Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with HER2-Positive Breast Cancer

Erika Hamilton, MD
Director, Breast and Gynecologic Research Program
Sarah Cannon Research Institute/Tennessee Oncology
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Commercial Support

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Dr Love — Disclosures

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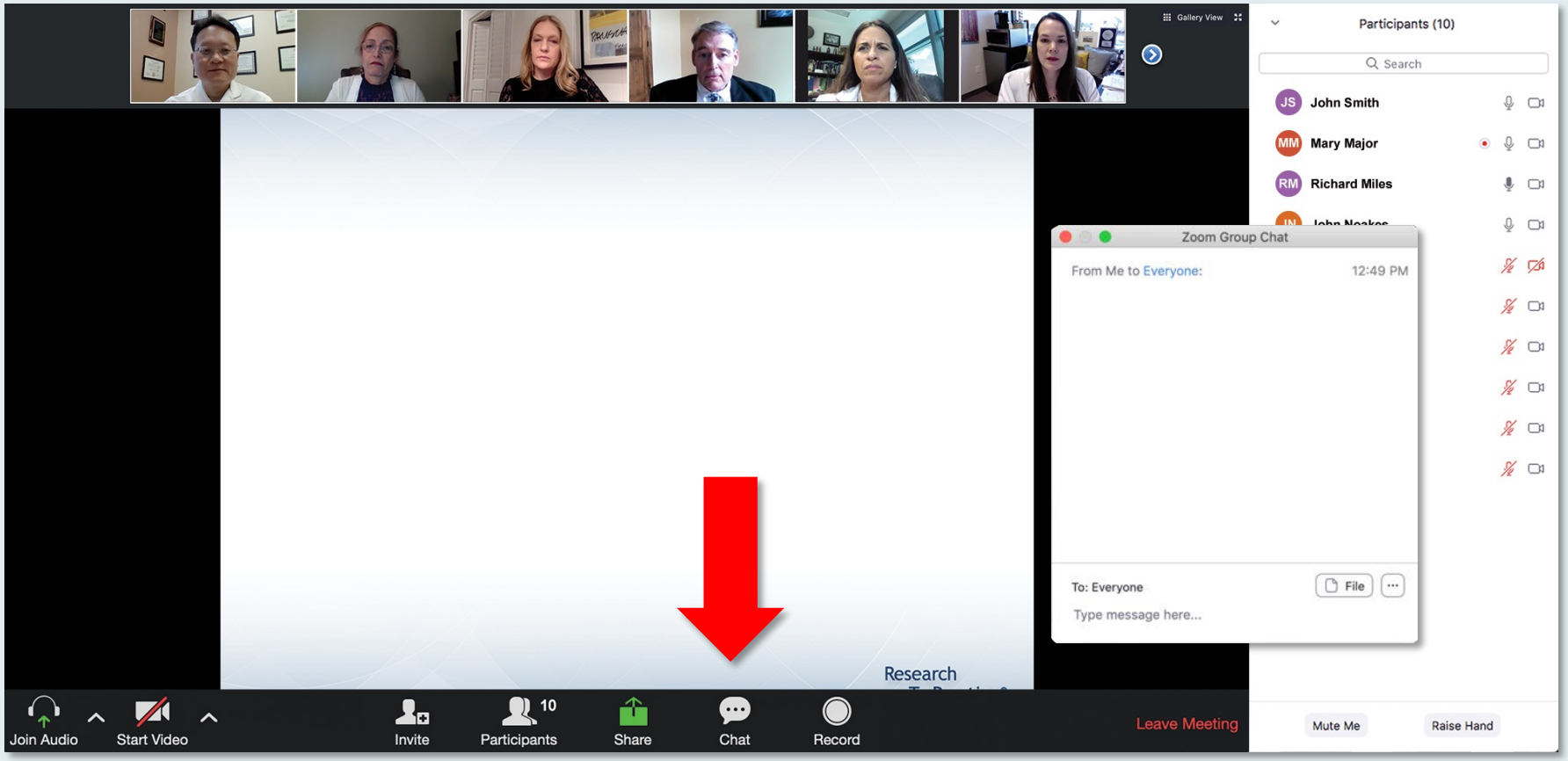

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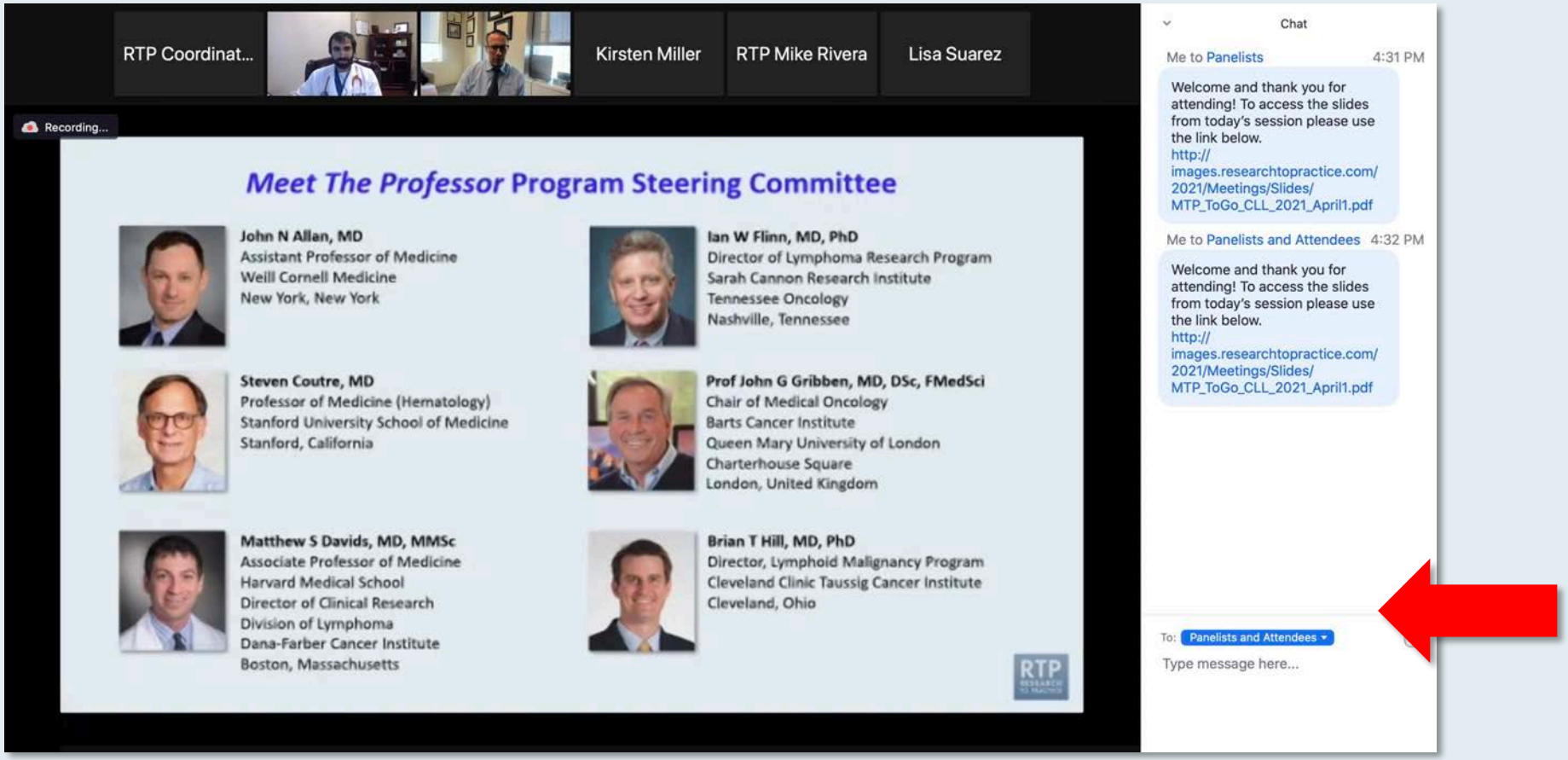

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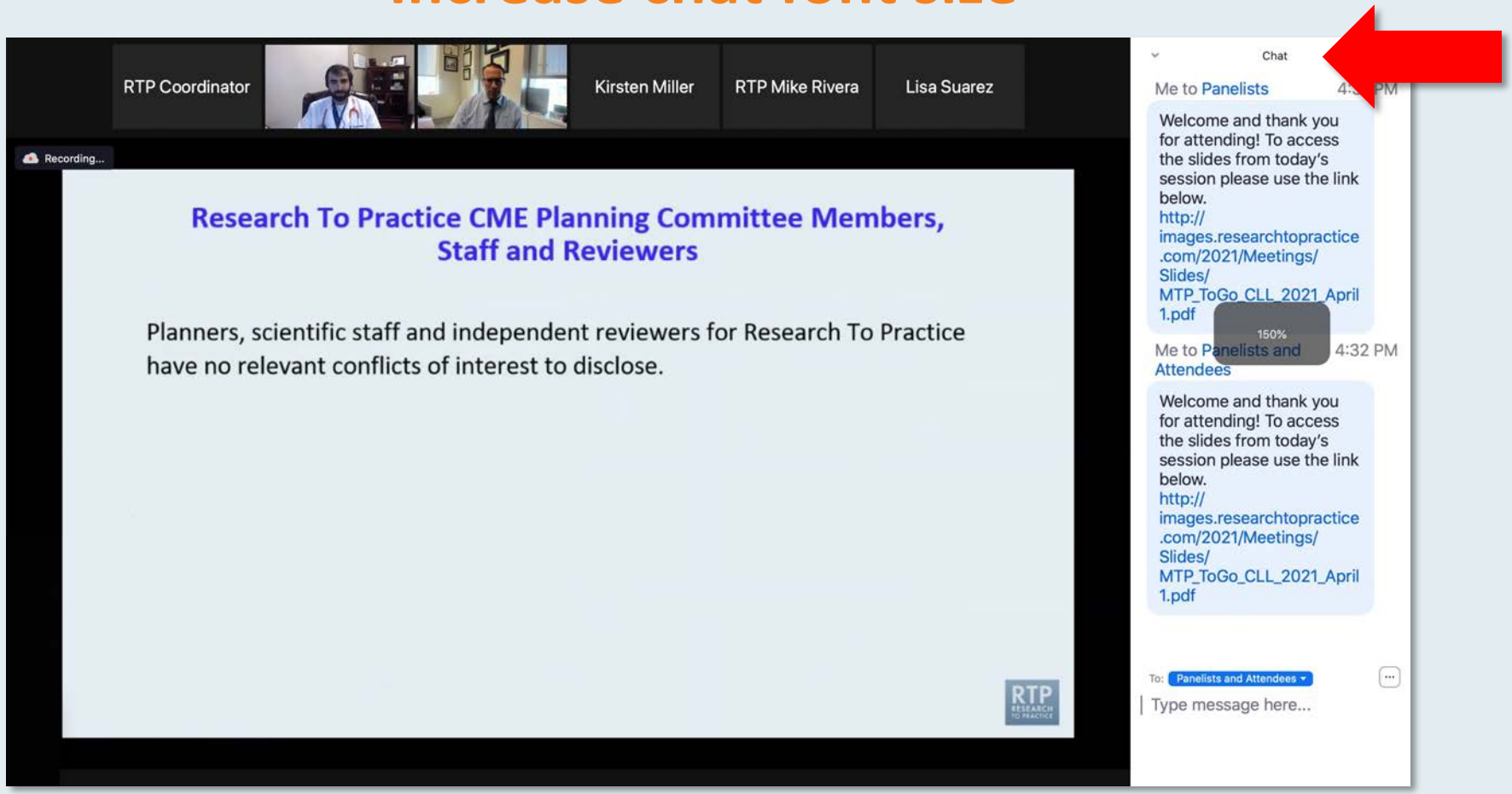

