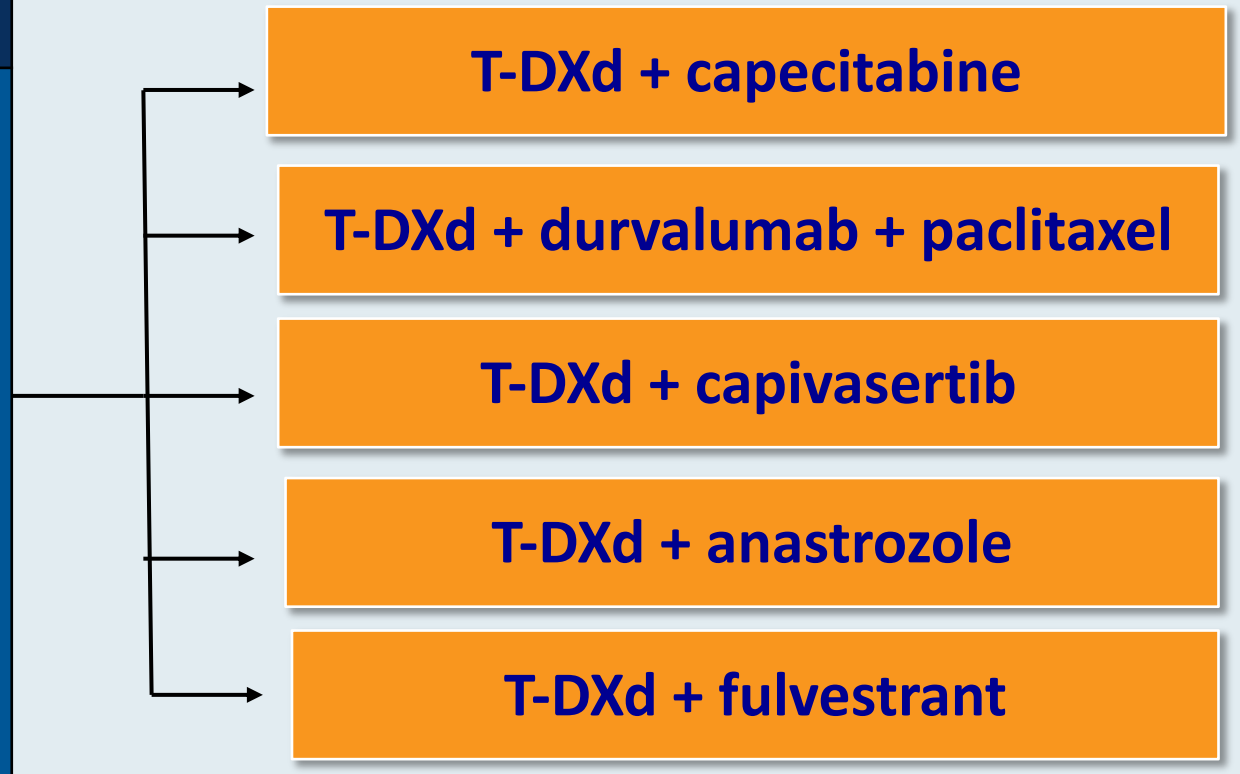
Primary endpoint: PFS in HR-positive, HER2-low population

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.

PARIS 2022 ESMO congress

Sacituzumab govitecan efficacy in HR+/HER2– metastatic breast cancer by HER2 immunohistochemistry status in the phase 3 TROPiCS-02 study

Peter Schmid,[1] Javier Cortes,[2] Frederik Marmé,[3] Hope S. Rugo,[4] Sara M. Tolaney,[5] Mafalda Oliveira,[6] Delphine Loirat,[7] Komal Jhaveri,[8] Oh Kyu Yoon,[9] Monica Motwani,[9] Hao Wang,[9] Rosemary Delaney,[10] Aditya Bardia[11]

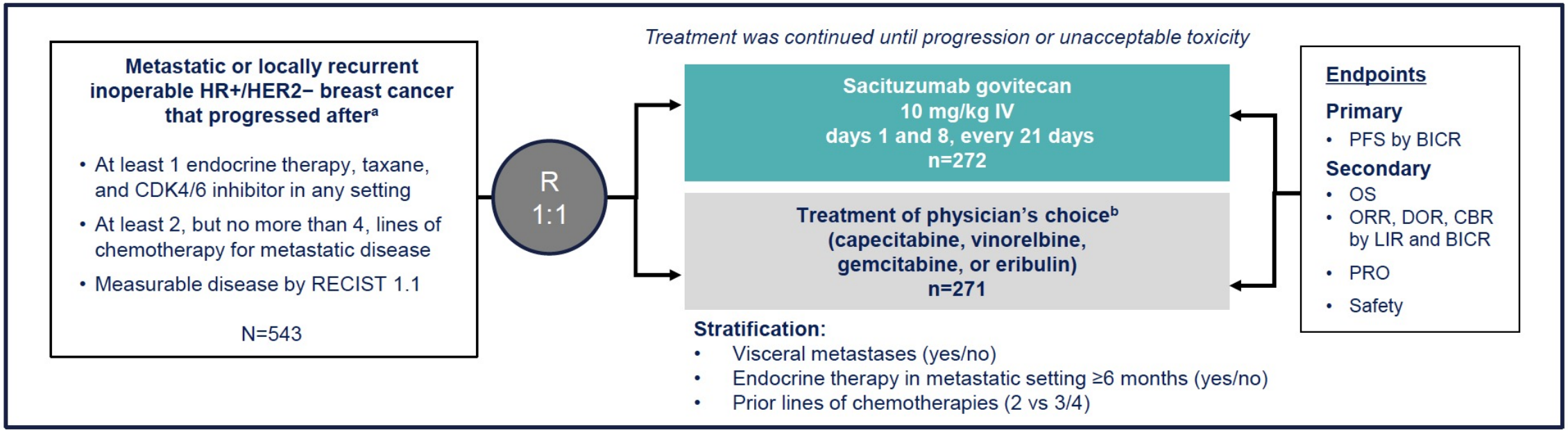
[1]Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; [2]International Breast Cancer Center (IBCC), Quiron Group, Madrid & Barcelona, Spain; [3]Heidelberg University, University Hospital Mannheim, Heidelberg, Germany; [4]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Institut Curie, Paris, France; [8]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [9]Gilead Sciences, Inc, Foster City, CA, USA; [10]Gilead Sciences, Inc, Morris Plains, NJ, USA; [11]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA

Presenter: Dr. Frederik Marmé

Saturday, September 10, 15:40 - 15:45
FPN 214MO

RTP RESEARCH TO PRACTICE

Phase III TROPiCS-02 Trial Schema and Post Hoc Analysis



- For this post hoc subgroup analysis, local IHC and ISH results for the ITT population of TROPiCS-02 were analyzed retrospectively to determine SG efficacy by HER2 IHC status:
  - 52% were HER2-Low (IHC1+, IHC2+ [ISH-negative/unverified[c]]): N=283 (SG, n=149; TPC, n=134)
  - 40% were HER2 IHC0: N=217 (SG, n=101; TPC, n=116)
  - 8% were excluded from the analysis due to missing HER2 IHC status: N=43 (SG, n=22; TPC, n=21)

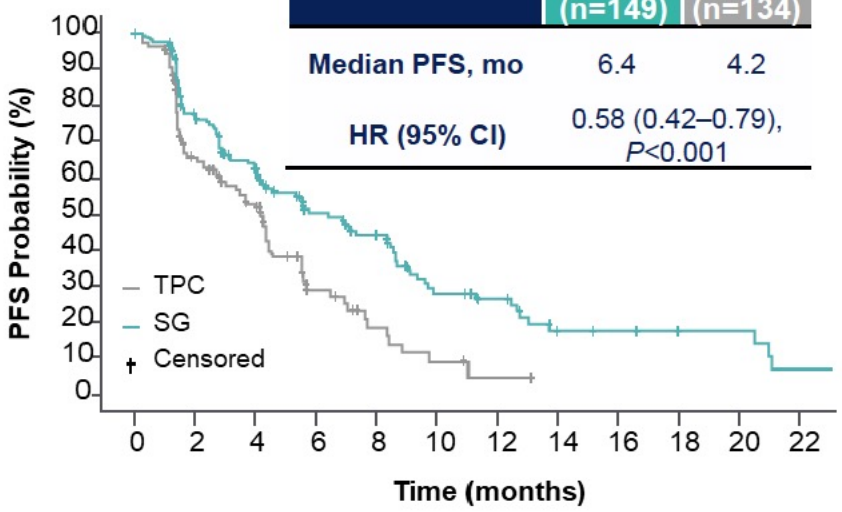
[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [c]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-Low, consistent with the trial eligibility criteria to enroll HER2-negative patients. A separate sensitivity analysis excluding the 39 ISH-unverified patients was also performed, with consistent results.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; SG, sacituzumab govitecan; Trop-2, trophoblast cell surface antigen 2.
1. Rugo HS,et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Marmé F et al. ESMO 2022;Abstract 214MO.

TROPiCS-02: Post Hoc Analysis of PFS with Sacituzumab Govitecan in HER2-Low Subgroup

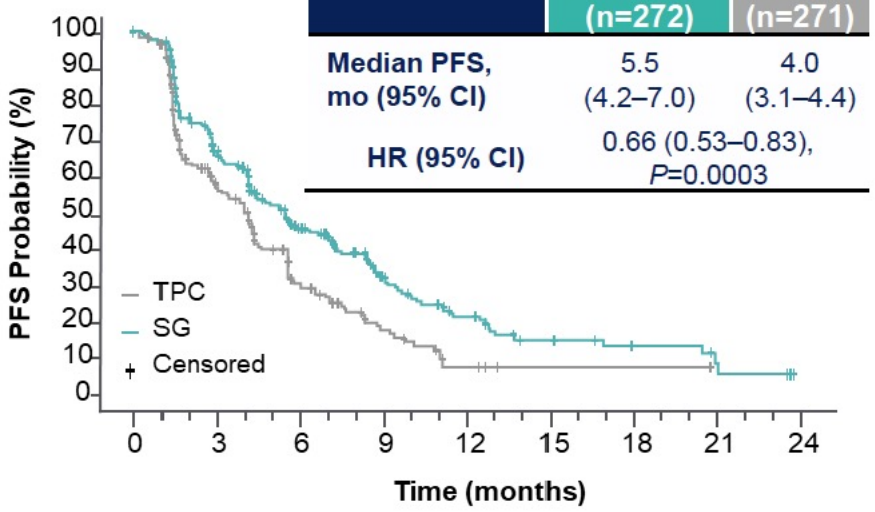
HER2-Low[a]

	SG (n=149)	TPC (n=134)
Median PFS, mo	6.4	4.2
HR (95% CI)	0.58 (0.42–0.79), *P*<0.001	



ITT[1]

	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
HR (95% CI)	0.66 (0.53–0.83), *P*=0.0003	



- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

Marmé F et al. ESMO 2022;Abstract 214MO.

TROPiCS-02: Post Hoc Analysis of Overall Response with Sacituzumab Govitecan by HER2 Status

	HER2-Low[a]		HER2 IHC0		ITT[1]	
	SG (n=149)	TPC (n=134)	SG (n=101)	TPC (n=116)	SG (n=272)	TPC (n=271)
ORR, n (%)	38 (26)	16 (12)	16 (16)	17 (15)	57 (21)	38 (14)
Odds ratio (95% CI)	2.52 (1.33-4.78)		1.10 (0.52-2.30)		1.63 (1.04-2.55)	
Best overall response, n (%)						
CR	2 (1)	0	0	0	2 (1)	0
PR	36 (24)	16 (12)	16 (16)	17 (15)	55 (20)	38 (14)
SD	73 (49)	61 (46)	56 (55)	39 (34)	142 (52)	106 (39)
SD ≥6 mo	18 (12)	10 (7)	15 (15)	8 (7)	35 (13)	21 (8)
PD	29 (19)	36 (27)	23 (23)	38 (33)	58 (21)	76 (28)
NE	9 (6)	21 (16)	6 (6)	22 (19)	15 (6)	51 (19)
CBR, n (%)	56 (38)	26 (19)	31 (31)	25 (22)	92 (34)	59 (22)
Odds ratio (95% CI)	2.50 (1.46-4.30)		1.61 (0.87-2.97)		1.84 (1.25-2.69)	
Median DOR, mo (95% CI)	7.4 (5.8-8.9)	4.1 (2.8-6.1)	8.1 (4.1-NE)	6.1 (2.8-8.3)	7.4 (6.5-8.6)	5.6 (3.8-7.9)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
CBR, clinical benefit rate; CR, complete response; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Marmé F et al. ESMO 2022;Abstract 214MO.

TROPiCS-02: Safety Summary with Sacituzumab Govitecan by HER2 Status

	HER2-Low[a]		HER2 IHC0		Overall Safety Population[1]	
	SG (n=147)	TPC (n=124)	SG (n=99)	TPC (n=107)	SG (n=268)	TPC (n=249)
Grade ≥3 TEAE	109 (74)	73 (59)	70 (71)	66 (62)	198 (74)	149 (60)
TEAEs leading to treatment discontinuation	9 (6)	2 (2)	7 (7)	8 (7)	17 (6)	11 (4)
TEAEs leading to dose delay	98 (67)	44 (35)	61 (62)	56 (52)	178 (66)	109 (44)
TEAEs leading to dose reductions	54 (37)	37 (30)	26 (26)	37 (35)	89 (33)	82 (33)
TE SAEs	38 (26)	25 (20)	33 (33)	15 (14)	74 (28)	47 (19)
TEAEs leading to death[b]	3 (2)	0	3 (3)	0	6 (2)	0
Treatment-related	1 (1)	0	0	0	1 (<1)	0

- The safety profile of SG in the HER2-Low and HER2 IHC0 groups were generally consistent with that of the overall TROPiCS-02 safety population

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date. Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than one event per preferred term.
[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified. [b]Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic shock due to neutropenic colitis). The other 5 were: COVID-19 pneumonia, pulmonary embolism, pulmonary sepsis, nervous system disorder, and arrhythmia. Upon detailed review of the TEAEs leading to death, no patterns were identified.
AE, adverse event; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; TE, treatment-emergent; TEAE, treatment-emergent adverse event; SAE, serious adverse event; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Marmé F et al. ESMO 2022;Abstract 214MO.