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR IAN KROP

DANA-FARBER CANCER INSTITUTE

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Fall Oncology Nursing Series

A Complimentary NCPD-Accredited Virtual Curriculum

Chronic Lymphocytic Leukemia

Thursday, October 14, 2021
5:00 PM – 6:00 PM ET

Faculty

Anthony R Mato, MD, MSCE
Corinne Hoffman, MS, APRN-CNP, AOCNP

Moderator

Neil Love, MD

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Fall Oncology Nursing Series

A Complimentary NCPD-Accredited Virtual Curriculum

Chimeric Antigen Receptor T-Cell Therapy in Chronic Lymphocytic Leukemia and Lymphomas

Monday, October 18, 2021
5:00 PM – 6:00 PM ET

Faculty

Jeremy Abramson, MD
Elizabeth Zerante, MS, AGACNP-BC

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Triple-Negative Breast Cancer

Wednesday, October 20, 2021
5:00 PM – 6:00 PM ET

Faculty

Aditya Bardia, MD, MPH

Moderator

Neil Love, MD

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Recent Advances and Future Directions in Oncology: A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

A CME-MOC/NCPD Accredited Virtual Event

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

Faculty

Neeraj Agarwal, MD
Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Brad S Kahl, MD
Mark Levis, MD, PhD
Ann Partridge, MD, MPH
Mark D Pegram, MD
Daniel P Petrylak, MD
Noopur Raje, MD
David Sallman, MD
Lecia V Sequist, MD, MPH
David R Spigel, MD
Saad Zafar Usmani, MD, MBA
Andrew D Zelenetz, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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Meet The Professor Program Participating Faculty

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Professor of Medicine
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Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Breast Cancer Clinical Research Program
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Director, Breast and Gynecologic Research Program
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Nashville, Tennessee

Reshma Mahtani, DO
Associate Professor of Medicine
Co-Leader, Breast Cancer Program
Sylvester Cancer Center
University of Miami
Miami, Florida

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Meet The Professor Program Participating Faculty

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Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

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

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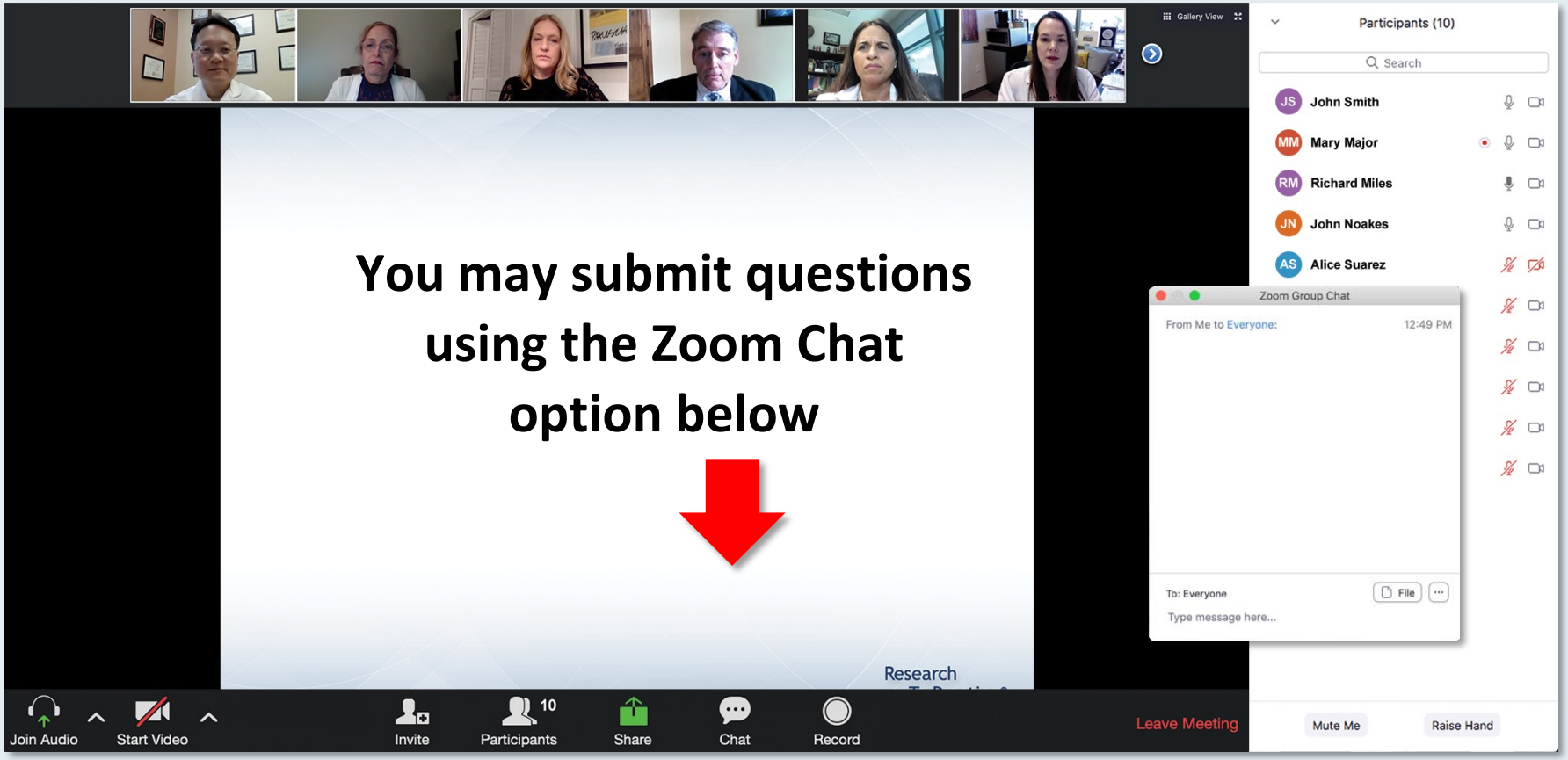

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FDA Approves Pembrolizumab Combination for the First-Line Treatment of Cervical Cancer

Press Release: October 13, 2021

"The Food and Drug Administration approved pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1), as determined by an FDA-approved test.

FDA also granted regular approval to pembrolizumab as a single agent for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test. In June 2018, FDA had granted accelerated approval to this indication with the companion diagnostic, PD-L1 IHC 22C3 pharmDx.

KEYNOTE-826 (NCT03635567), a multicenter, randomized, double-blind, placebo-controlled trial… enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy. Patients were enrolled irrespective of PD-L1 expression status. Patients were randomized (1:1) to pembrolizumab 200 mg plus chemotherapy with or without bevacizumab or placebo plus chemotherapy with or without bevacizumab. Pembrolizumab was continued until disease progression, unacceptable toxicity, or 24 months of treatment."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-combination-first-line-treatment-cervical-cancer

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FDA Approves Adjuvant Abemaciclib with Endocrine Therapy for Resected High-Risk Early Breast Cancer

Press Release: October 13, 2021

"The FDA approved abemaciclib plus endocrine therapy (ET) as adjuvant treatment for patients with hormone receptor (HR)-positive, HER2-negative, node-positive early breast cancer who are at high risk of recurrence and have a Ki-67 score of 20% or greater.

Results of the open-label, multicenter phase 3 monarchE trial (NCT03155997) support the FDA's decision. Patients with HR-positive, HER2-negative resected early breast cancer and with clinical and pathological features associated with a high-risk of disease recurrence were randomized in a 1:1 fashion to receive 2 years of abemaciclib 150 mg twice per day plus ET or ET alone, with adjuvant ET continuing for up to 10 years as recommended by their treating clinician.

Abemaciclib resulted in an improvement in the primary end point of invasive disease-free survival (IDFS)."

www.cancernetwork.com/view/fda-approves-adjuvant-abemaciclib-plus-et-for-resected-high-risk-early-breast-cancer

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Nick Leasure, MD
Oncologist at Tower Health Reading
Co-Director of Multidisciplinary Breast Clinic
Hematology/Oncology Fellowship Program Director
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Associate Director, Community Outreach
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Ruth O'Regan, MD
Chair, Department of Medicine
Charles A Dewey Professor of Medicine
University of Rochester
Rochester, New York

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Meet The Professor with Dr Hamilton

Introduction

MODULE 1: Case Presentations

- Dr Leasure: A 50-year-old woman with metastatic HER2-positive breast cancer
- Dr Rodriguez: A 56-year-old woman with metastatic ER/PR-negative, HER2-positive breast cancer
- Dr Kumar: Three patients with metastatic HER2-positive disease
- Dr Leasure: A 43-year-old woman with localized ER/PR-negative, HER2-positive breast cancer
- Dr O'Regan: A 39-year-old woman with localized triple-positive breast cancer
- Dr Leasure: A 47-year-old woman with localized ER/PR-positive, HER2-positive breast cancer and residual disease
- Dr Patt: A 60-year-old woman with high-risk, localized ER-positive, HER2-positive breast cancer

MODULE 2: Journal Club with Dr Hamilton

MODULE 3: Beyond the Guidelines

MODULE 4: Key Data Sets

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Trastuzumab Deruxtecan Significantly Improved PFS Over T-DM1 for HER2-Positive Metastatic Breast Cancer

Press Release – August 9, 2021

"Trastuzumab deruxtecan demonstrated superior progression-free survival (PFS) outcomes over trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer, based on the phase 3 DESTINY-Breast03 trial (NCT03529110). The study's planned interim analysis identified a statistically significant and clinically meaningful improvement in the primary end point of PFS as assessed by an Independent Data Monitoring Committee (IDMC) for patients with HER2-positive, unresectable and/or metastatic breast cancer who received prior treatment with trastuzumab and a taxane.

Approximately 500 patients were enrolled in the DESTINY-Breast03 trial, who were randomized to either the experimental trastuzumab deruxtecan arm or the comparator T-DM1 arm. The primary end point was PFS assessed by IDMC, with secondary end points including overall survival (OS), objective response rate (ORR), duration of response, and PFS based on investigator assessment.

While patients treated with trastuzumab deruxtecan trended toward OS improvement, the data were immature. Furthermore, the safety profile was consistent with previously reported data regarding trastuzumab deruxtecan, with no new safety signals or grade 4/5 treatment-related interstitial lung disease events observed."