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

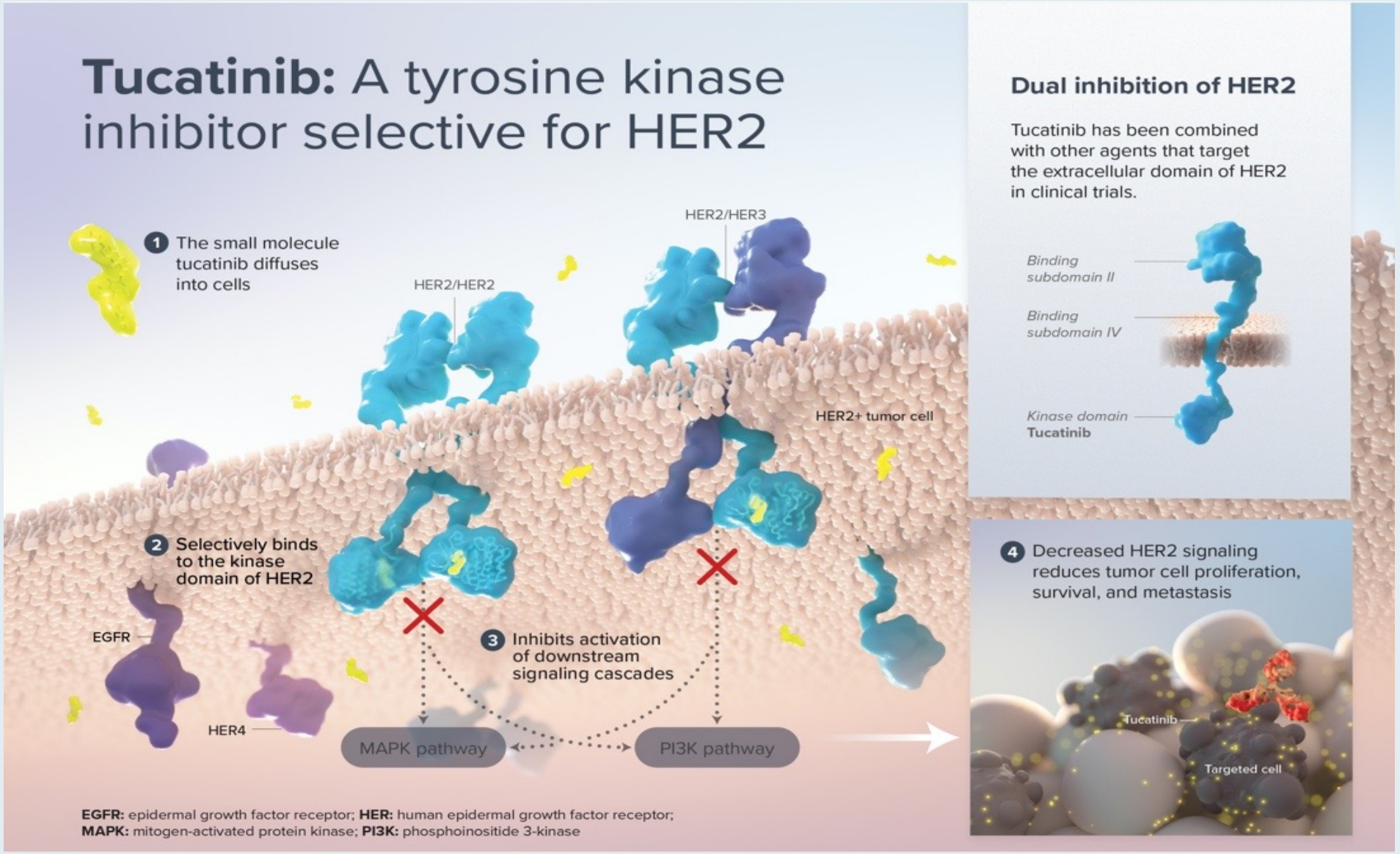
ORIGINAL ARTICLE

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

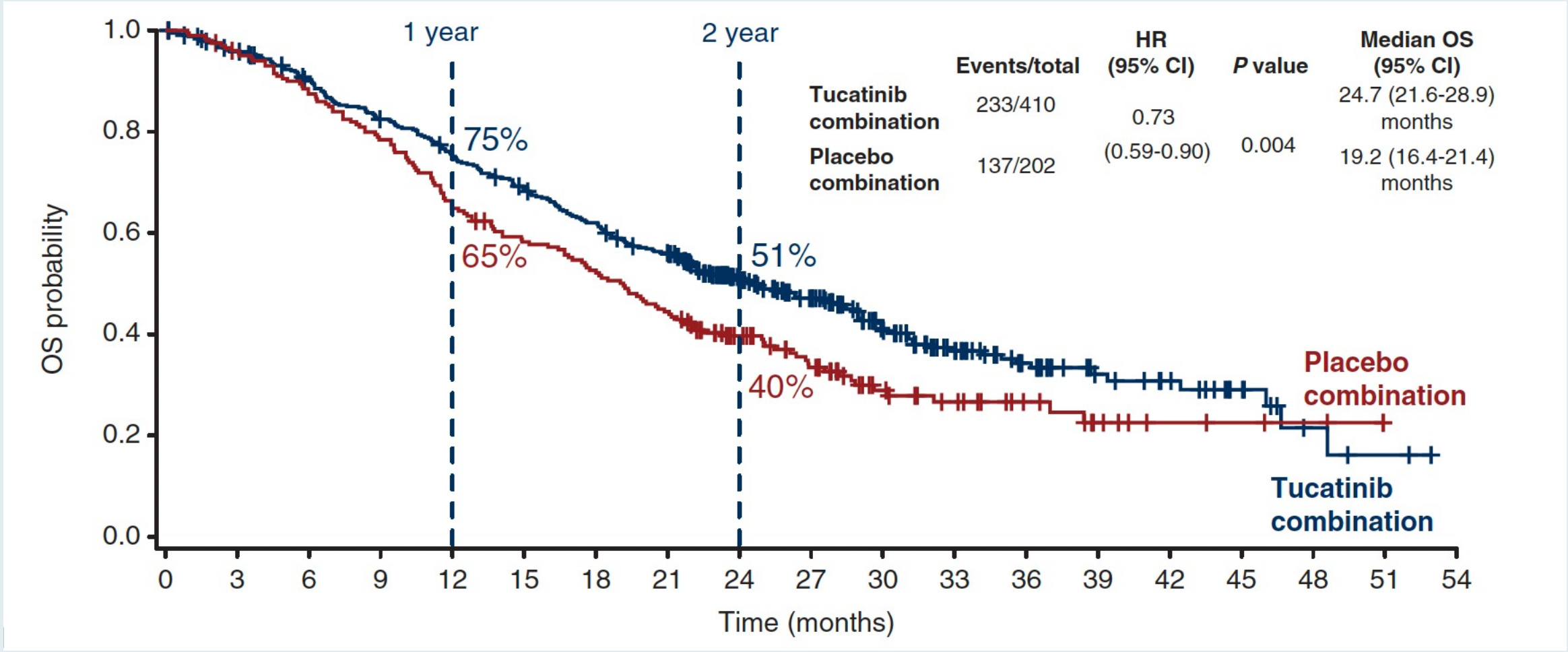
Tucatinib Mechanism of Action



www.seagen.com/science/pipeline/tucatinib

RTP RESEARCH TO PRACTICE

HER2CLIMB: Overall Survival

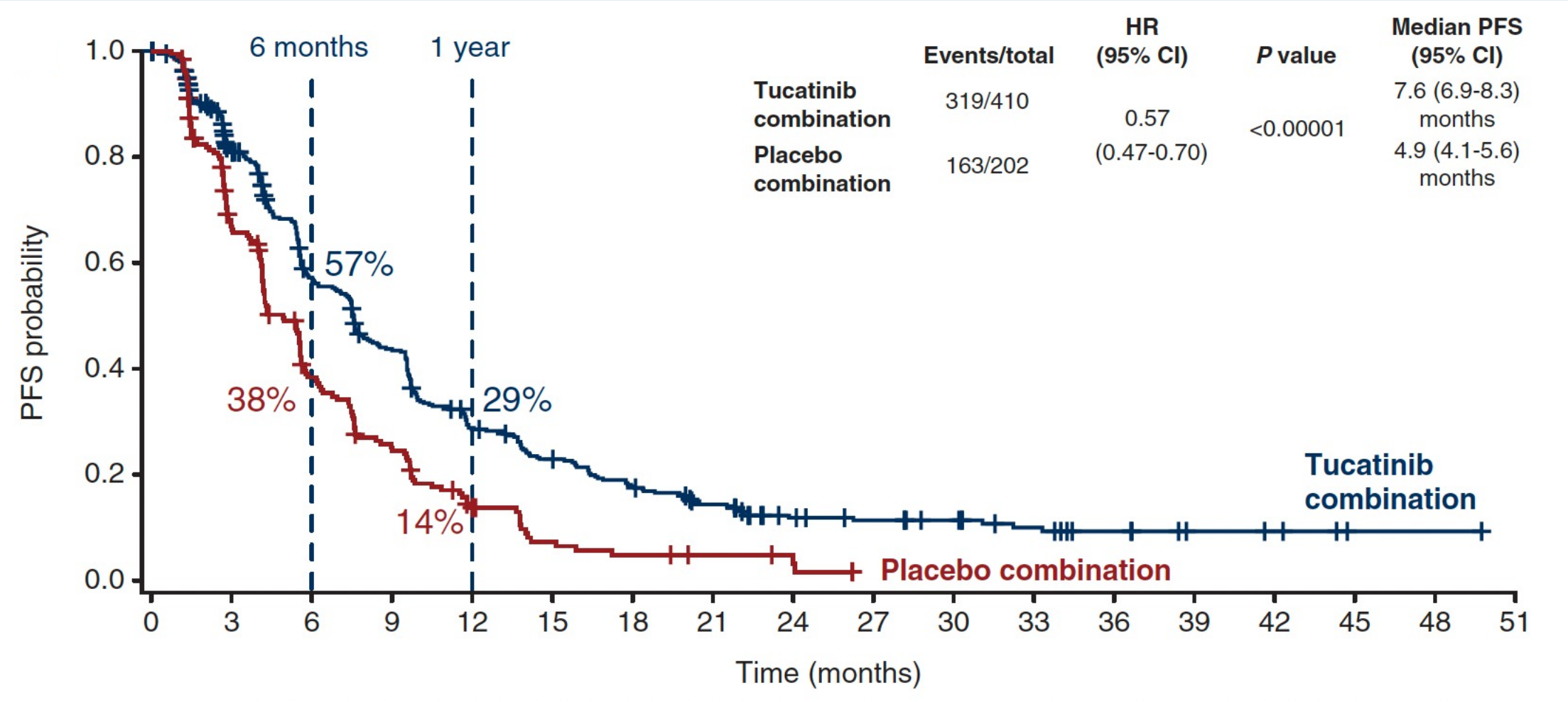


	Events/total	HR (95% CI)	*P* value	Median OS (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	0.004	24.7 (21.6-28.9) months
Placebo combination	137/202			19.2 (16.4-21.4) months

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

RTP RESEARCH TO PRACTICE

HER2CLIMB: Progression-Free Survival



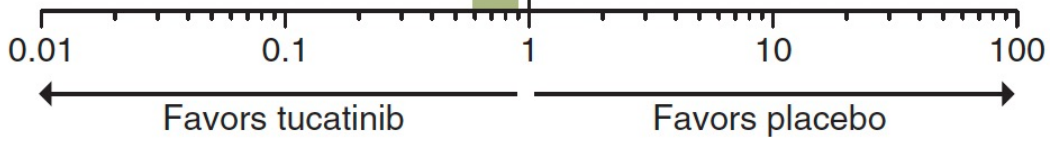
	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

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.

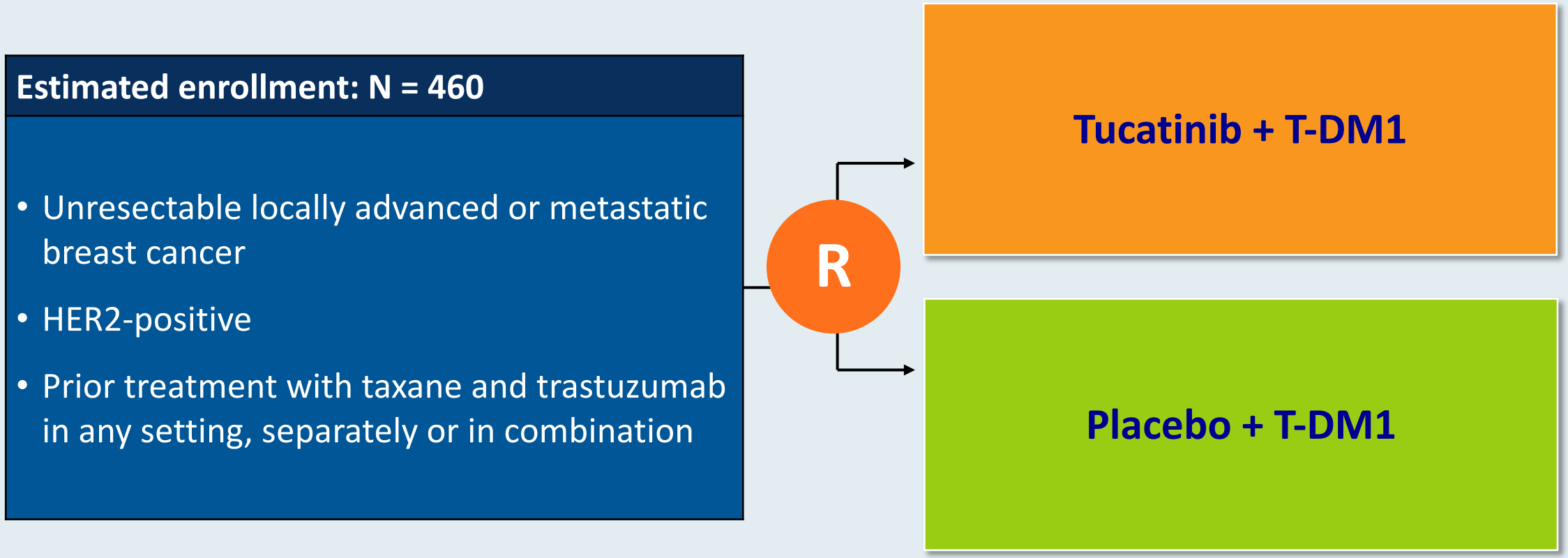
HER2CLIMB: Adverse Events

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

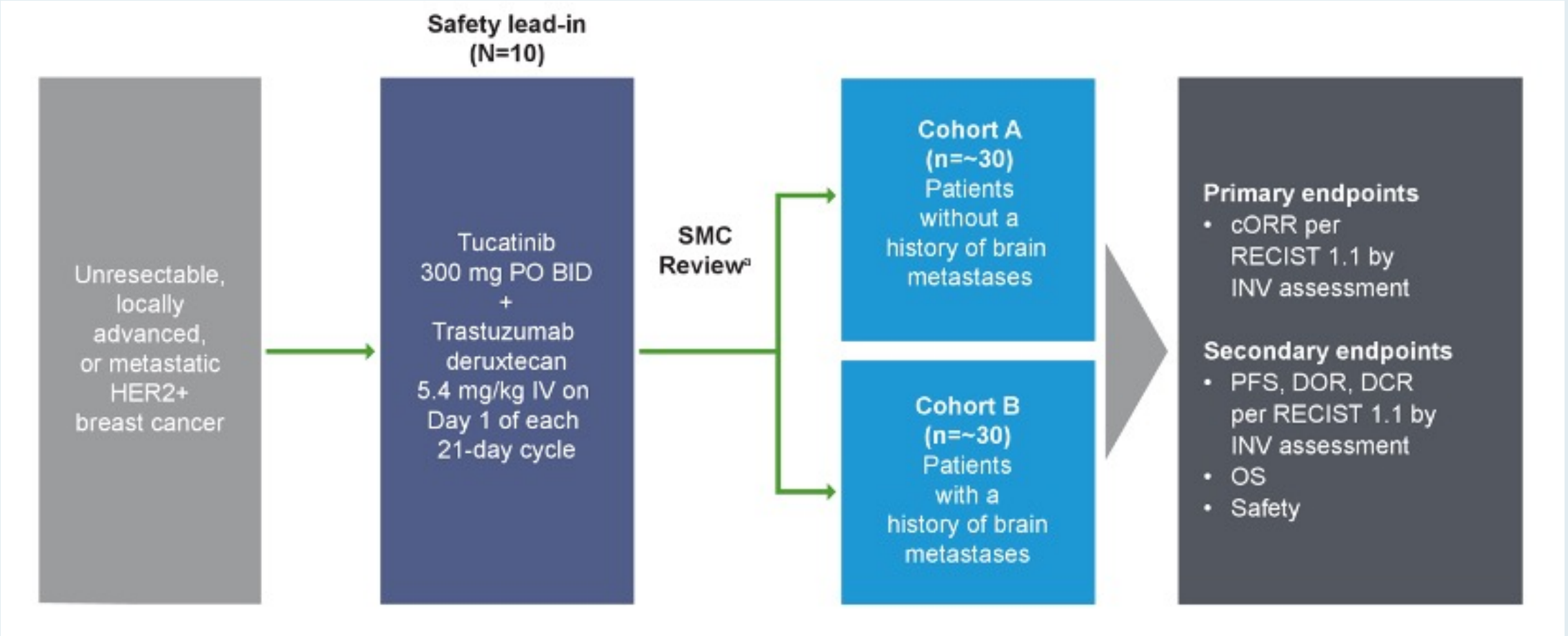
HER2CLIMB-02 Phase III Trial Design



Primary endpoint: PFS by investigator assessment

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

HER2CLIMB-04 Phase II Study Schema



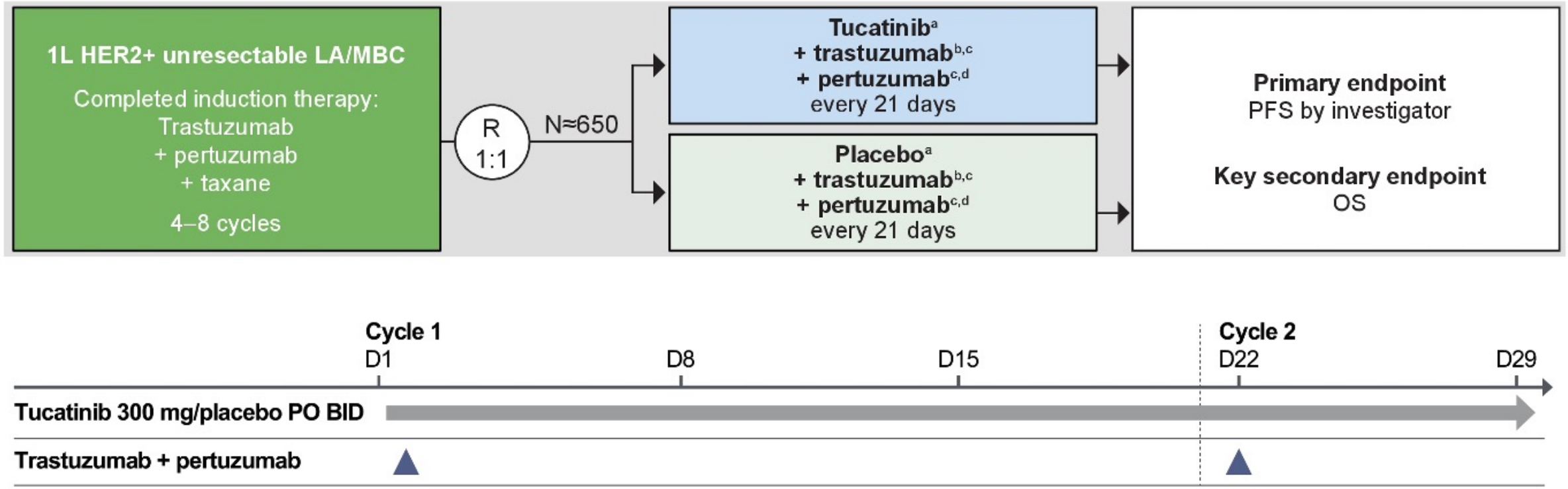
Eligibility

- 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

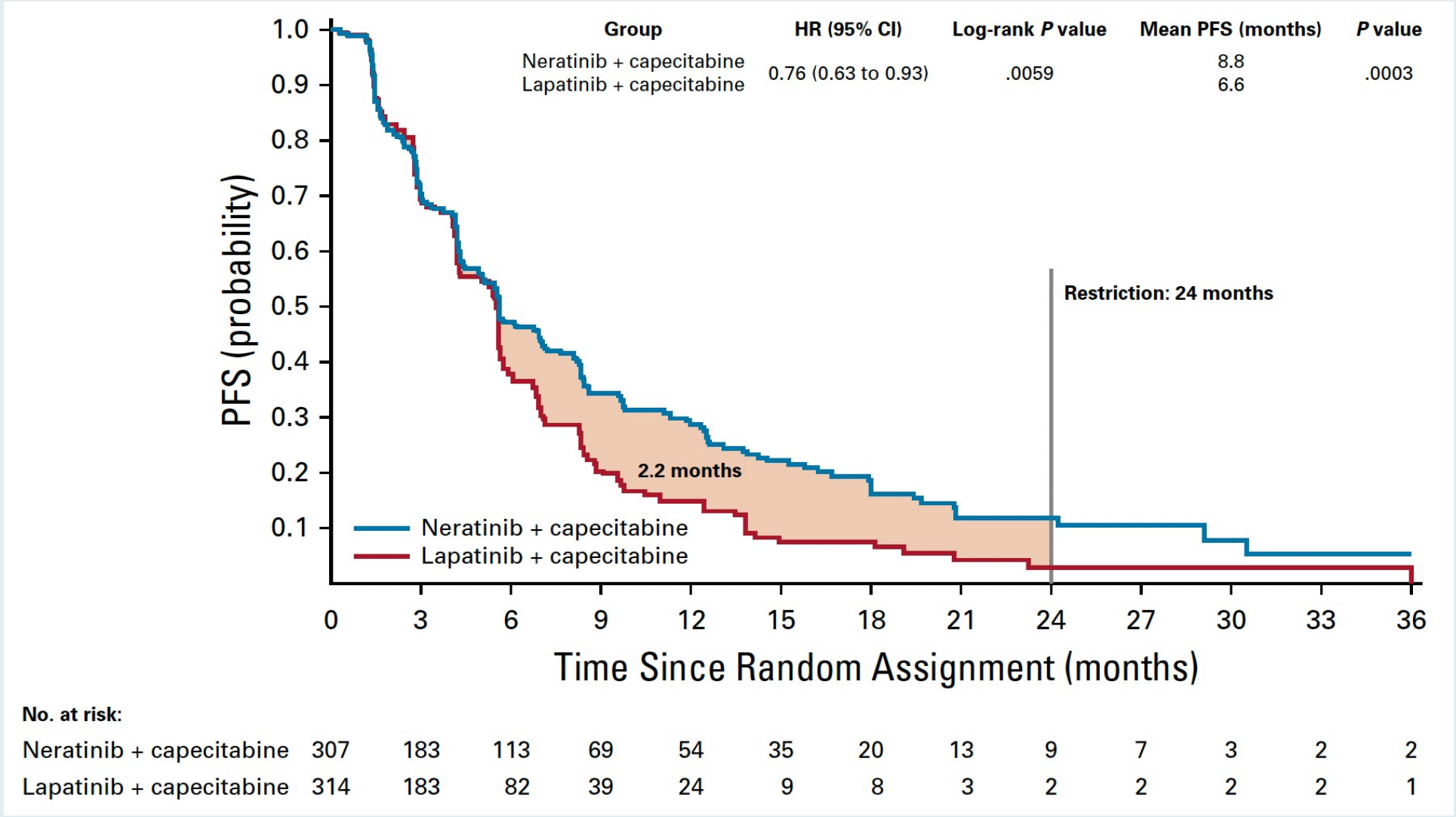
Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial

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.

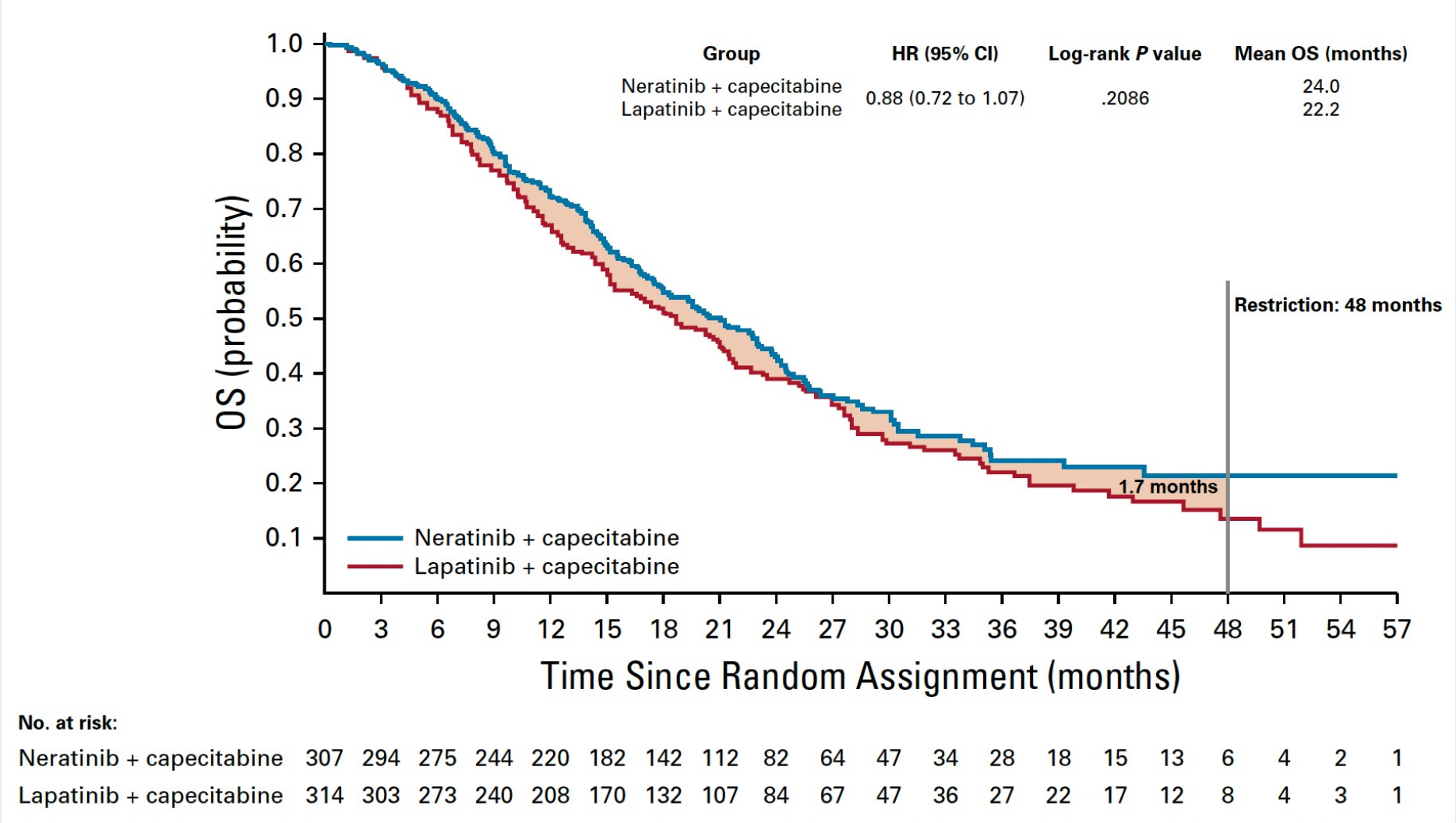
RTP RESEARCH TO PRACTICE

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.

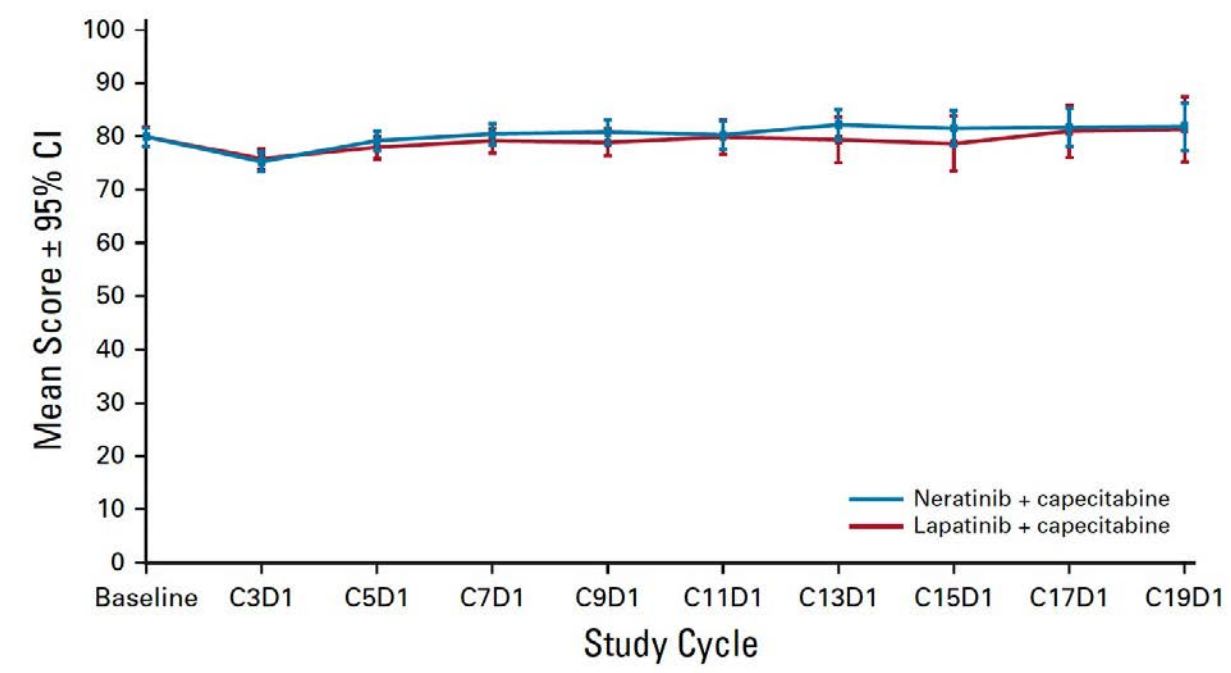
NALA: Treatment-Emergent AEs in >15% of Patients

	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)

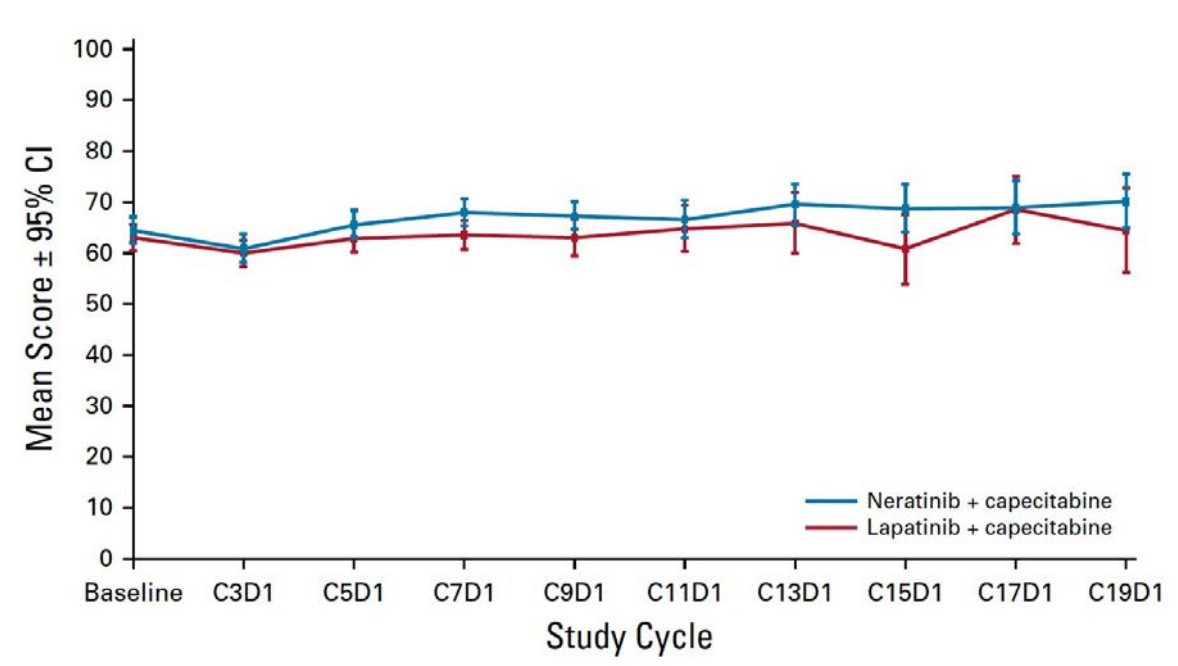
Saura C et al. *J Clin Oncol* 2020;38:3138-49.