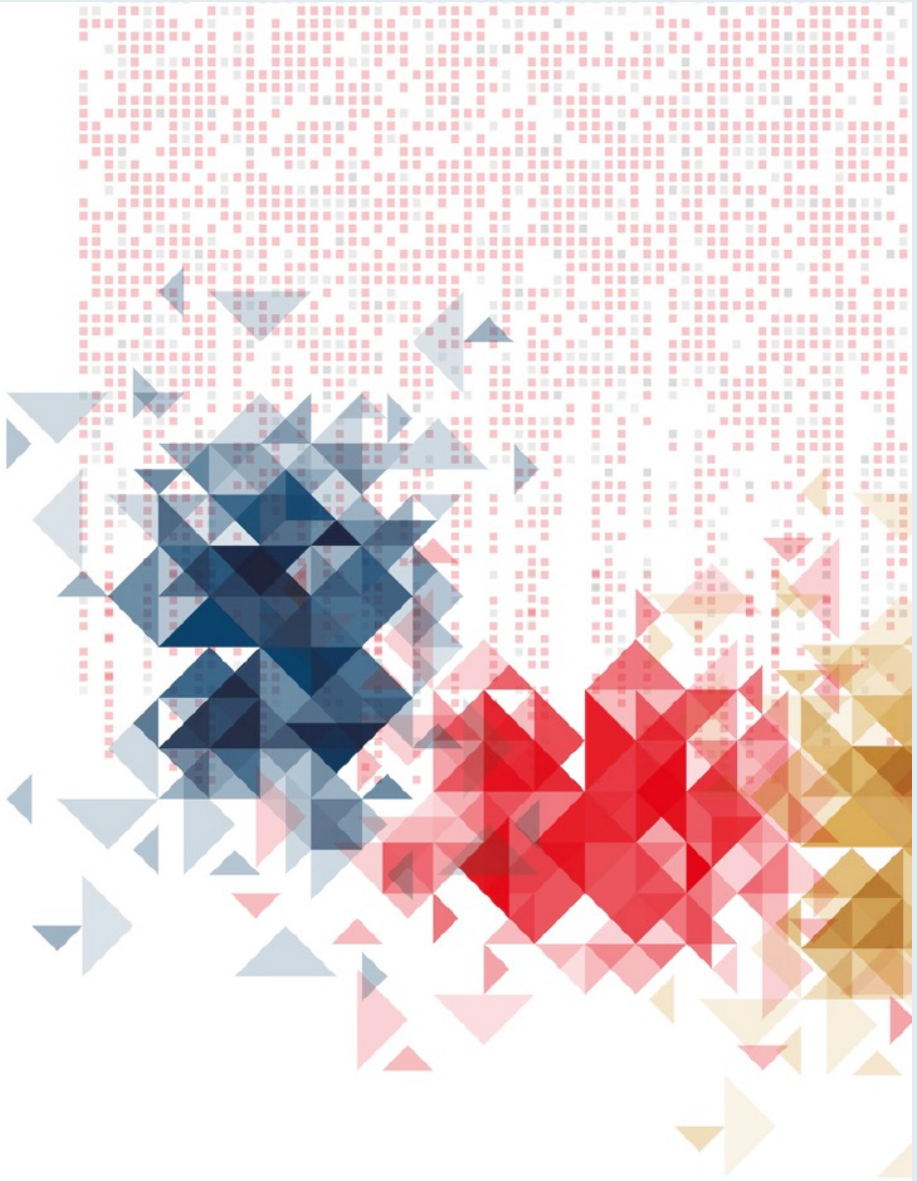
https://www.cancernetwork.com/view/trastuzumab-deruxtecan-significantly-improved-pfs-over-tdm-1-for-her2-metastatic-breast-cancer

2021 ESMO congress

Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Results of the Randomized, Phase 3 Study DESTINY-Breast03

Javier Cortés, MD[a], Sung-Bae Kim, Wei-Pang Chung, Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung, Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee, Yali Liu, Jillian Cathcart, Emarjola Bako, Sunil Verma, Sara Hurvitz
On behalf of the DESTINY-Breast03 investigators

[a]Medical Oncology, International Breast Cancer Center (IBCC), Quironsalud Group, and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain.



Abstract LBA1

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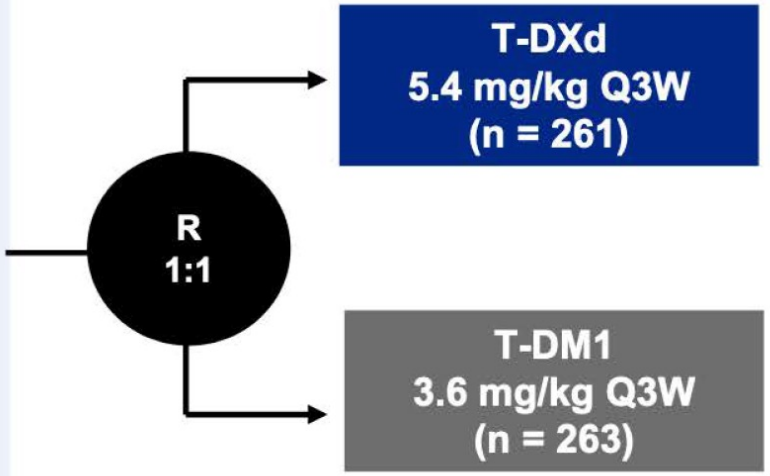
DESTINY-Breast03 Phase III Trial Schema

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

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



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

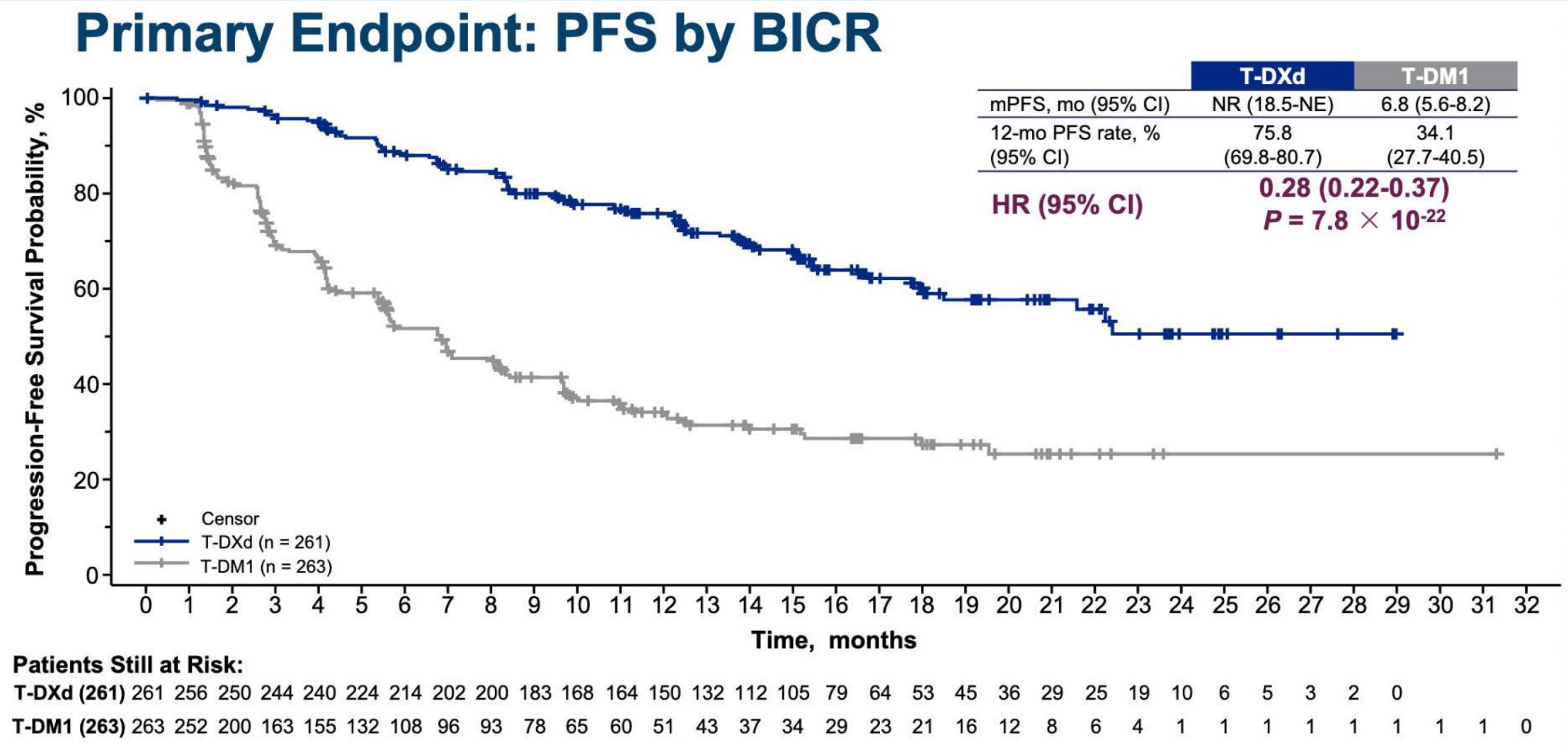
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Cortés J et al. ESMO 2021;Abstract LBA1.

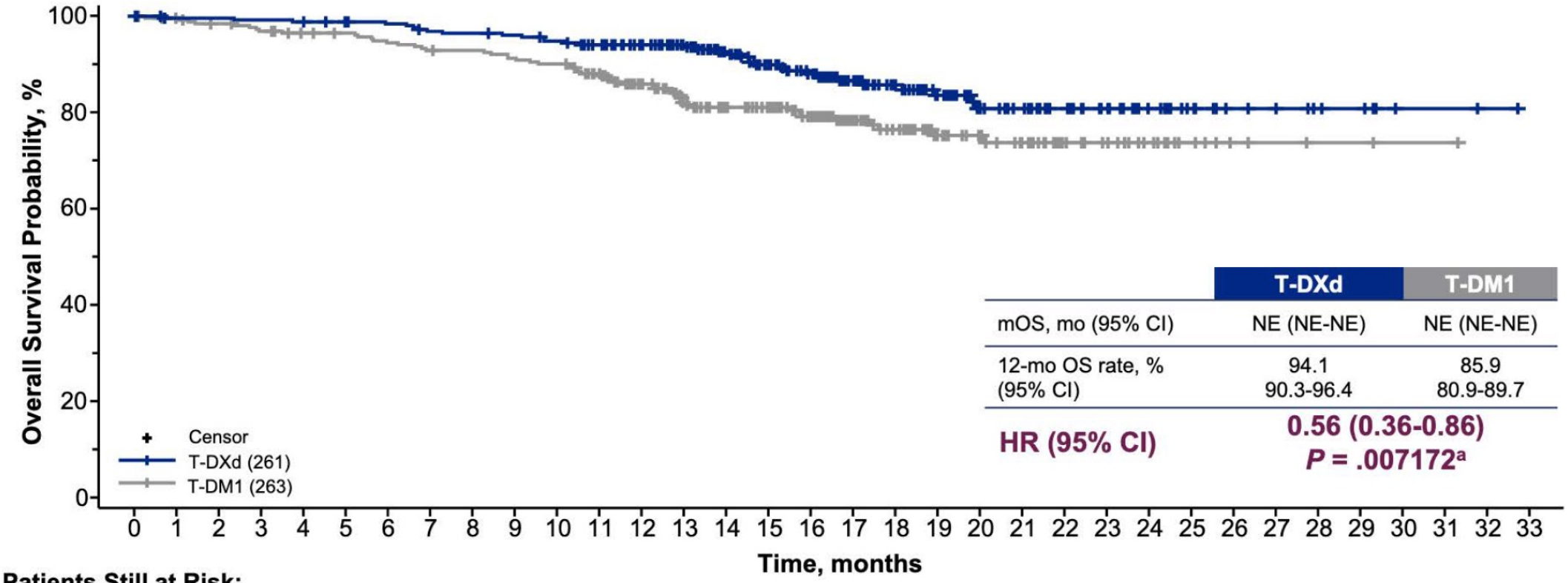
DESTINY-Breast03: PFS by BICR



Cortés J et al. ESMO 2021;Abstract LBA1.

DESTINY-Breast03: OS by BICR

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)** *P* = .007172[a]	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

2021 ESMO congress

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

Cortés J et al. ESMO 2021;Abstract LBA1.