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

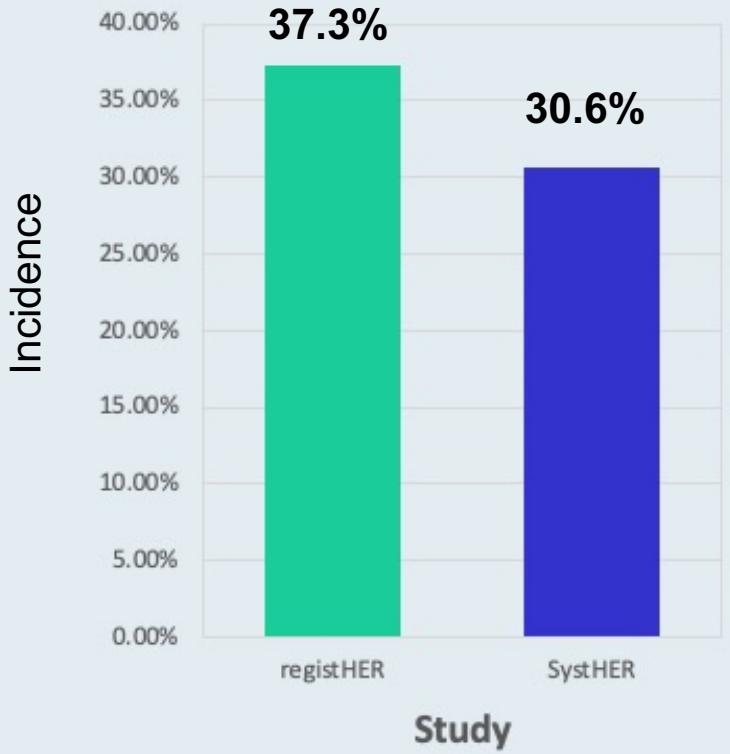
Key Considerations in the Care of Patients with HER2-Positive BC with Brain Metastasis

RTP
RESEARCH
TO PRACTICE

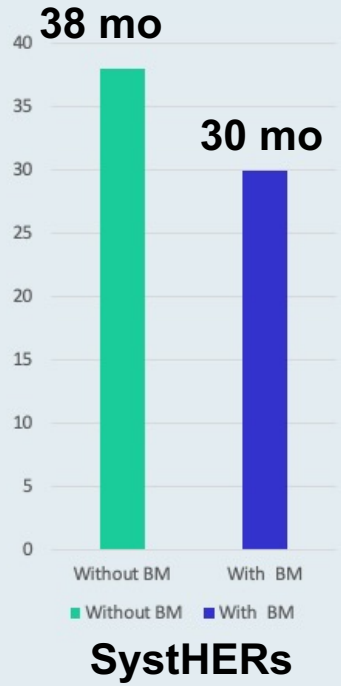
Incidence and Prognosis of HER2-Positive CNS Metastases

- **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

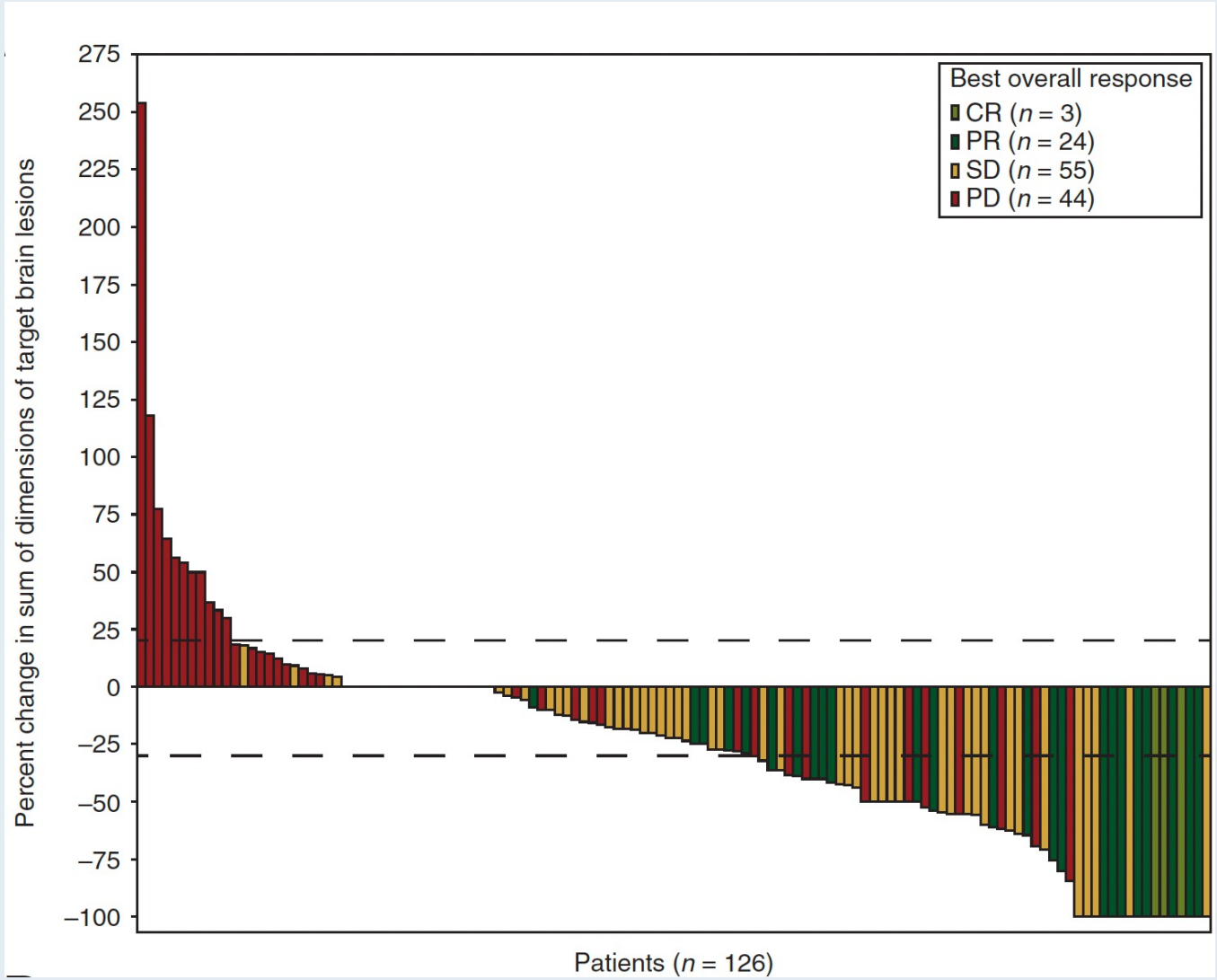
ORIGINAL ARTICLE

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]

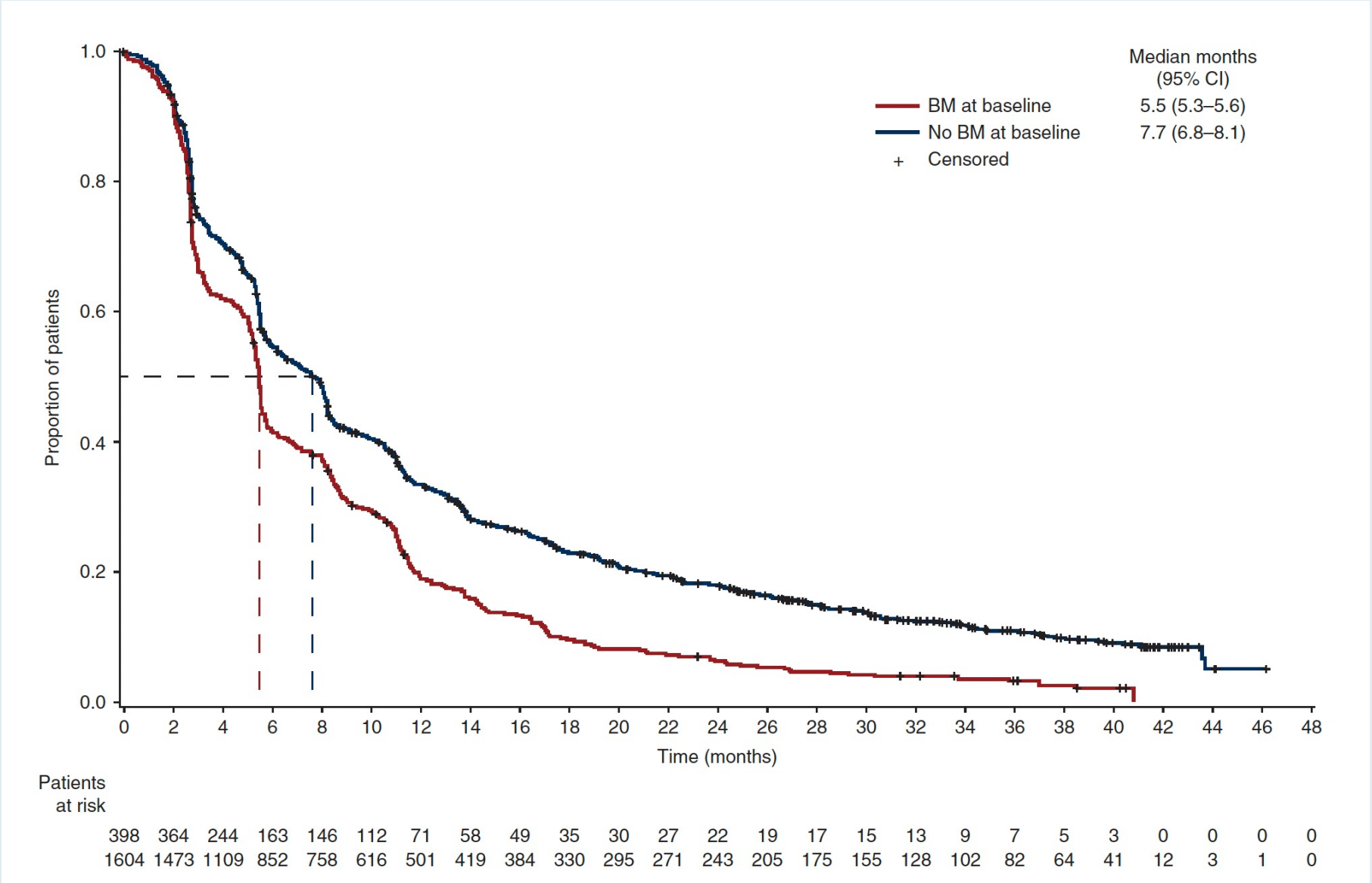
RTP RESEARCH TO PRACTICE

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

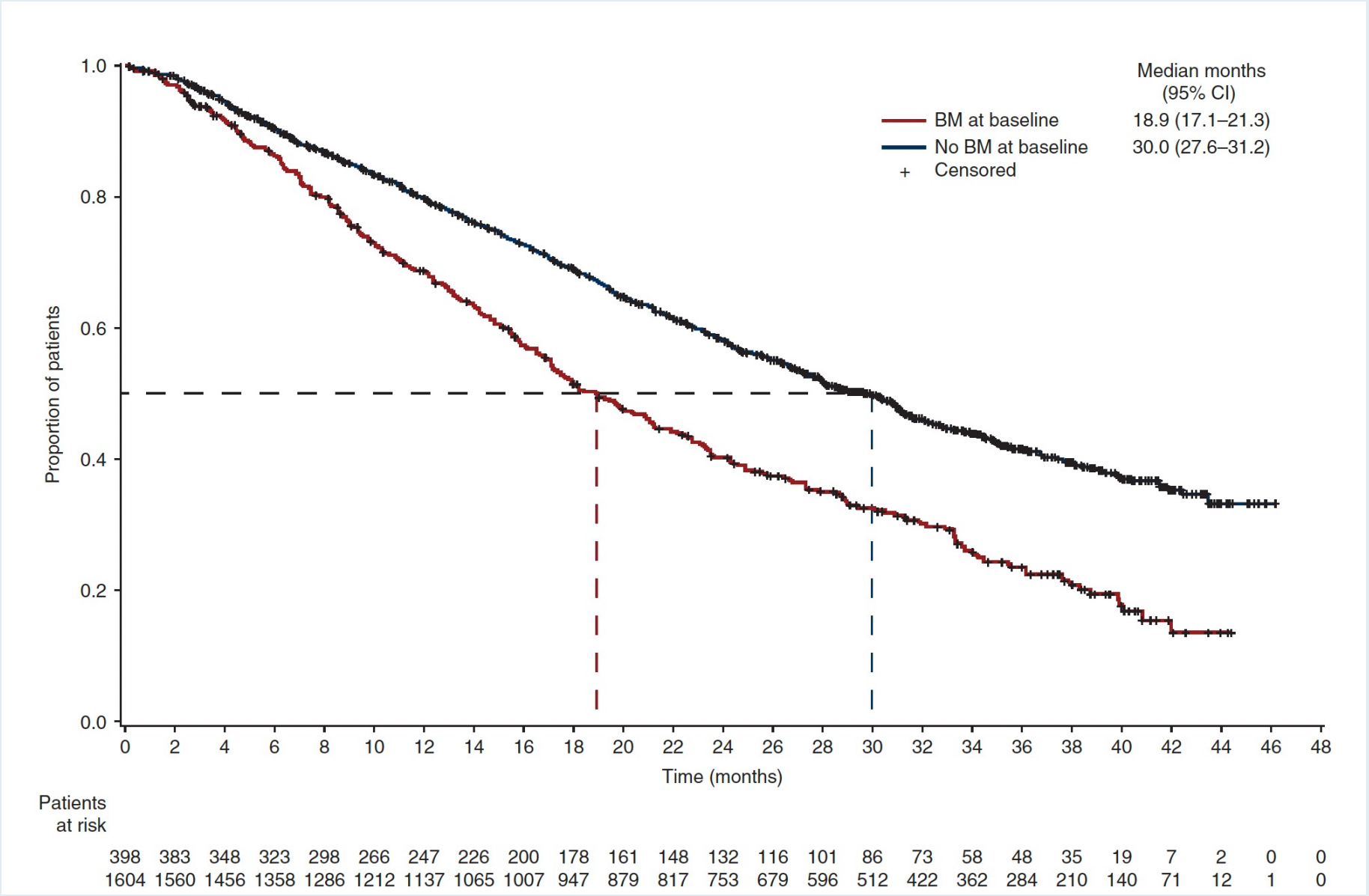


BM = brain metastases

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

RTP RESEARCH TO PRACTICE

KAMILLA: Overall Survival



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

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

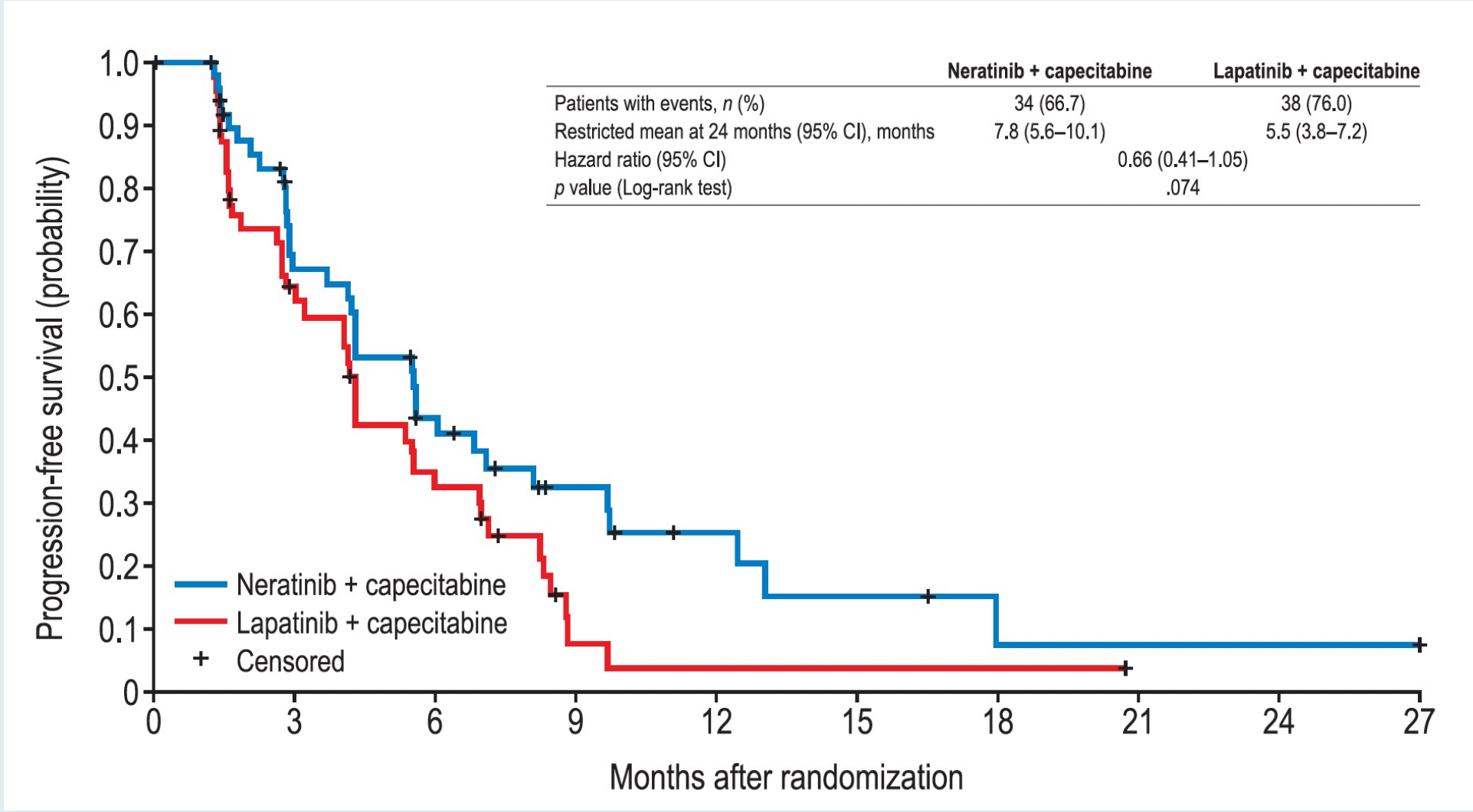
The Oncologist®

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]