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DESTINY-Breast03: Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

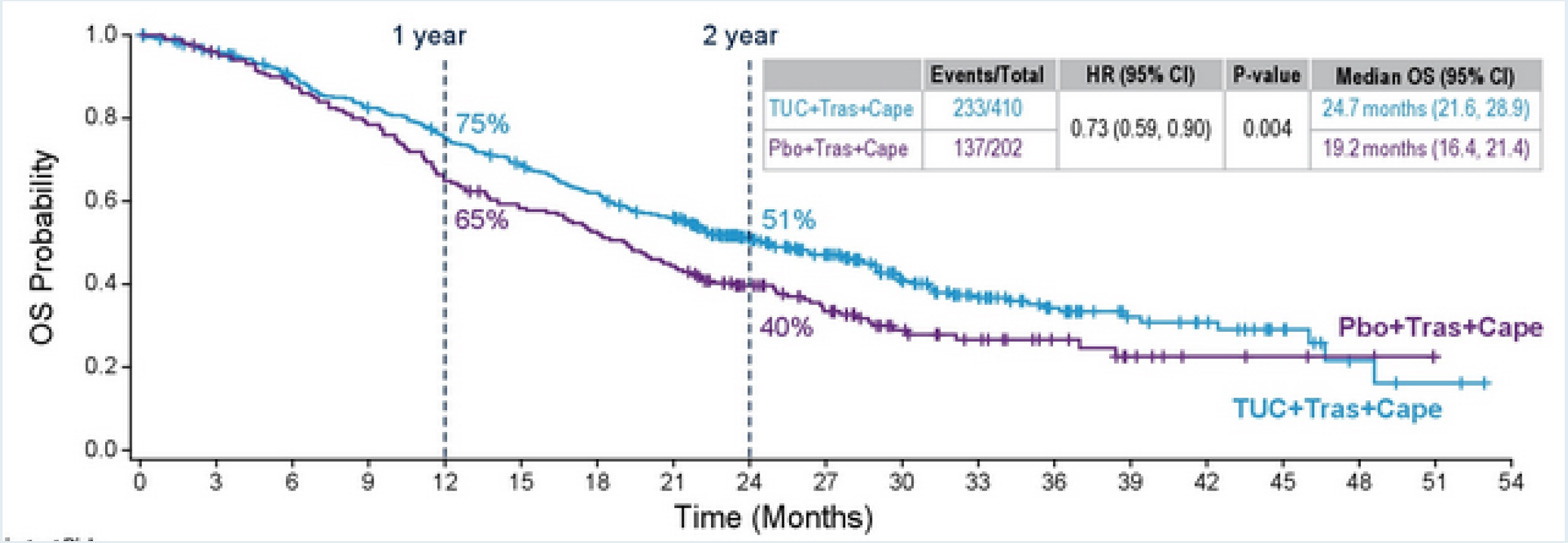
Cortés J et al. ESMO 2021;Abstract LBA1.

Updated Results of Tucatinib versus Placebo Added to Trastuzumab and Capecitabine for Patients with Pretreated HER2+ Metastatic Breast Cancer with and without Brain Metastases (HER2CLIMB)

Curigliano G et al.

ASCO 2021;Abstract 1043.

HER2CLIMB: Overall Survival



	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

Curigliano G et al. ASCO 2021;Abstract 1043.

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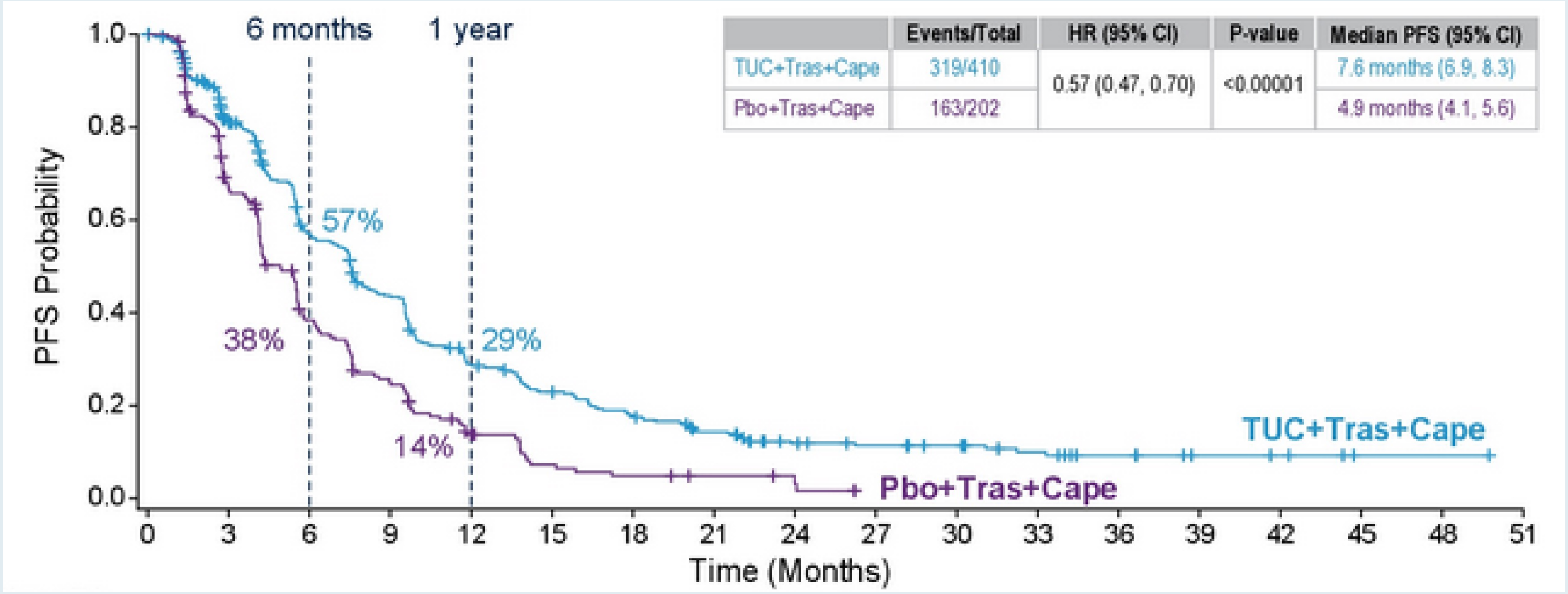
HER2CLIMB: Progression-Free Survival



	Events/Total	HR (95% CI)	P-value	Median PFS (95% CI)
TUC+Tras+Cape	319/410	0.57 (0.47, 0.70)	<0.00001	7.6 months (6.9, 8.3)
Pbo+Tras+Cape	163/202			4.9 months (4.1, 5.6)

Curigliano G et al. ASCO 2021;Abstract 1043.

Tucatinib vs Placebo in Combination with Trastuzumab and Capecitabine for Patients with Locally Advanced Unresectable or HER2-Positive Metastatic Breast Cancer (HER2CLIMB): Outcomes by Hormone Receptor Status

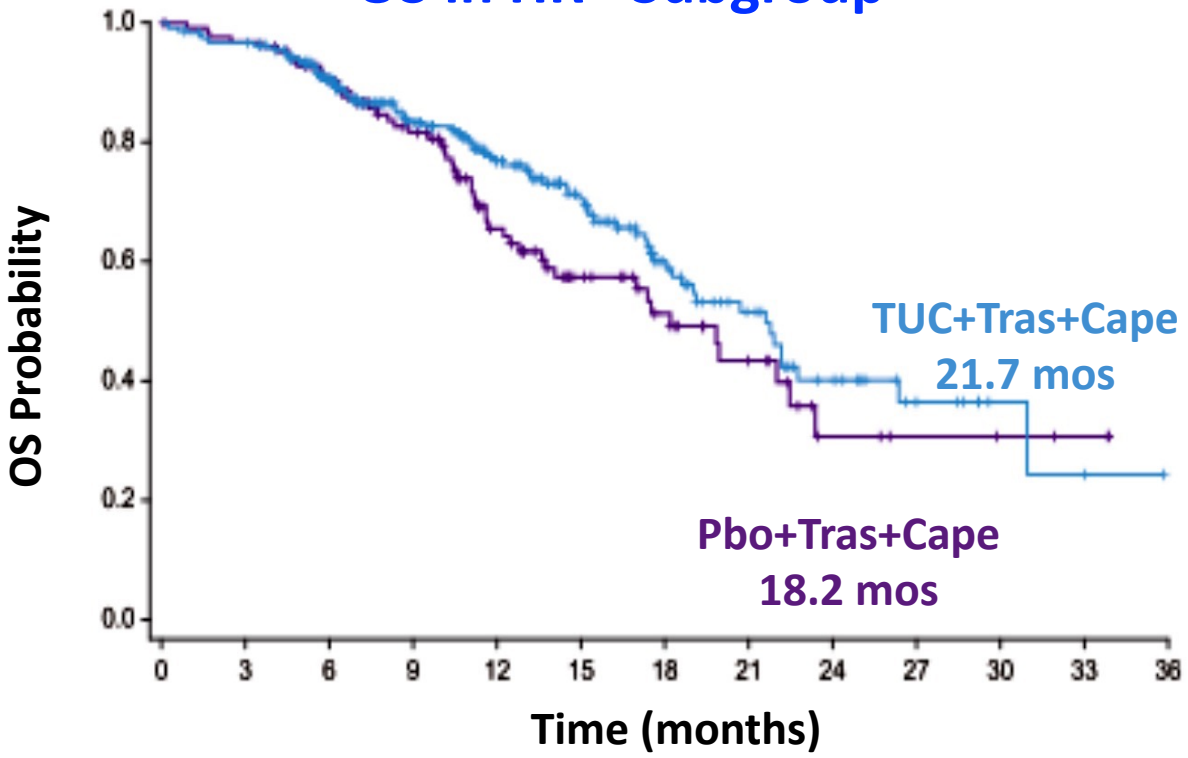
Hamilton E et al.

SABCS 2020;Abstract PD3-08.

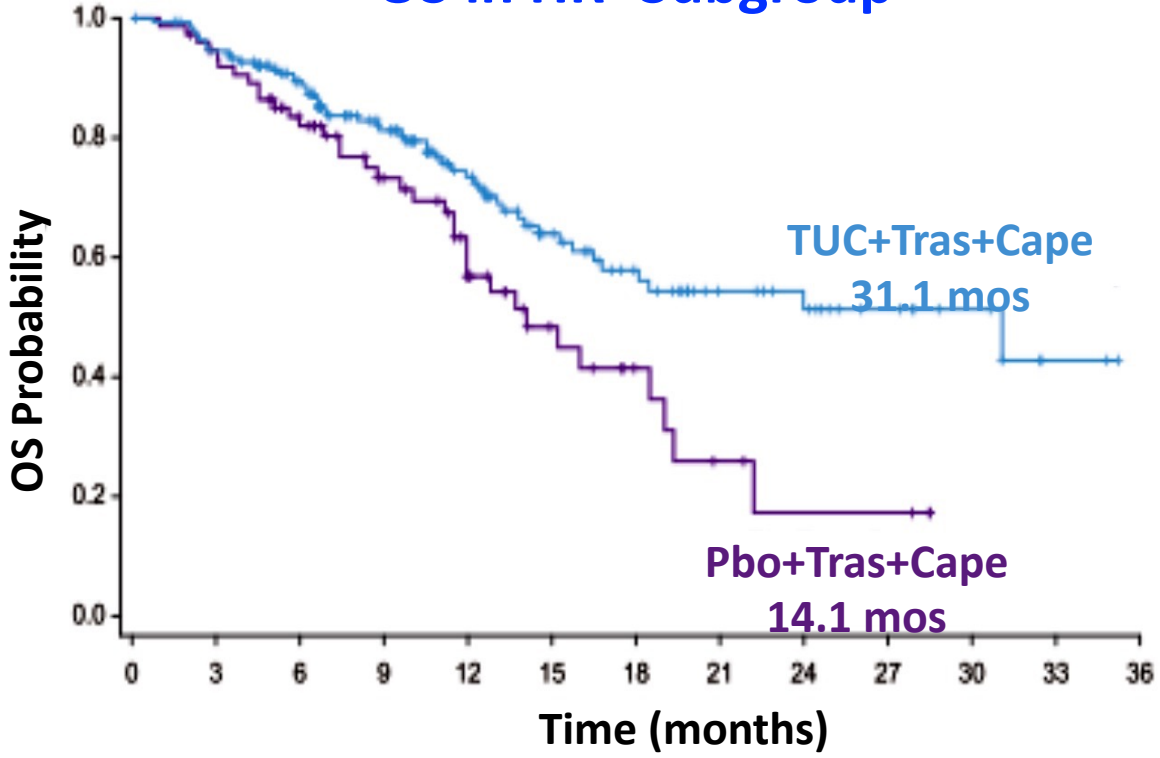
OS by HR Status in the Total Study Population

- Clinically meaningful improvement of OS was observed in patients on the tucatinib arm regardless of hormone receptor status.