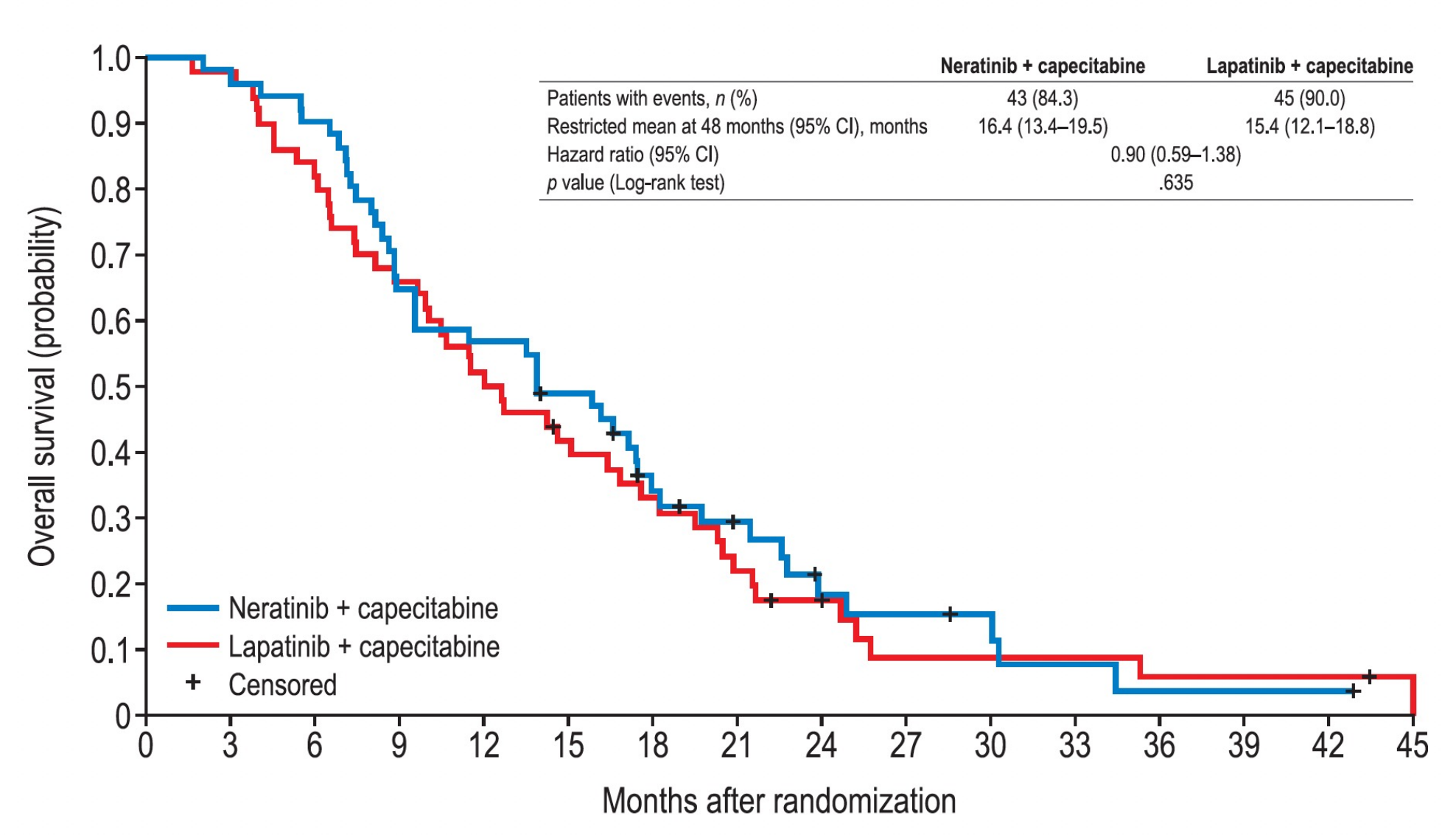
NALA: PFS for Patients with CNS Metastases at Baseline



	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.

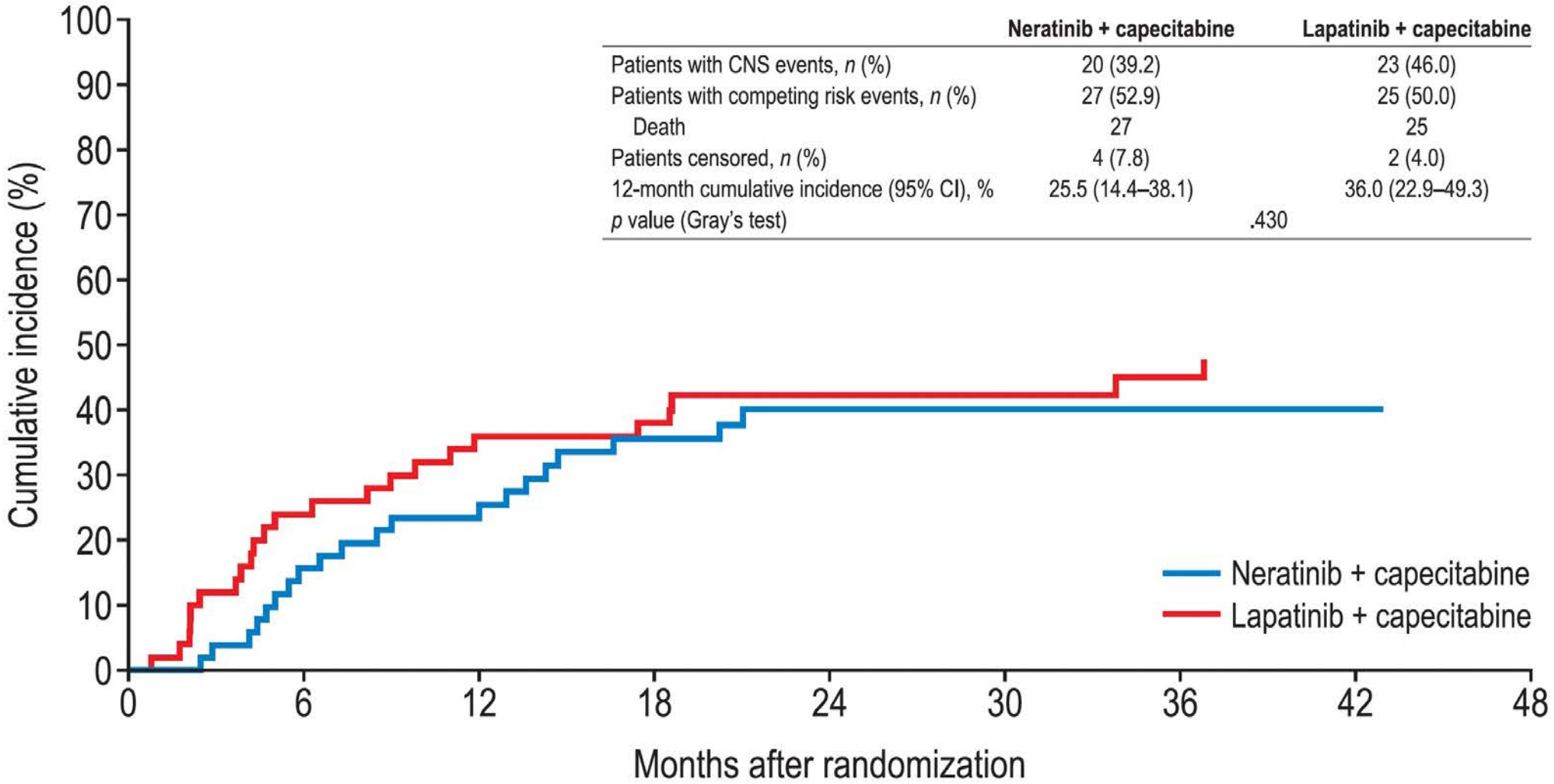
NALA: Efficacy in Patients with CNS Metastases at Baseline

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	

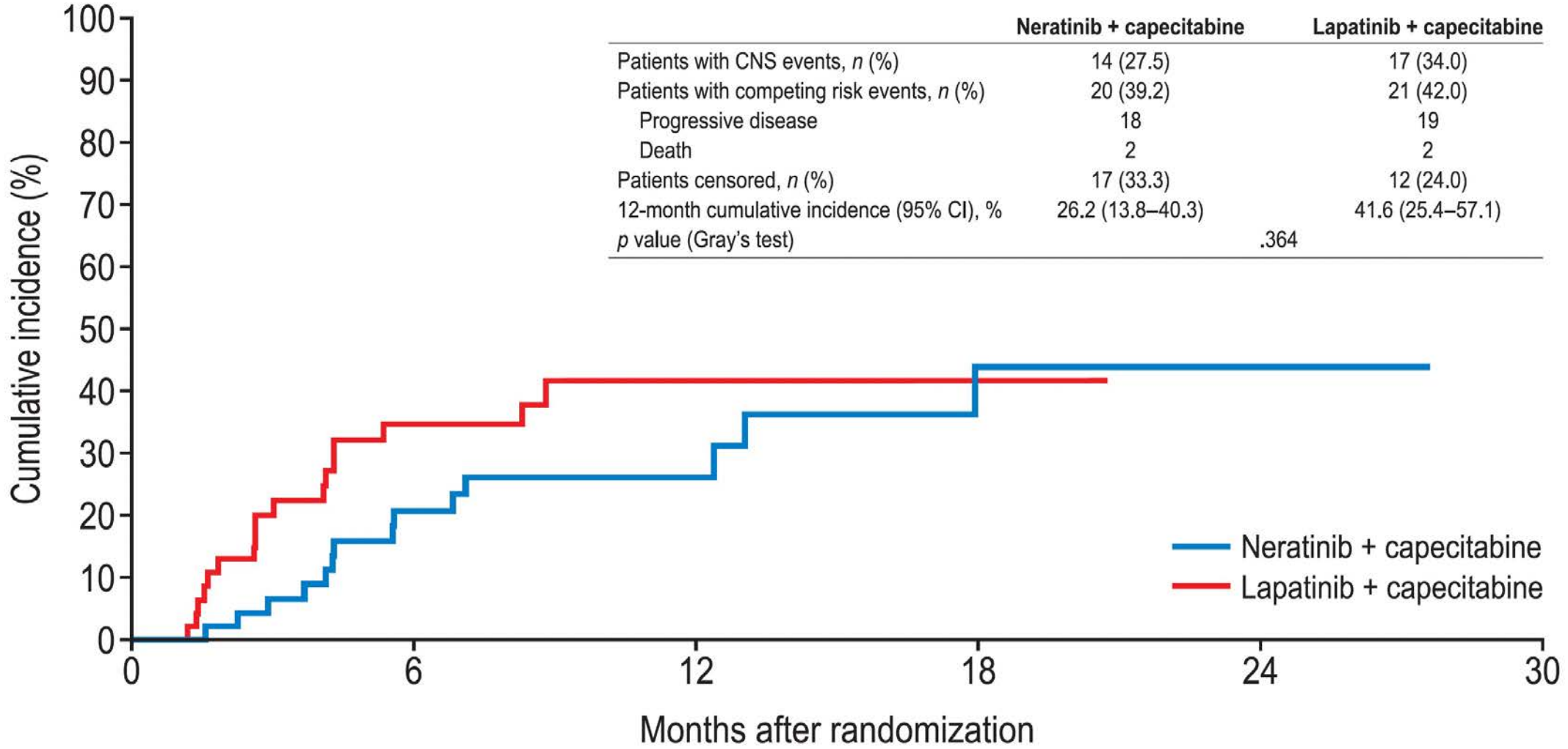


Hurvitz SA et al. *Oncologist* 2021 August;26(8):e1327-38.

RTP RESEARCH TO PRACTICE

NALA: Time to Intervention for CNS Disease – CNS PFS

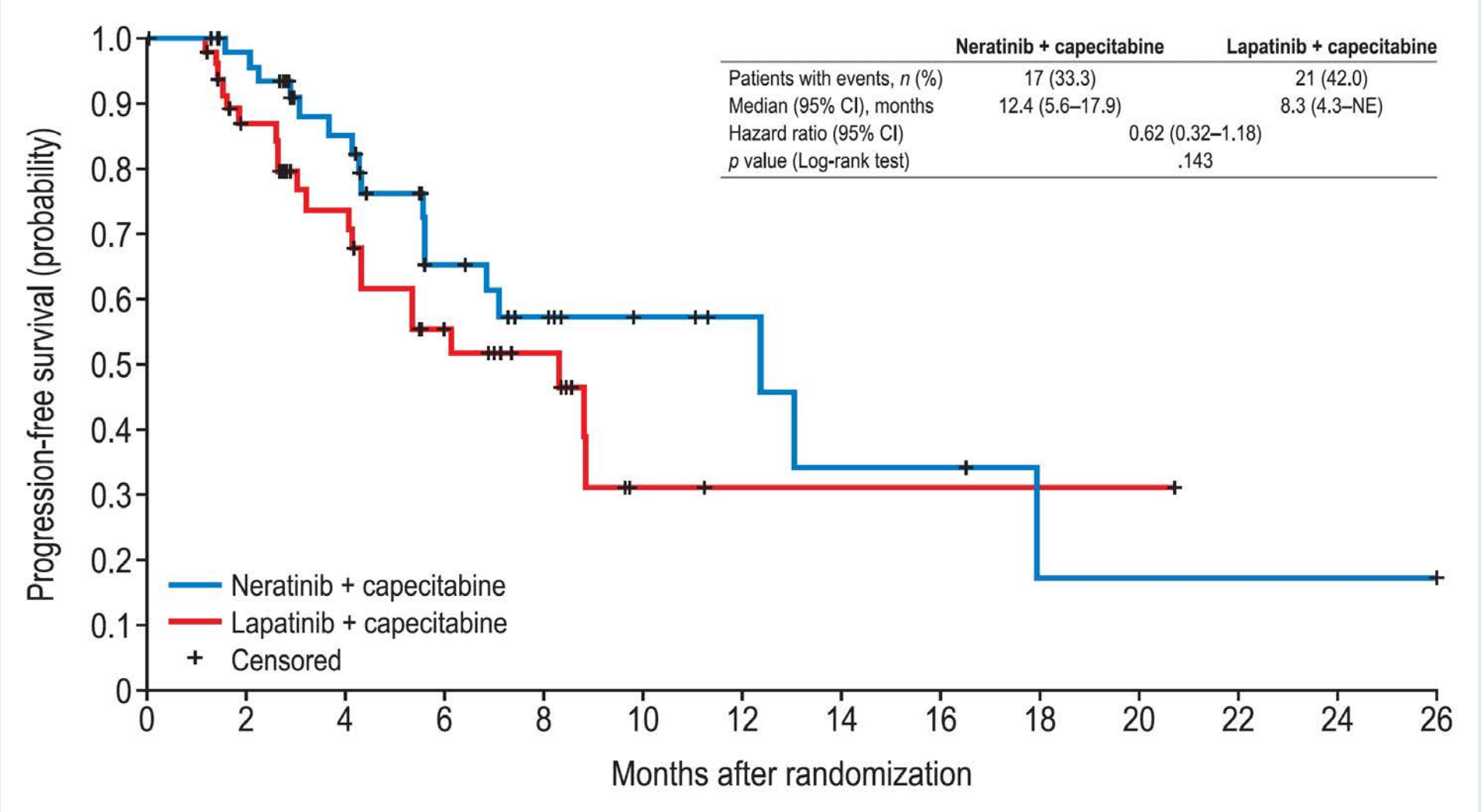
	Neratinib + capecitabine	Lapatinib + capecitabine
Patients with CNS events, *n* (%)	14 (27.5)	17 (34.0)
Patients with competing risk events, *n* (%)	20 (39.2)	21 (42.0)
Progressive disease	18	19
Death	2	2
Patients censored, *n* (%)	17 (33.3)	12 (24.0)
12-month cumulative incidence (95% CI), %	26.2 (13.8–40.3)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