OS in HR+ Subgroup



OS in HR- Subgroup



Hamilton E et al. SABCS 2020;Abstract PD3-08.

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HER2CLIMB: Safety Outcomes

Select AE	Tucatinib (n = 404)		Placebo (n = 197)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	99.3%	55.2%	97.0%	48.7%
Diarrhea	80.9%	12.9%	53.3%	8.6%
PPE syndrome	63.4%	13.1%	52.8%	9.1%
Nausea	58.4%	3.7%	43.7%	3.0%
Fatigue	45.0%	4.7%	43.1%	4.1%
Vomiting	35.9%	3.0%	25.4%	3.6%
Stomatitis	25.5%	2.5%	14.2%	0.5%
Increased AST	21.3%	4.5%	11.2%	0.5%
Increased ALT	20.0%	5.4%	6.6%	0.5%

Murthy R et al. SABCS 2019;Abstract GS1-01; Murthy RK et al. *N Engl J Med* 2020;382(7):597-609.

Select Trials in Progress for HER2-Positive Breast Cancer

- ESMO 2021: 330TiP Trastuzumab deruxtecan (T-DXd; DS-8201) in HER2-positive (HER2+) and HER2-low expressing (HER-LE) metastatic breast cancer (MBC) with brain metastases (BM) and/or leptomeningeal carcinomatosis (LMC): DEBBRAH
  Presenter: Marta Vaz Batista

- ESMO 2021: 329TiP KATE3 – A phase III study of trastuzumab emtansine (T-DM1) in combination with atezolizumab or placebo in patients with previously treated HER2-positive and PD-L1–positive locally advanced or metastatic breast cancer
  Presenter: Sherene Loi

- ESMO 2021: 328TiP Phase III study of trastuzumab deruxtecan (T-DXd) with or without pertuzumab vs a taxane, trastuzumab and pertuzumab in first-line (1L), human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (mBC): DESTINY-Breast09
  Presenter: Sara Tolaney

Select Trials in Progress for HER2-Positive Breast Cancer (Continued)

- ESMO 2021: 331TiP HER2CLIMB-04 – Phase II trial of tucatinib + trastuzumab deruxtecan in patients with HER2+ locally advanced or metastatic breast cancer with and without brain metastases
  Presenter: Lisa Carey

- ESMO 2020: 353TiP HER2CLIMB-02 – A randomized, double-blind, phase III study of tucatinib or placebo with T-DM1 for unresectable locally advanced or metastatic HER2+ breast cancer
  Presenter: Sara Hurvitz

- ASCO 2021: TPS595 Postneoadjuvant T-DM1 + tucatinib/placebo in patients with residual HER2-positive invasive breast cancer
  Presenter: Ciara Catherine Maria O'Sullivan

- ASCO 2021: TPS596 eMonarcHER – A phase 3 study of abemaciclib plus standard adjuvant endocrine therapy in patients with HR+, HER2+, node-positive, high-risk early breast cancer
  Presenter: Sara Tolaney

Select Trials in Progress for HER2-Positive Breast Cancer (Continued)

- ASCO 2021: TPS1099 Phase I/II study of radiation therapy followed by intrathecal trastuzumab/pertuzumab in the management of HER2+ breast leptomeningeal disease
  Presenter: Kamran A Ahmed

- SABCS 2020: OT-03-01 Trastuzumab deruxtecan (T-DXd; DS-8201) vs trastuzumab emtansine (T-DM1) in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy: A randomized, phase 3 trial (DESTINY-Breast05)
  Presenter: Charles Geyer

- SABCS 2020: OT-28-01 HER2CLIMB-02 – A randomized, double-blind, phase 3 study of tucatinib or placebo with T-DM1 for unresectable locally-advanced or metastatic HER2+ breast cancer
  Presenter: Sara Hurvitz

- SABCS 2020: OT-28-03 VICKI – A Phase Ib/II, randomized, placebo-controlled, study of venetoclax plus ado-trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-positive locally advanced (LA) or metastatic breast cancer (MBC)
  Presenter: Geoffrey Lindeman

Select Trials in Progress for HER2-Positive Breast Cancer (Continued)

- SABCS 2019: OT2-01-02 TBCRC049 – A phase II non-randomized study to assess the safety and efficacy of the combination of tucatinib and trastuzumab and capecitabine for treatment of leptomeningeal metastases in HER2 positive breast cancer
  Presenter: Rashmi K Murthy

Meet The Professor with Dr Hamilton

Introduction

MODULE 1: Case Presentations

- Dr Leasure: A 50-year-old woman with metastatic HER2-positive breast cancer
- Dr Rodriguez: A 56-year-old woman with metastatic ER/PR-negative, HER2-positive breast cancer
- Dr Kumar: Three patients with metastatic HER2-positive disease
- Dr Leasure: A 43-year-old woman with localized ER/PR-negative, HER2-positive breast cancer
- Dr O'Regan: A 39-year-old woman with localized triple-positive breast cancer
- Dr Leasure: A 47-year-old woman with localized ER/PR-positive, HER2-positive breast cancer and residual disease
- Dr Patt: A 60-year-old woman with high-risk, localized ER-positive, HER2-positive breast cancer

MODULE 2: Journal Club with Dr Hamilton

MODULE 3: Beyond the Guidelines

MODULE 4: Key Data Sets

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Leasure: A 50-year-old woman with metastatic HER2-positive breast cancer

Dr Nick Leasure

- Presented to hospital with difficulty breathing and hypoxia after having neglected a breast cancer
- Workup revealed extensive liver and lung metastases, and a lesion in the brain; respiratory issues treated with steroids
- Presents at clinic several days later in respiratory extremis
- Taxane with trastuzumab and pertuzumab initiated
- She immediately improved within a week or two of starting therapy
- Brain lesion followed with observation

Case Presentation – Dr Rodriguez: A 56-year-old woman with metastatic ER/PR-negative, HER2-positive breast cancer

Dr Estelamari Rodriguez

- Presented 8 years ago with fatigue, shortness of breath, and abdominal pain
- CT scan revealed extensive metastatic disease to liver, lung, and right breast
- Biopsies confirmed metastatic right breast carcinoma, ER/PR-negative breast cancer, HER2-positive by FISH
- Paclitaxel/trastuzumab/pertuzumab → intolerant to paclitaxel due to neuropathy, switched to *nab* paclitaxel with better tolerance
- Maintenance trastuzumab/pertuzumab

Questions

- What would you have recommended as a first-line regimen for a patient with an ER/PR-negative, HER2-positive breast cancer who's never had prior therapy?

RTP RESEARCH TO PRACTICE

Dr Kumar: Three patients with metastatic HER2-positive disease

Dr KS Kumar

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Case Presentation – Dr Leasure: A 43-year-old woman with localized ER/PR-negative, HER2-positive breast cancer

Dr Nick Leasure

- Self-palpated a mass in the upper outer quadrant of the right breast
- Diagnostic mammography: spiculated mass 2.4 cm in size with an adjacent 7 mm nodule
- Biopsy: Grade 3 IDC; ER/PR-negative, strongly HER2-positive
- Imaging of the chest/abdomen/pelvis shows no systemic metastatic disease or axillary adenopathy

Questions

- Would you be comfortable de-escalating chemotherapy in the neoadjuvant setting for this patient?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Leasure: A 43-year-old woman with localized ER/PR-negative, HER2-positive breast cancer (continued)

Dr Nick Leasure

- Self-palpated a mass in the upper outer quadrant of the right breast
- Diagnostic mammography: spiculated mass 2.4 cm in size with an adjacent 7 mm nodule
- Biopsy: Grade 3 IDC; ER/PR-negative, strongly HER2-positive
- Imaging of the chest/abdomen/pelvis shows no systemic metastatic disease or axillary adenopathy
- ***Enrolled on ECOG-EA1181 trial of neoadjuvant taxane along with trastuzumab and pertuzumab x 12 cycles***

Case Presentation – Dr O'Regan: A 39-year-old woman with localized triple-positive breast cancer

Dr Ruth O'Regan

- Late 2019: Diagnosed with clinical stage cT2, N1 triple-positive breast cancer
- Neoadjuvant TCHP → bilateral mastectomies
  - ypT2, N0, ER-positive, PR-positive, HER2-positive
- Adjuvant T-DM1
- Neratinib x 1 year

Questions

- Would you re-check receptors, particularly HER2, on the surgical specimen?
- Would you administer neratinib to a patient such as this woman? How do you manage neratinib-associated diarrhea, and what success have you had with neratinib dose escalation?
- What are your thoughts about why neratinib looks effective in ER-positive but not ER-negative tumors?
- Would you recommend paclitaxel and trastuzumab/pertuzumab based on the German data?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Leasure: A 47-year-old woman with localized ER/PR-positive, HER2-positive breast cancer and residual disease

Dr Nick Leasure

- Diagnosed with a Grade 3, 2-cm IDC, ER/PR-positive, HER2 strongly positive by IHC; Ki-67 80%
- Enrolled on EA1181 of neoadjuvant paclitaxel with trastuzumab and pertuzumab x 12 cycles
- Clinical resolution of 2-cm mass, repeat mammography and ultrasound suggested shrinkage of the primary tumor
- Partial mastectomy revealed 7 mm of residual invasive carcinoma and 15 axillary lymph nodes positive for disease

Questions

- Should I offer her T-DM1? Would neratinib be reasonable?
- Given the extent of residual disease, did she get much benefit from the anti-HER2 treatment? Is this really a hormone receptor-positive driven cancer, and should I be thinking more about maximizing her hormonal therapy with ovarian suppression and aromatase inhibitor? Would you consider a CDK inhibitor even though she has HER2-positive disease?

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Case Presentation – Dr Patt: A 60-year-old woman with high-risk, localized ER-positive, HER2-positive breast cancer

Dr Debra Patt

- 2011: DCIS, s/p mastectomy
- Past year, patient noticed changes in her right breast, with pinching of the skin in the right lateral outer quadrant, which have increased and become painful
- Biopsy: Invasive cancer, but receptors not available
- Resection: 5.5-cm tumor, ER/PR positive, HER2 amplified; involvement of the dermis and the skeletal muscle
- Plan to administer TCHP followed by re-resection and postmastectomy radiation

Questions

- Are there any other treatments or approaches that may be brought to the table to reduce her risk, such as T-DM1?