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

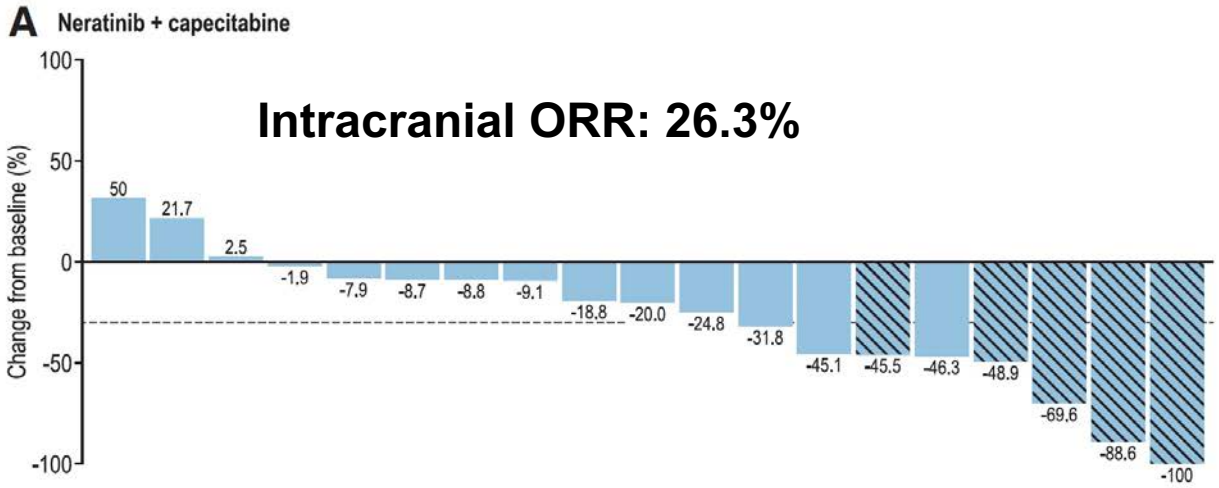
RTP RESEARCH TO PRACTICE

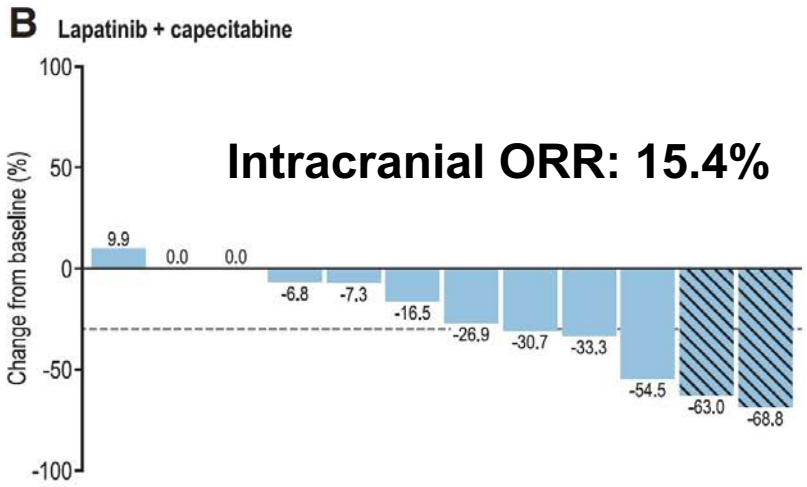
NALA: Time to Intervention for CNS Disease – Patients with CNS Metastases at Baseline



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

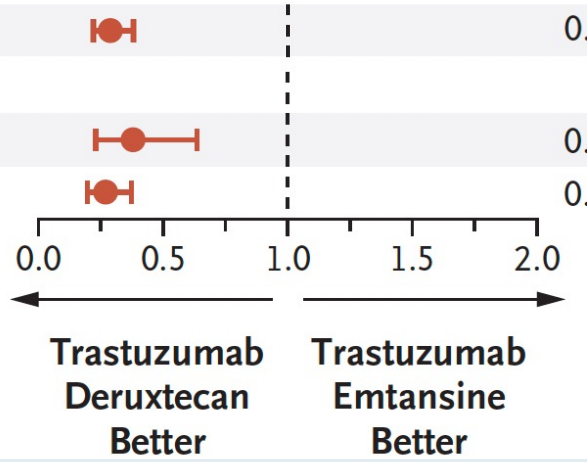
ORIGINAL ARTICLE

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.

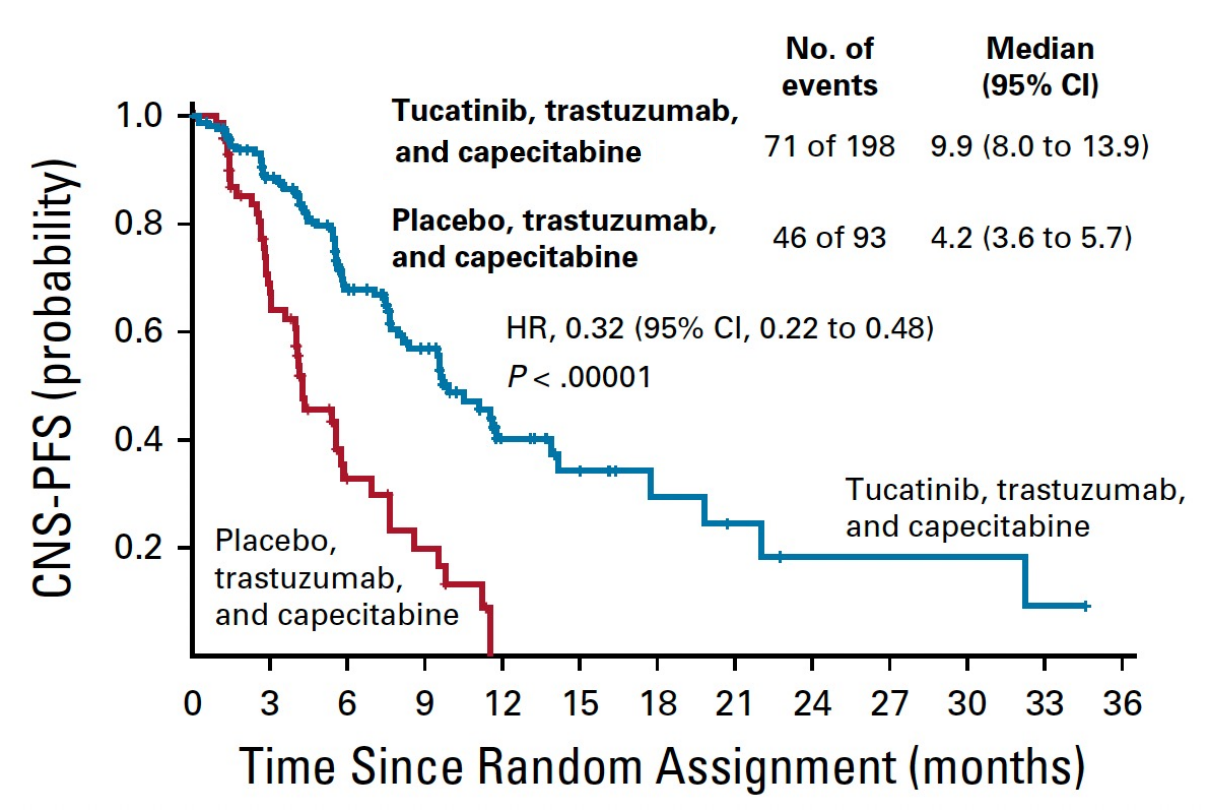
rapid communications

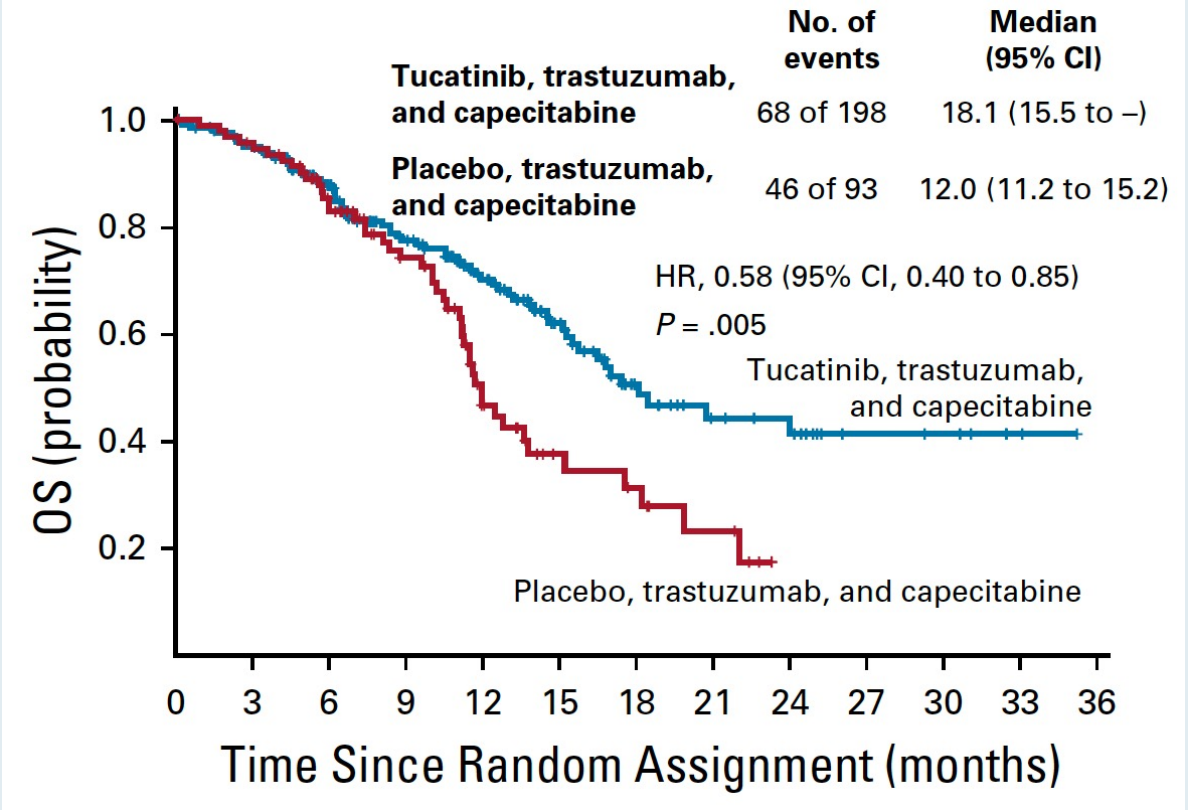
Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial

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

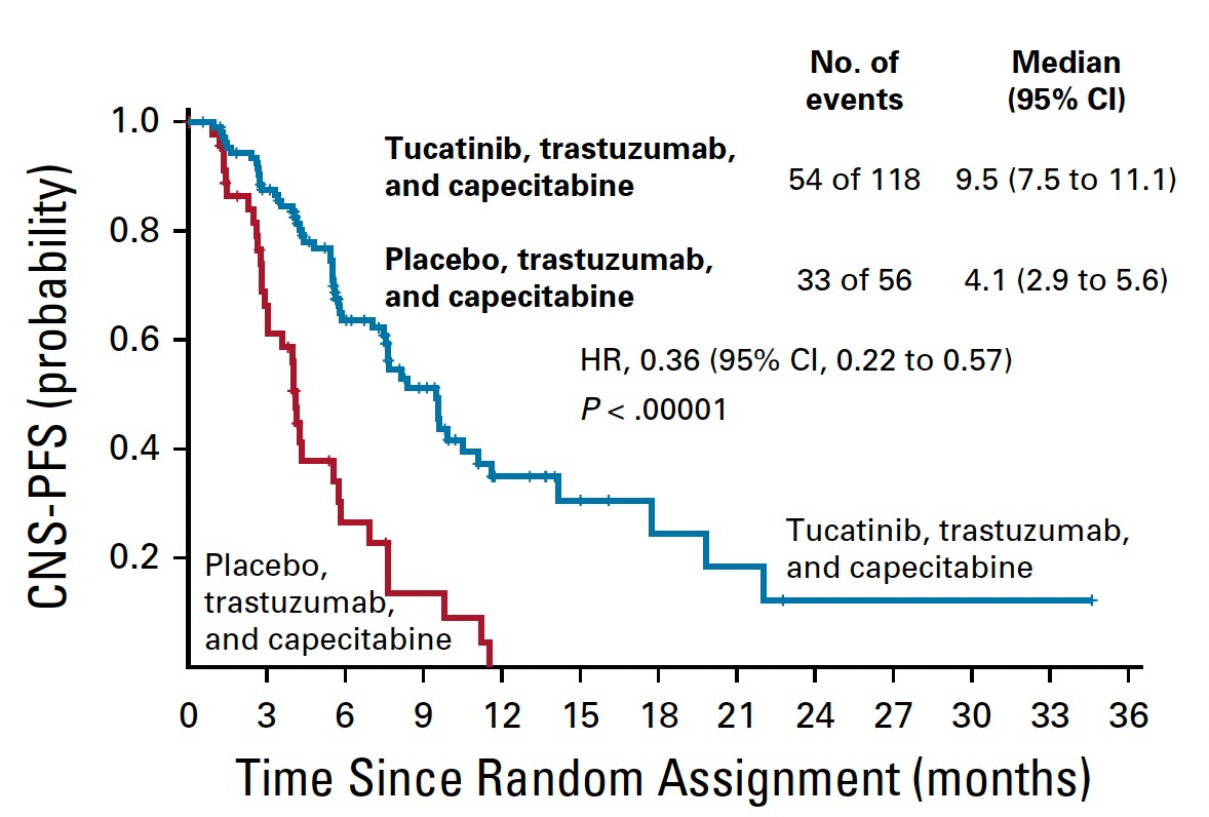


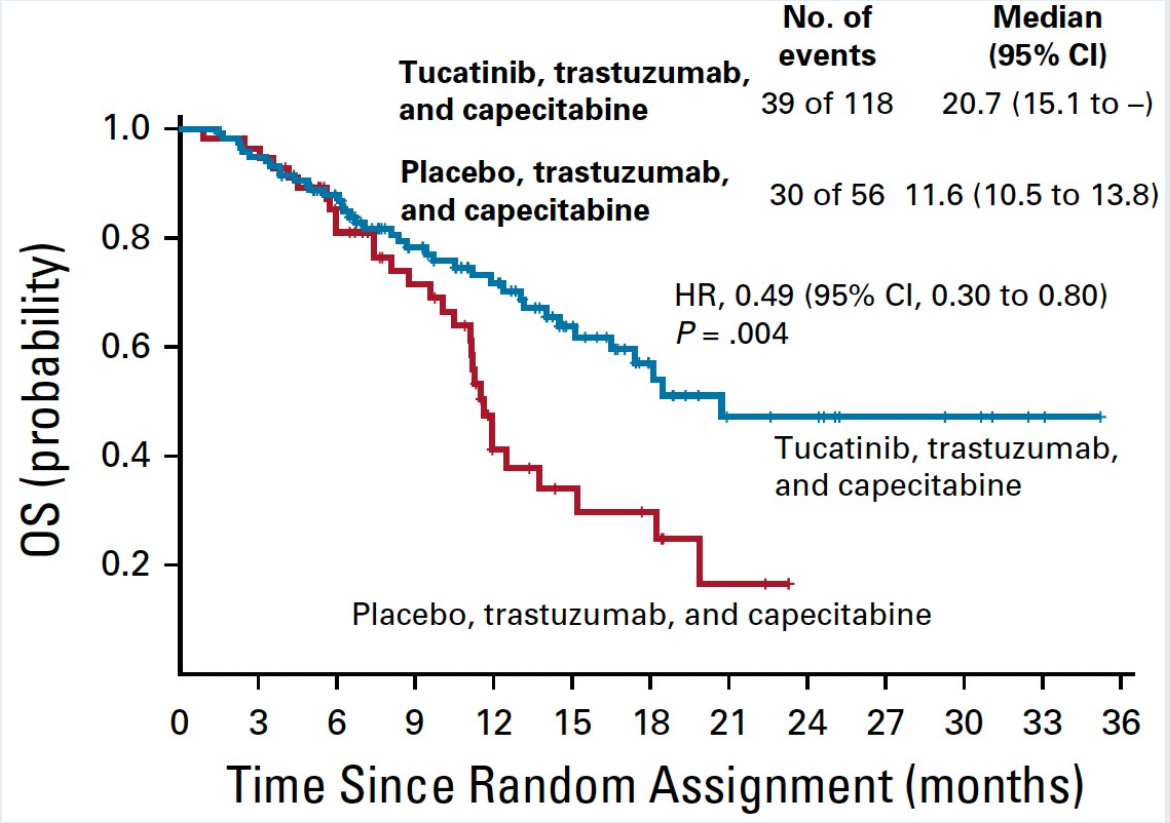


Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

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

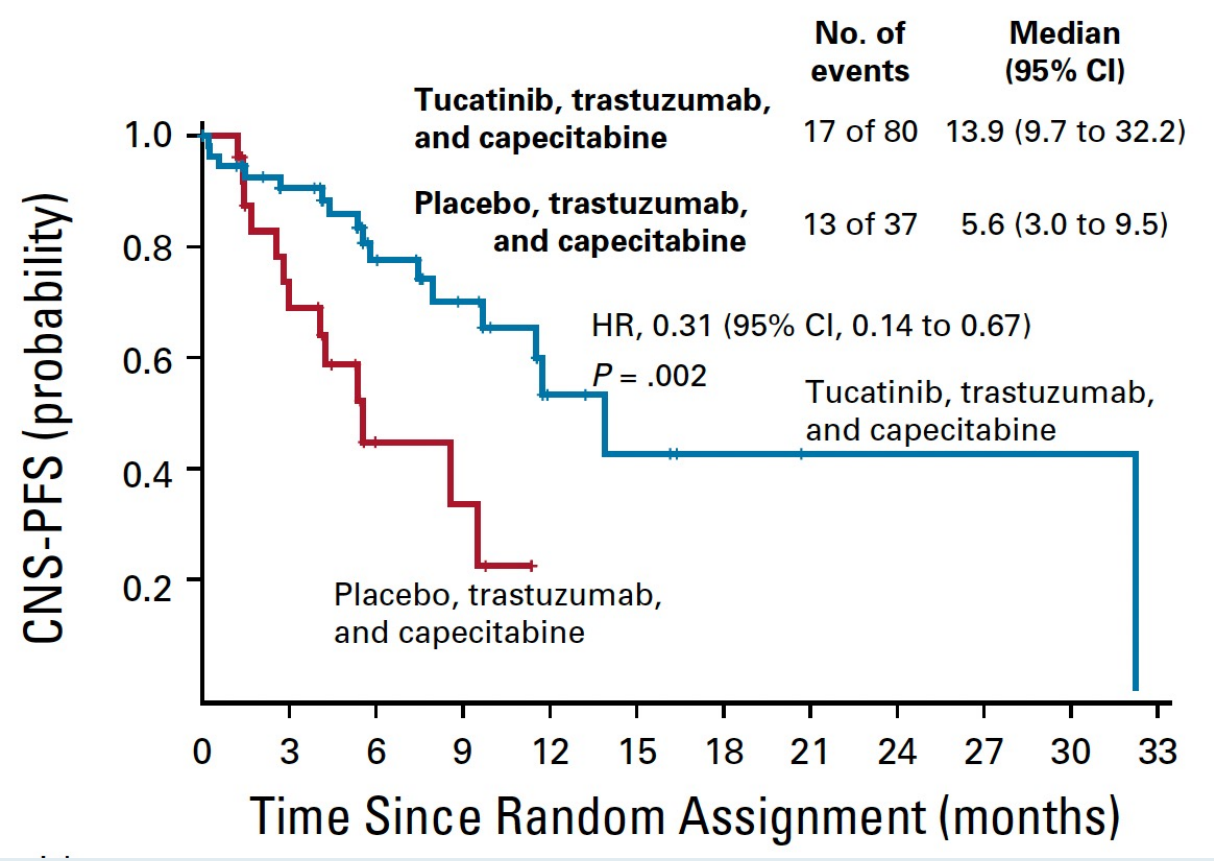
Response	Tucatinib, trastuzumab and capecitabine (n = 55)	Placebo, trastuzumab and capecitabine (n = 20)
Best overall intracranial response		
Complete response	5.5%	5%
Partial response	41.8%	15.0%
Stable disease	43.6%	80.0%
Progressive disease	3.6%	0
Intracranial ORR	47.3%	20.0%
Intracranial DoR	6.8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

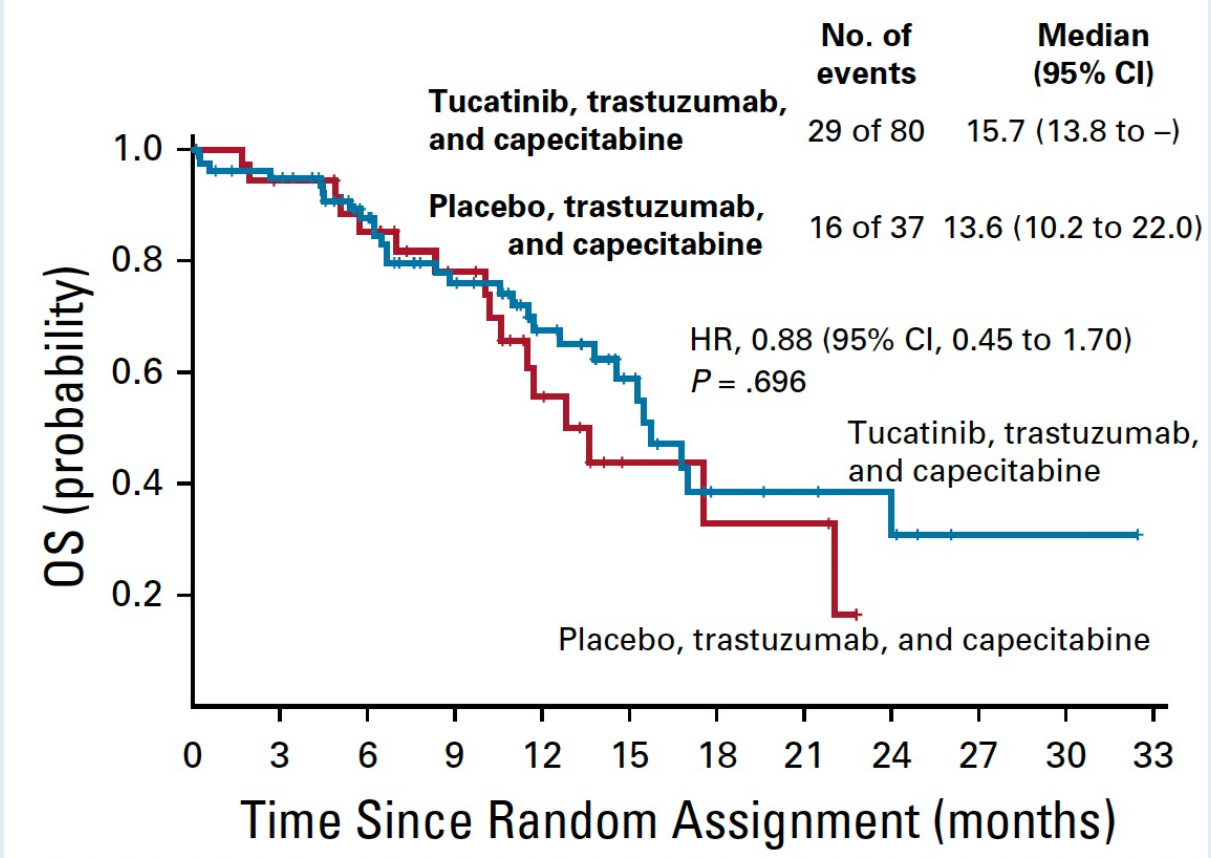
DoR = duration of response

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

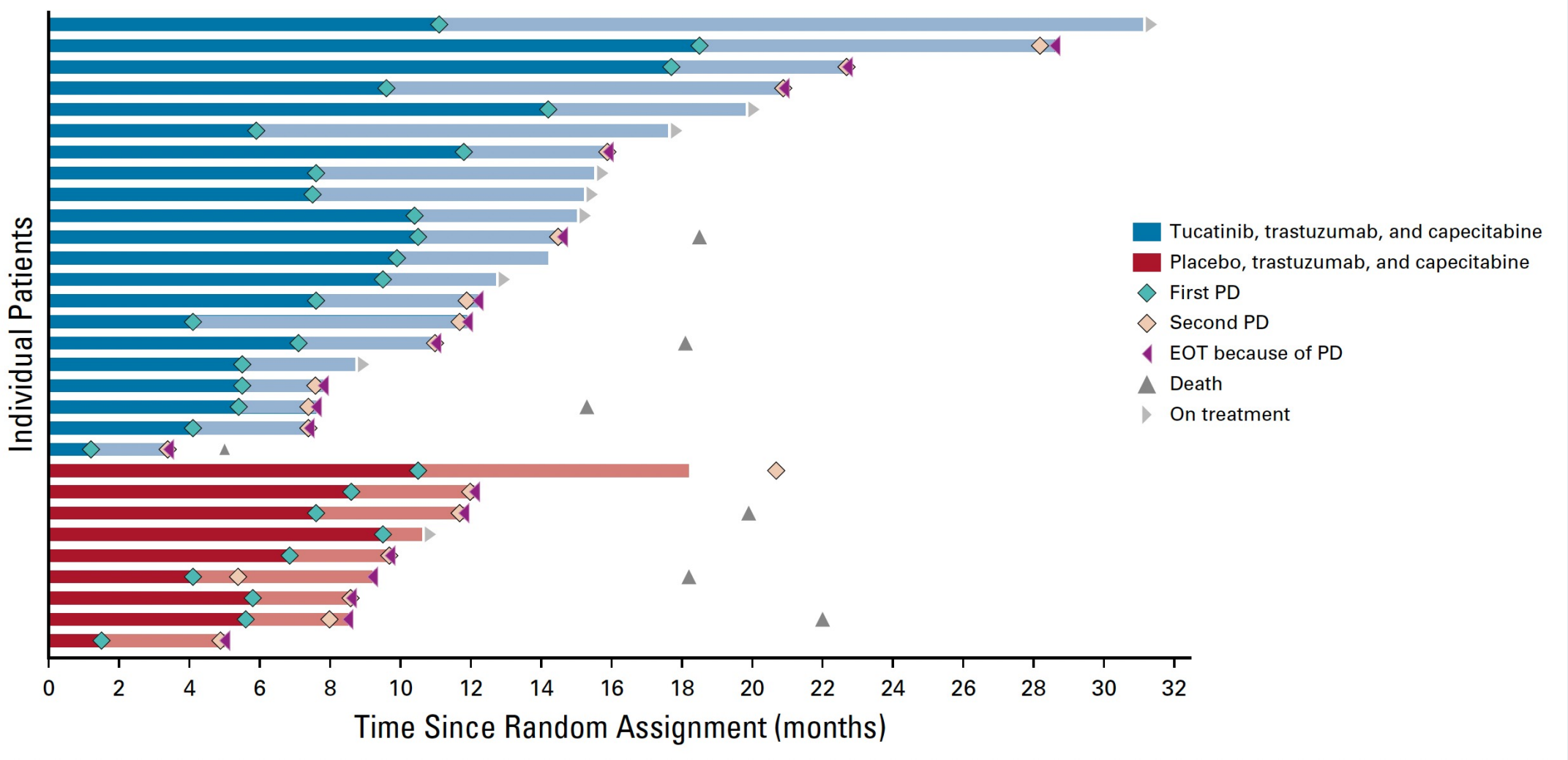




Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

RTP RESEARCH TO PRACTICE

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

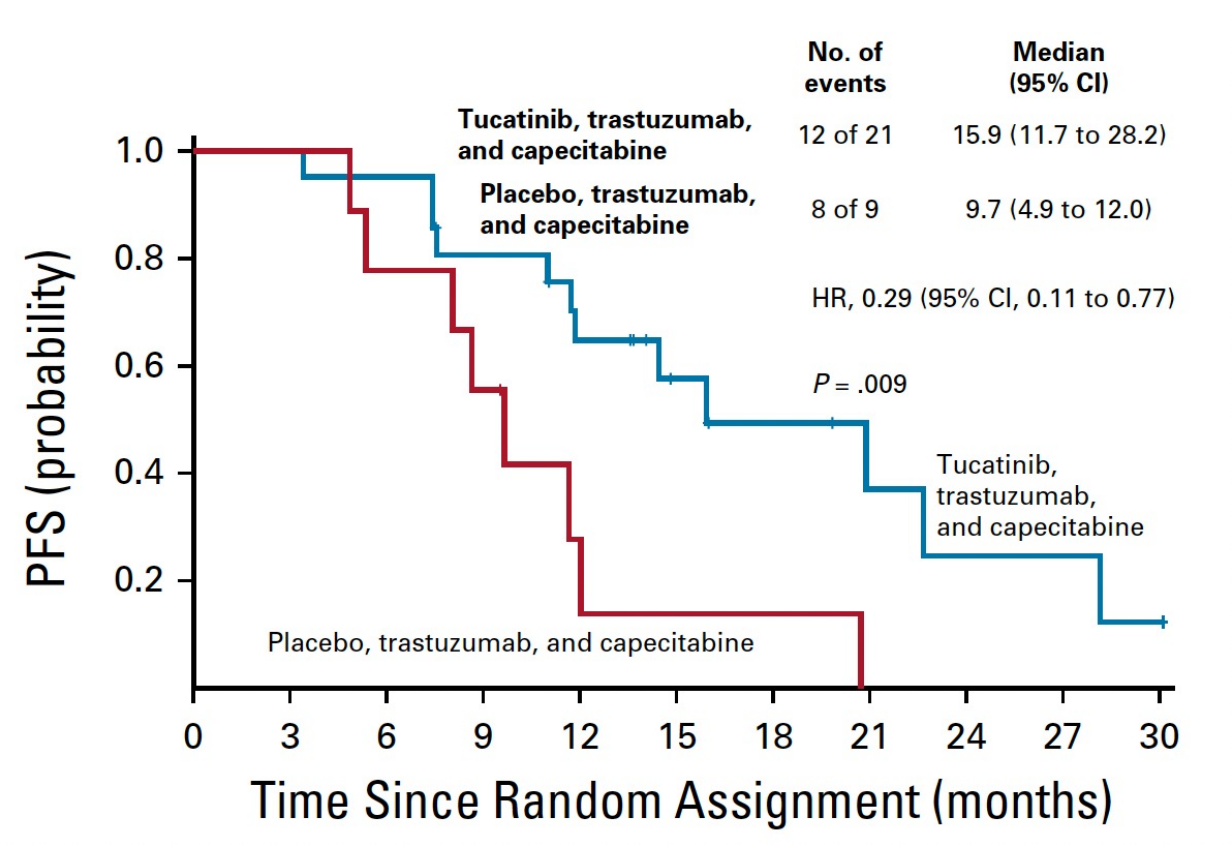


Lin NU et al. *J Clin Oncol* 2020;38:2610-9.