Meet The Professor with Dr Hamilton

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MODULE 3: Beyond the Guidelines

MODULE 4: Key Data Sets

RTP RESEARCH TO PRACTICE

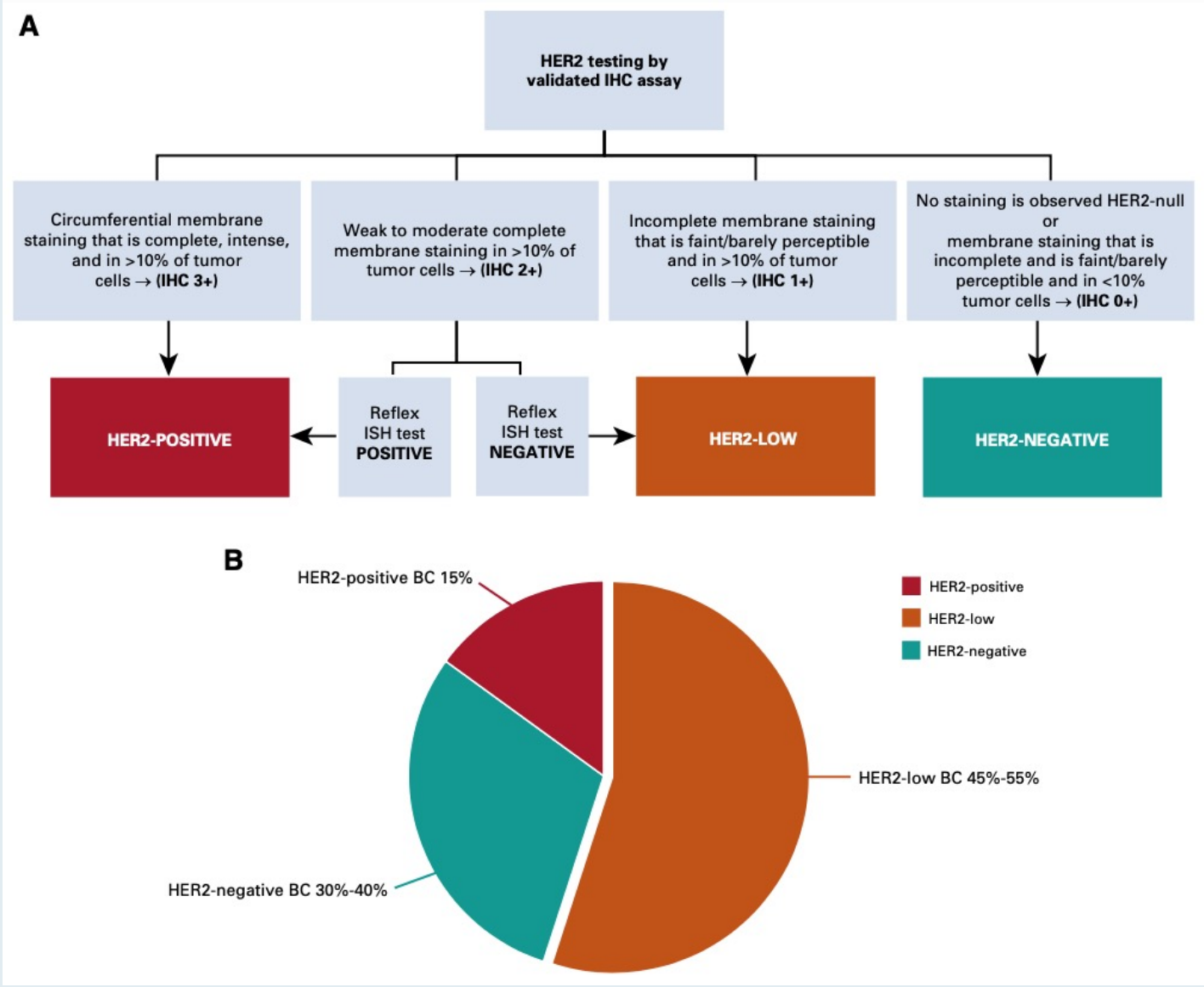
J Clin Oncol 2020;38(17):1951-62.

review articles

HER2-Low Breast Cancer: Pathological and Clinical Landscape

Paolo Tarantino, MD[1,2]; Erika Hamilton, MD[3]; Sara M. Tolaney, MD, MPH[4]; Javier Cortes, MD, PhD[5,6]; Stefania Morganti, MD[1,2]; Emanuela Ferraro, MD[1,2]; Antonio Marra, MD[1,2]; Giulia Viale, MD[1,2]; Dario Trapani, MD[1,2]; Fatima Cardoso, MD[7]; Frédérique Penault-Llorca, MD, PhD[8,9]; Giuseppe Viale, MD[1,2]; Fabrice Andrè, MD, PhD[10]; and Giuseppe Curigliano, MD, PhD[1,2]

Proposal of an Algorithm for Defining HER2-Low Breast Cancer



Tarantino P et al. *J Clin Oncol* 2020;38(17):1951-62.

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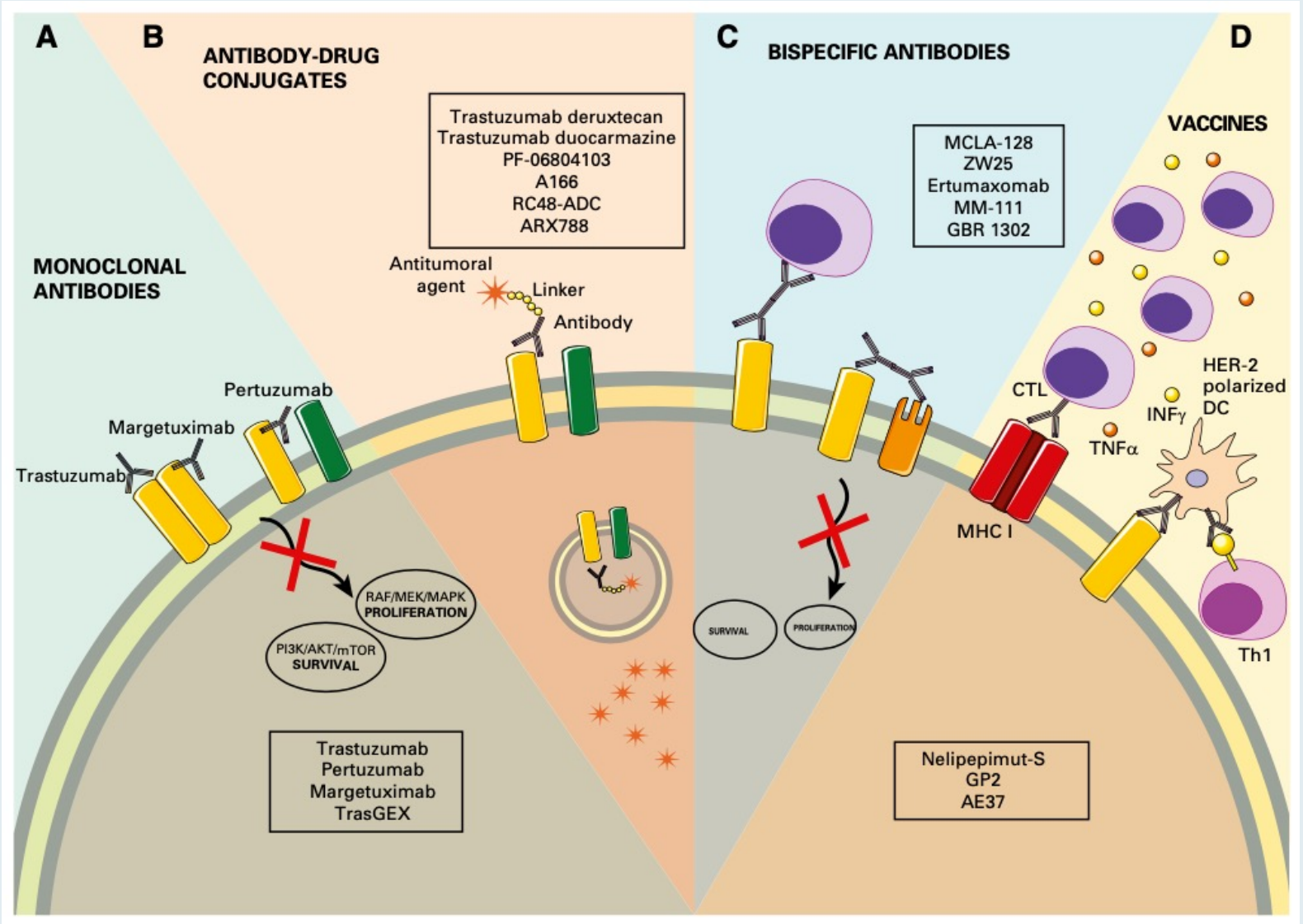
Novel Agents and Mechanisms Enabling the Targeting of HER2 Low-Expressing Breast Cancer



Tarantino P et al. *J Clin Oncol* 2020;38(17):1951-62.

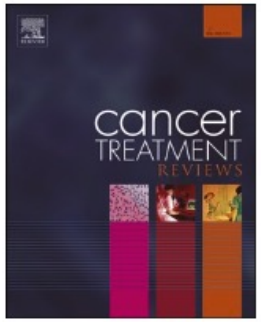
RTP RESEARCH TO PRACTICE

Cancer Treatment Reviews 100 (2021) 102286

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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



Targeting HER2 heterogeneity in breast cancer

Erika Hamilton [a,*], Mythili Shastry [b], S. Michelle Shiller [c], Rongqin Ren [c]

Journal Club with Dr Hamilton

- Andre F et al. **Trastuzumab deruxtecan (T-DXd) combinations in patients with HER2-positive advanced or metastatic breast cancer: A phase 1b/2, open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast07).** ASCO 2021;Abstract TPS1096.
- Hamilton EP et al. **Impact of anti-HER2 treatments combined with atezolizumab on the tumor immune microenvironment in early or metastatic breast cancer: Results from a phase Ib study.** *Clin Breast Cancer* 2021;[Online ahead of print].
- Okines AFC et al. **Management of adverse events in patients with HER2+ metastatic breast cancer treated with tucatinib, trastuzumab, and capecitabine (HER2CLIMB).** ASCO 2020;Abstract 1043.
- Hamilton EP et al. **Trastuzumab deruxtecan (T-DXd; DS-8201) with nivolumab in patients with HER2-expressing, advanced breast cancer: A 2-part, phase 1b, multicenter, open-label study.** SABCS 2020;Abstract PD3-07.
- Burris HA et al. **A first-in-human study of AO-176, a highly differentiated anti-CD47 antibody, in patients with advanced solid tumors.** ASCO 2021;Abstract 2516.

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Journal Club with Dr Hamilton – Continued

- Pegram MD et al. **First-in-human, phase 1 dose-escalation study of biparatopic anti-HER2 antibody-drug conjugate MEDI4276 in patients with HER2-positive advanced breast or gastric cancer.** *Mol Cancer Ther* 2021;20(8):1442-53.
- Pistilli P et al. **Clinical activity of MCLA-128 (zenocutuzumab) in combination with endocrine therapy (ET) in ER+/HER2-low, non-amplified metastatic breast cancer (MBC) patients (pts) with ET-resistant disease who had progressed on a CDK4/6 inhibitor (CDK4/6i).** ASCO 2020;Abstract 1037.
- Hamilton EP et al. **Clinical activity of MCLA-128 (zenocutuzumab), trastuzumab, and vinorelbine in HER2 amplified metastatic breast cancer (MBC) patients (pts) who had progressed on anti-HER2 ADCs.** ASCO 2020;Abstract 3093.

Meet The Professor with Dr Hamilton

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RTP RESEARCH TO PRACTICE

Management of Metastatic HER2-Positive Breast Cancer

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A 65-year-old woman with an ER-negative, HER2-positive IDC experiences disease recurrence in the liver 6 months after completing neoadjuvant TCHP followed by adjuvant T-DM1. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

1. Trastuzumab/pertuzumab/docetaxel
2. Neratinib + paclitaxel
3. Neratinib + capecitabine
4. Tucatinib + trastuzumab/capecitabine
5. Trastuzumab deruxtecan
6. Trastuzumab + capecitabine
7. Other

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A 65-year-old woman with an ER-negative, HER2-positive IDC experiences disease recurrence in the liver 6 months after completing neoadjuvant TCHP followed by adjuvant T-DM1. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Trastuzumab deruxtecan	 Dr Mahtani	Trastuzumab deruxtecan
 Dr Hamilton	Trastuzumab deruxtecan	 Dr Rugo	Trastuzumab deruxtecan
 Dr Hurvitz	Trastuzumab deruxtecan	 Dr Tolaney	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

A 65-year-old woman with an ER-negative, HER2-positive IDC experiences disease recurrence in the liver 6 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

1. Trastuzumab/pertuzumab/docetaxel
2. T-DM1
3. Neratinib + paclitaxel
4. Neratinib + capecitabine
5. Tucatinib + trastuzumab/capecitabine
6. Trastuzumab deruxtecan
7. Trastuzumab + capecitabine
8. Other

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A 65-year-old woman with an ER-negative, HER2-positive IDC experiences disease recurrence in the liver 6 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Trastuzumab deruxtecan	 Dr Mahtani	Trastuzumab deruxtecan
 Dr Hamilton	Trastuzumab deruxtecan	 Dr Rugo	Trastuzumab deruxtecan
 Dr Hurvitz	Trastuzumab deruxtecan	 Dr Tolaney	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

A 65-year-old woman with an ER-negative, HER2-positive IDC experiences disease recurrence in the liver and brain 18 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

1. Trastuzumab/pertuzumab/docetaxel
2. T-DM1
3. Neratinib + paclitaxel
4. Neratinib + capecitabine
5. Tucatinib + trastuzumab/capecitabine
6. Trastuzumab deruxtecan
7. Trastuzumab + capecitabine
8. Other

RTP
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TO PRACTICE

A 65-year-old woman with an ER-negative, HER2-positive IDC experiences disease recurrence in the liver and brain 18 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Tucatinib + trastuzumab/ capecitabine
 Dr Hamilton	Tucatinib + trastuzumab/ capecitabine	 Dr Rugo	Tucatinib + trastuzumab/ capecitabine
 Dr Hurvitz	Trastuzumab deruxtecan	 Dr Tolaney	Trastuzumab/ pertuzumab/paclitaxel

RTP RESEARCH TO PRACTICE

A 65-year-old woman with an ER-positive, HER2-positive IDC experiences recurrence in the liver and brain 18 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab and postadjuvant neratinib and is receiving adjuvant anastrozole. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Trastuzumab deruxtecan
 Dr Hamilton	Tucatinib + trastuzumab/ capecitabine	 Dr Rugo	Trastuzumab deruxtecan
 Dr Hurvitz	Tucatinib + trastuzumab/ capecitabine	 Dr Tolaney	Trastuzumab/ pertuzumab/paclitaxel

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP followed by second-line T-DM1 on disease progression. She now presents with further low-volume, asymptomatic progression but no evidence of CNS involvement. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Tucatinib + trastuzumab/ capecitabine
 Dr Hamilton	Tucatinib + trastuzumab/ capecitabine	 Dr Rugo	Trastuzumab deruxtecan
 Dr Hurvitz	Tucatinib + trastuzumab/ capecitabine	 Dr Tolaney	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP followed by second-line T-DM1 on disease progression. She now presents with further high-volume, moderately symptomatic progression but no evidence of CNS involvement. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Trastuzumab deruxtecan
 Dr Hamilton	Trastuzumab deruxtecan	 Dr Rugo	Trastuzumab deruxtecan
 Dr Hurvitz	Trastuzumab deruxtecan	 Dr Tolaney	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

At what grade of ILD would you permanently discontinue therapy with trastuzumab deruxtecan for a patient with HER2-positive mBC?

 Dr Gelmon	Grade 2	 Dr Mahtani	Grade 2
 Dr Hamilton	Grade 2	 Dr Rugo	Grade 2
 Dr Hurvitz	Grade 2	 Dr Tolaney	Grade 2

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP but after 1 year experiences disease progression, including 1 brain metastasis that is resected. Regulatory and reimbursement issues aside, what systemic treatment would you recommend next?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Tucatinib + trastuzumab/ capecitabine
 Dr Hamilton	Tucatinib + trastuzumab/ capecitabine	 Dr Rugo	Trastuzumab deruxtecan
 Dr Hurvitz	Trastuzumab deruxtecan	 Dr Tolaney	Trastuzumab deruxtecan

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP but after 1 year experiences disease progression, including multiple brain metastases. Regulatory and reimbursement issues aside, what systemic treatment would you recommend next?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Tucatinib + trastuzumab/ capecitabine
 Dr Hamilton	Tucatinib + trastuzumab/ capecitabine	 Dr Rugo	Tucatinib + trastuzumab/ capecitabine
 Dr Hurvitz	Tucatinib + trastuzumab/ capecitabine	 Dr Tolaney	Tucatinib + trastuzumab/ capecitabine

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP followed by second-line T-DM1 on disease progression. She now presents with a single brain metastasis that is resected with no other evidence of progression. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Continue T-DM1	 Dr Mahtani	Continue T-DM1
 Dr Hamilton	Continue T-DM1	 Dr Rugo	Continue T-DM1
 Dr Hurvitz	Continue T-DM1	 Dr Tolaney	Continue T-DM1

RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-negative, HER2-positive mBC receives first-line THP followed by second-line T-DM1 on disease progression. She now presents with further disease progression, including multiple new brain metastases. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 Dr Gelmon	Tucatinib + trastuzumab/ capecitabine	 Dr Mahtani	Tucatinib + trastuzumab/ capecitabine
 Dr Hamilton	Tucatinib + trastuzumab/ capecitabine	 Dr Rugo	Tucatinib + trastuzumab/ capecitabine
 Dr Hurvitz	Tucatinib + trastuzumab/ capecitabine	 Dr Tolaney	Tucatinib + trastuzumab/ capecitabine

RTP RESEARCH TO PRACTICE

Localized HER2-Positive Breast Cancer

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Which neoadjuvant systemic therapy, if any, would you generally recommend for a 65-year-old patient with a 2.5-cm ER-negative, HER2-positive, clinically node-negative IDC?

1. None
2. TCHP
3. TCH
4. Paclitaxel/trastuzumab
5. Paclitaxel/trastuzumab/pertuzumab
6. ACTH
7. Other

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 65-year-old patient with a 2.5-cm ER-negative, HER2-positive, clinically node-negative IDC?

 Dr Gelmon	TCHP (TCH/pertuzumab) or ACTH/pertuzumab	 Dr Mahtani	TCHP
 Dr Hamilton	TCHP	 Dr Rugo	Paclitaxel/trastuzumab /pertuzumab
 Dr Hurvitz	TCHP	 Dr Tolaney	TCHP

RTP RESEARCH TO PRACTICE

A 65-year-old woman presents with a 3.4-cm ER-positive, HER2-positive IDC with biopsy-proven axillary nodes, receives neoadjuvant TCHP and at surgery is found to have 0.5 cm of residual tumor in the breast and no disease in the nodes. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

1. Trastuzumab
2. Trastuzumab/pertuzumab
3. T-DM1
4. Trastuzumab → neratinib
5. Trastuzumab/pertuzumab → neratinib
6. T-DM1 → neratinib
7. Other

RTP
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A 65-year-old woman presents with a 3.4-cm ER-positive, HER2-positive IDC with biopsy-proven axillary nodes, receives neoadjuvant TCHP and at surgery is found to have 0.5 cm of residual tumor in the breast and no disease in the nodes. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

 Dr Gelmon	T-DM1	 Dr Mahtani	T-DM1
 Dr Hamilton	T-DM1 or T-DM1 → neratinib	 Dr Rugo	T-DM1
 Dr Hurvitz	T-DM1 → neratinib	 Dr Tolaney	T-DM1

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Hamilton

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RTP RESEARCH TO PRACTICE

Management of Metastatic HER2-Positive Breast Cancer

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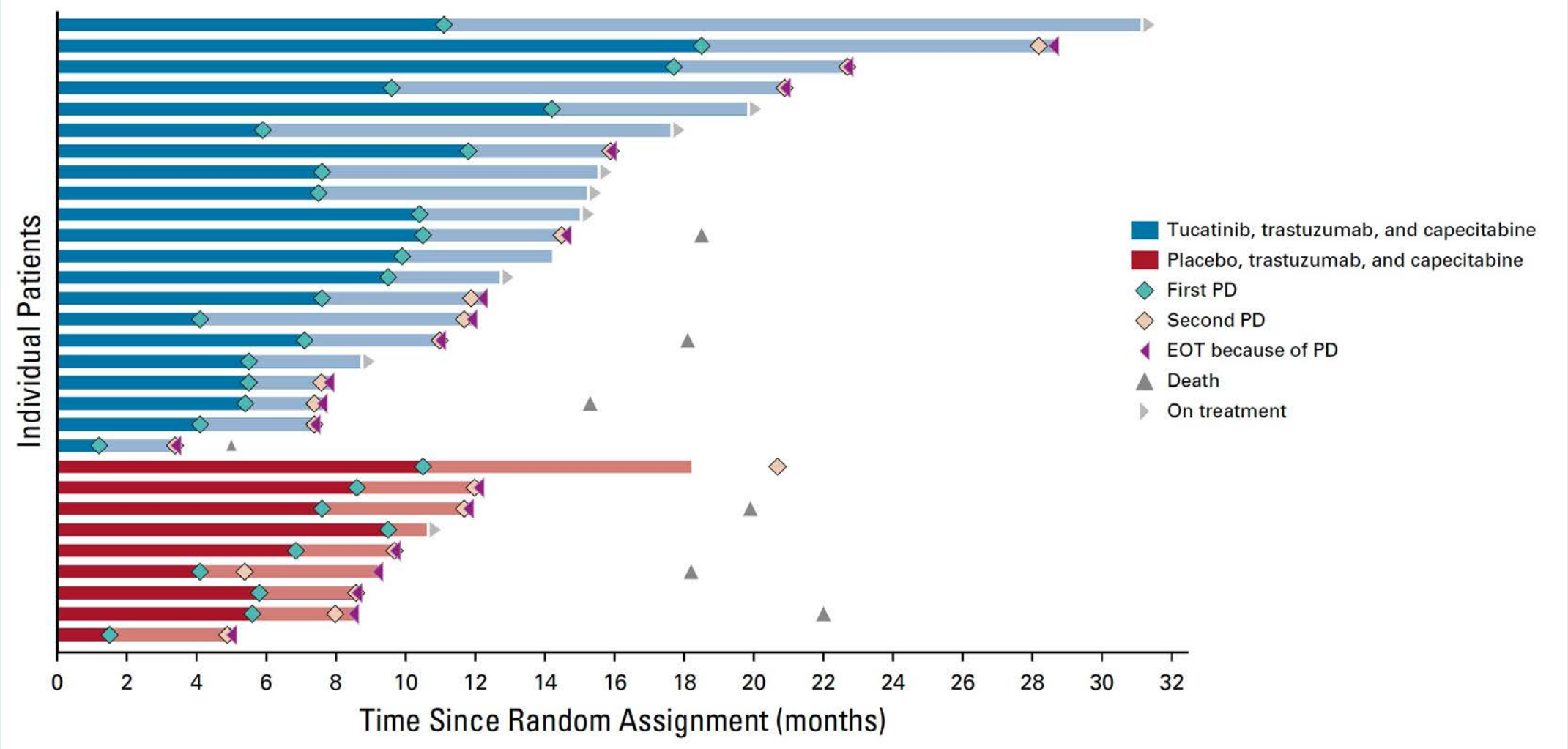
rapid communications