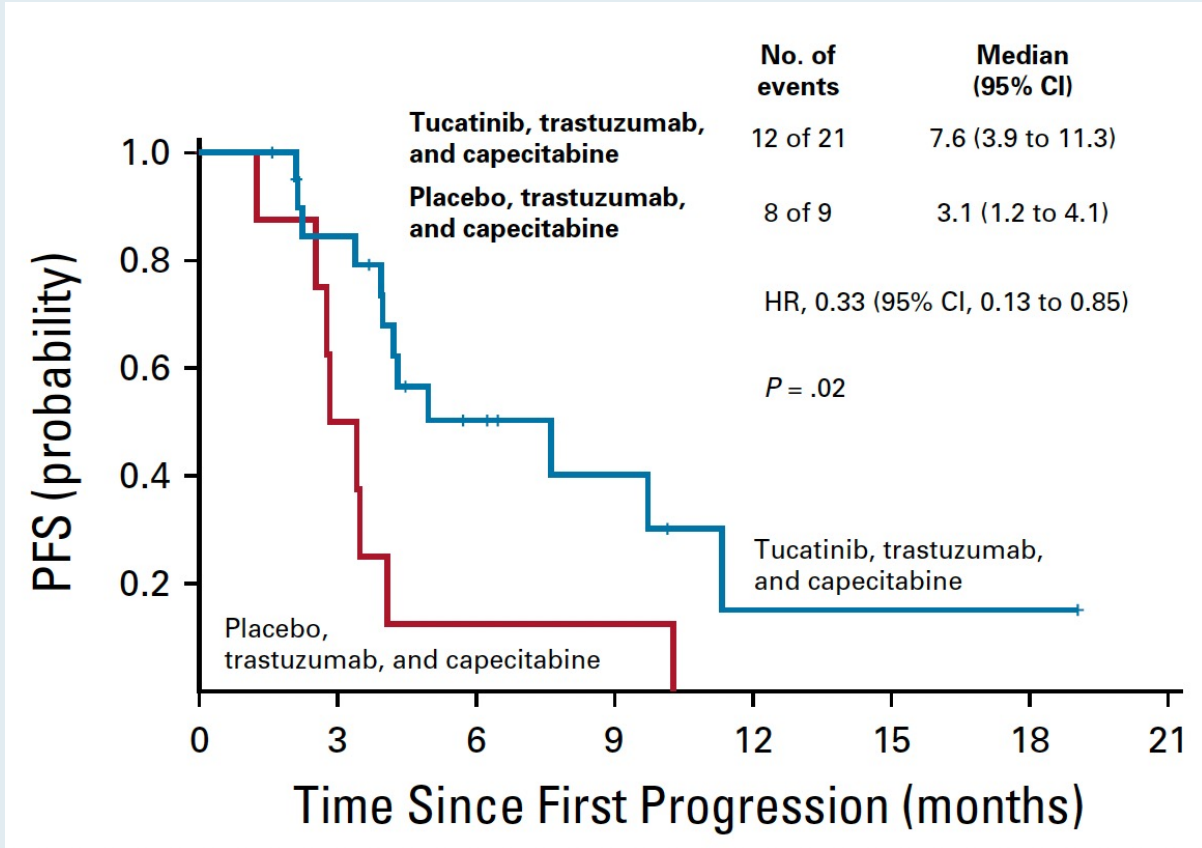
RTP RESEARCH TO PRACTICE

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.

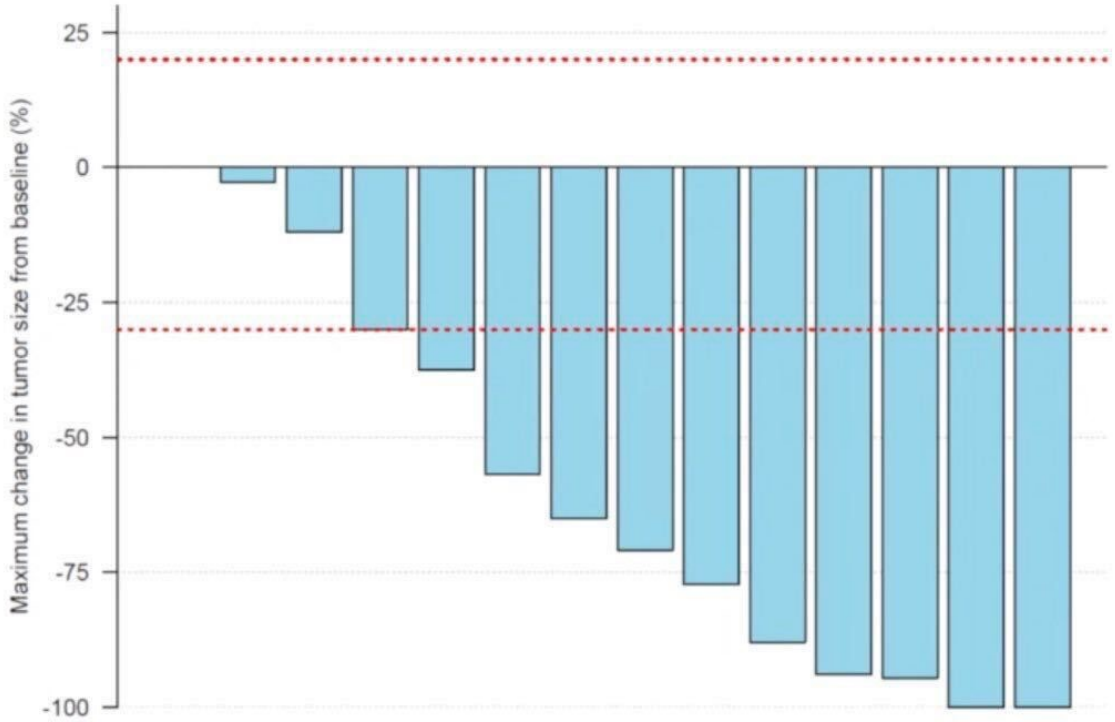
Simon Two Stage Design
- RR (CNS) >60% suggests clinically relevant activity
- RR (CNS) <26% suggests no benefit compared to previous systemic treatment options
- Stage 1: 6 pts. (at least three responses); Stage 2: 9 pts; overall 15 pts. (at least 7 responses)
- Type 1 error rate 5%; power 80%

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)

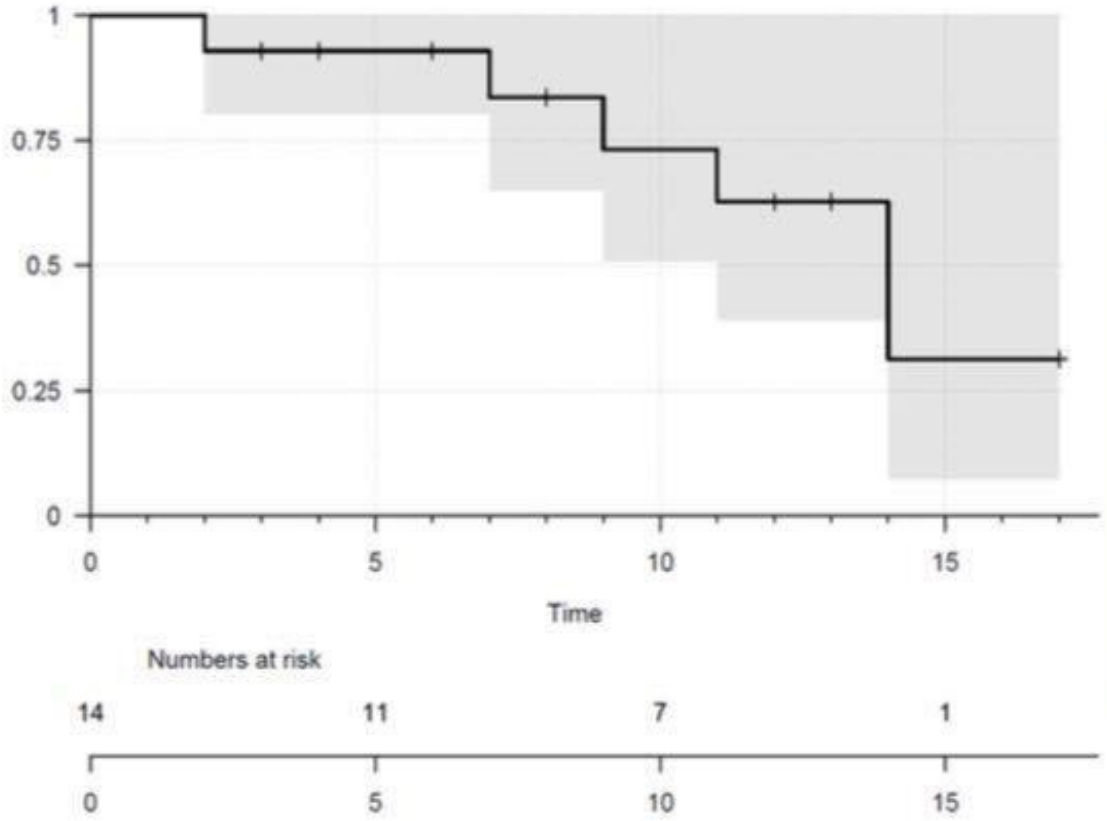


One patient with dural metastases

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

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

Secondary Endpoints

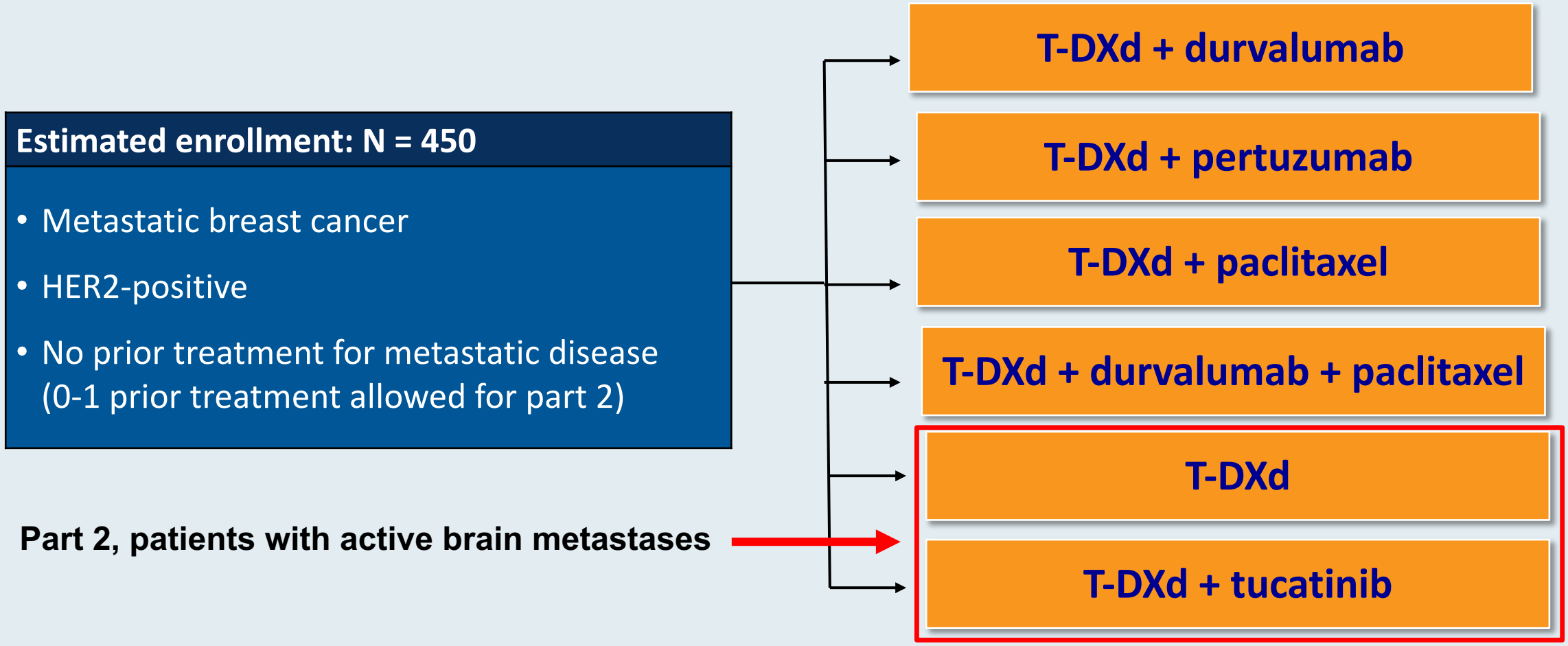


- PFS: 14 months (95% CI 11.0-n.r.)
- Median follow-up 11 months (range 3 – 17 months)

- 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

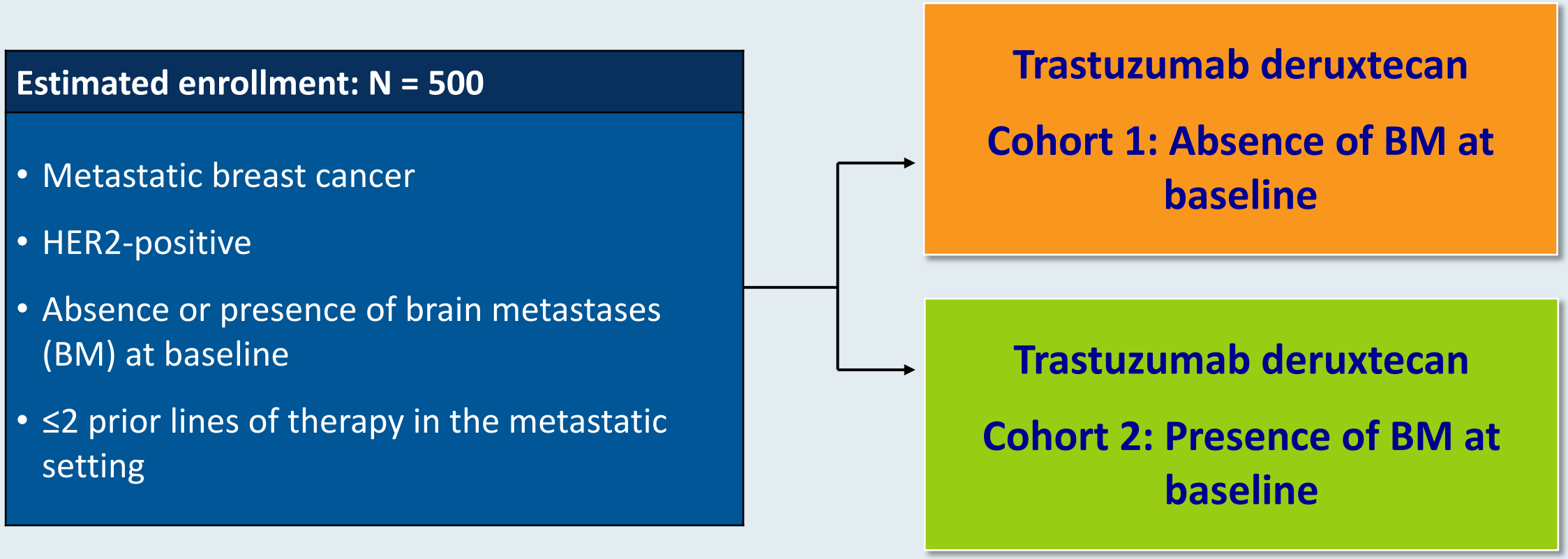


Primary endpoints: AEs, serious AEs

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.

Meet The Professor

Optimizing the Management of Multiple Myeloma

Wednesday, October 5, 2022
5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, 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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