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]

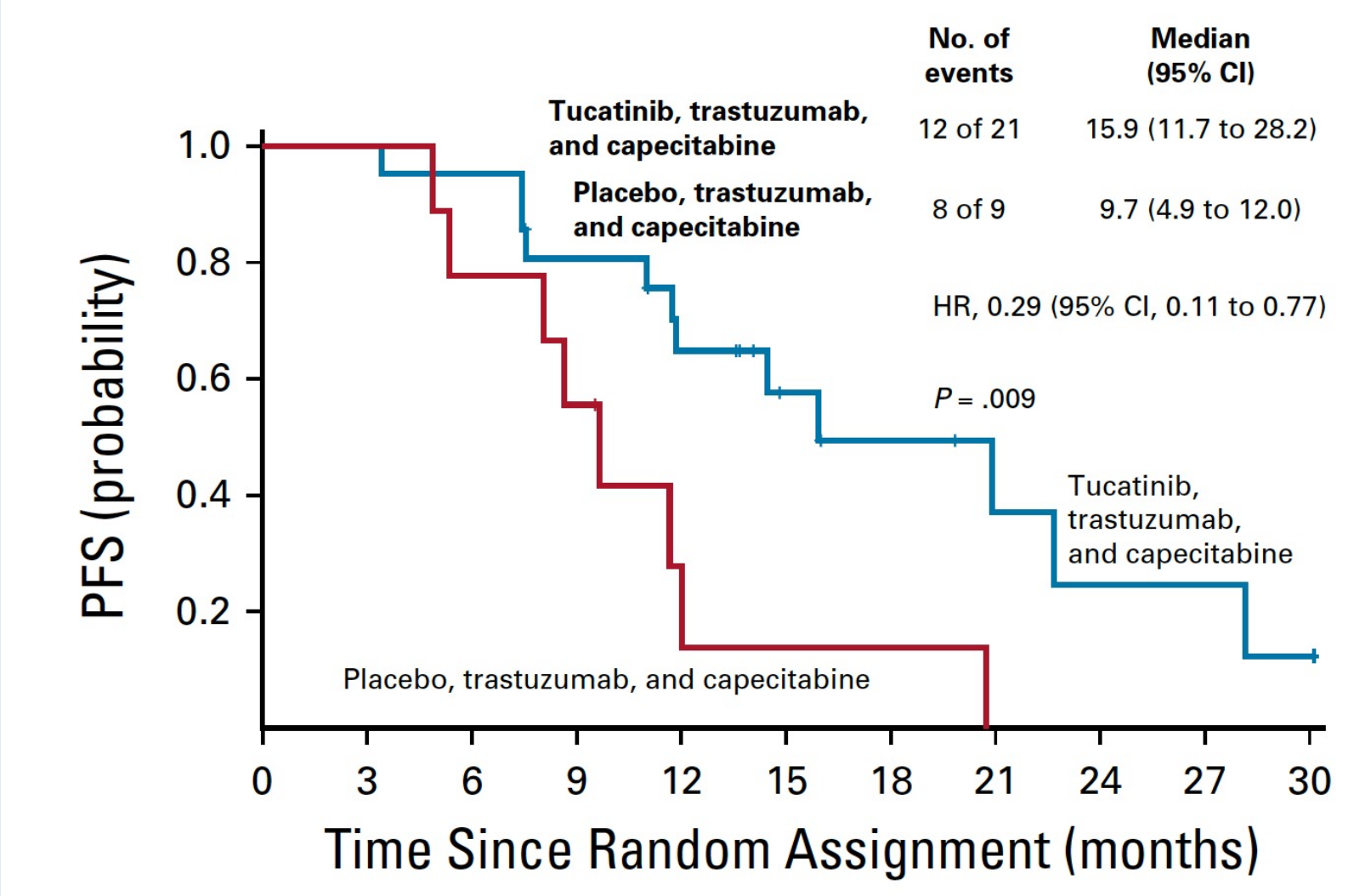
J Clin Oncol 2020;38(23):2610-9.

Duration of Treatment



Lin NU et al. *J Clin Oncol* 2020;38(23):2610-9.

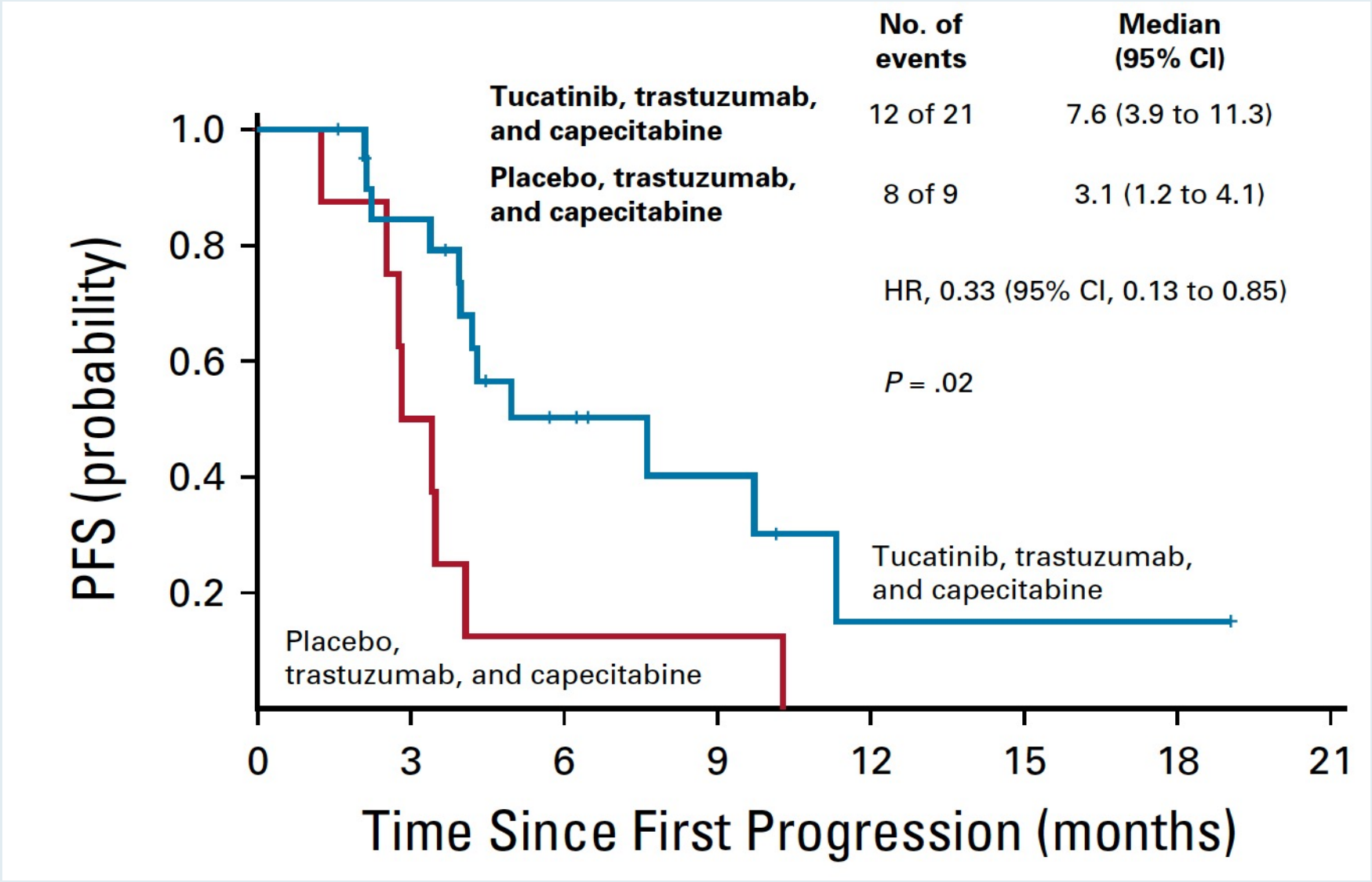
Time from Random Assignment to Second Disease Progression by Investigator Assessment or Death



Lin NU et al. *J Clin Oncol* 2020;38(23):2610-9.

RTP RESEARCH TO PRACTICE

Time from First PD to Second PD by Investigator Assessment or Death



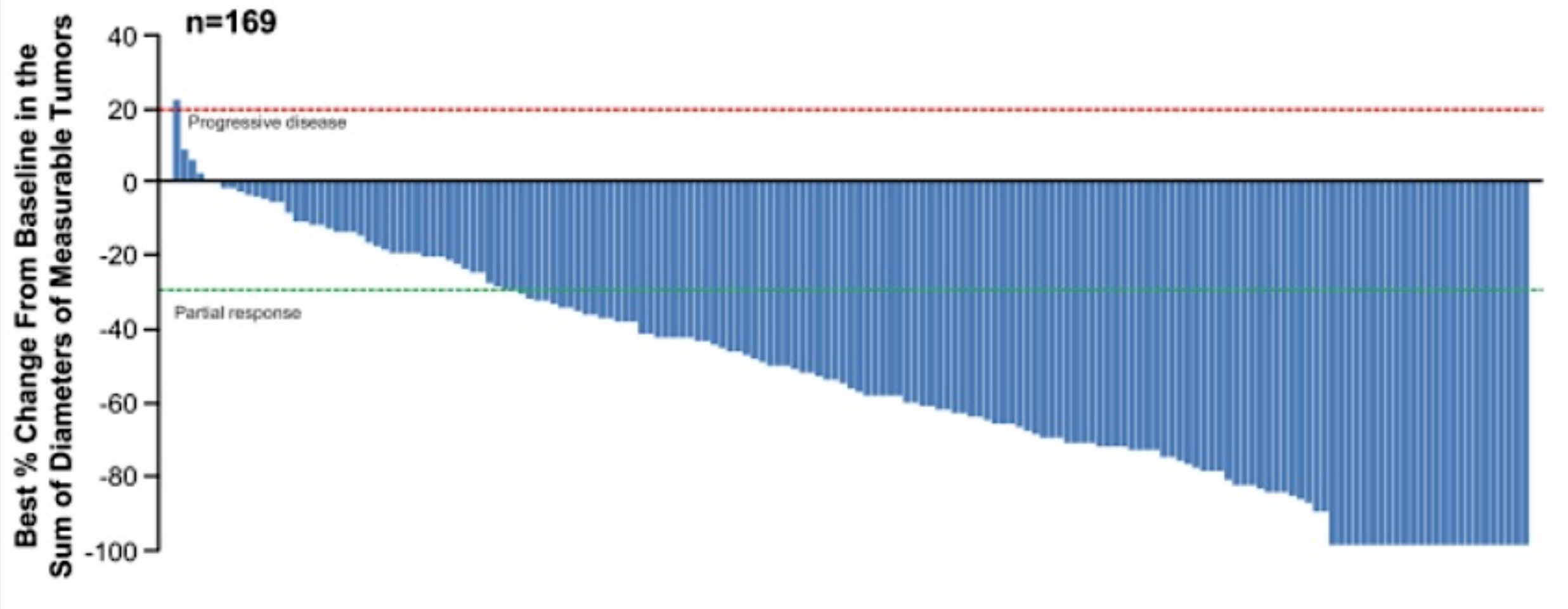
Lin NU et al. *J Clin Oncol* 2020;38(23):2610-9.

Updated Results from DESTINY-Breast01, a Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in HER2-Positive Metastatic Breast Cancer

Modi S et al.

SABCS 2020;Abstract PD3-06.

DESTINY-Breast01: Best Percent Change in Tumor Size from Baseline



Modi S et al. SABCS 2020;Abstract PD3-06.

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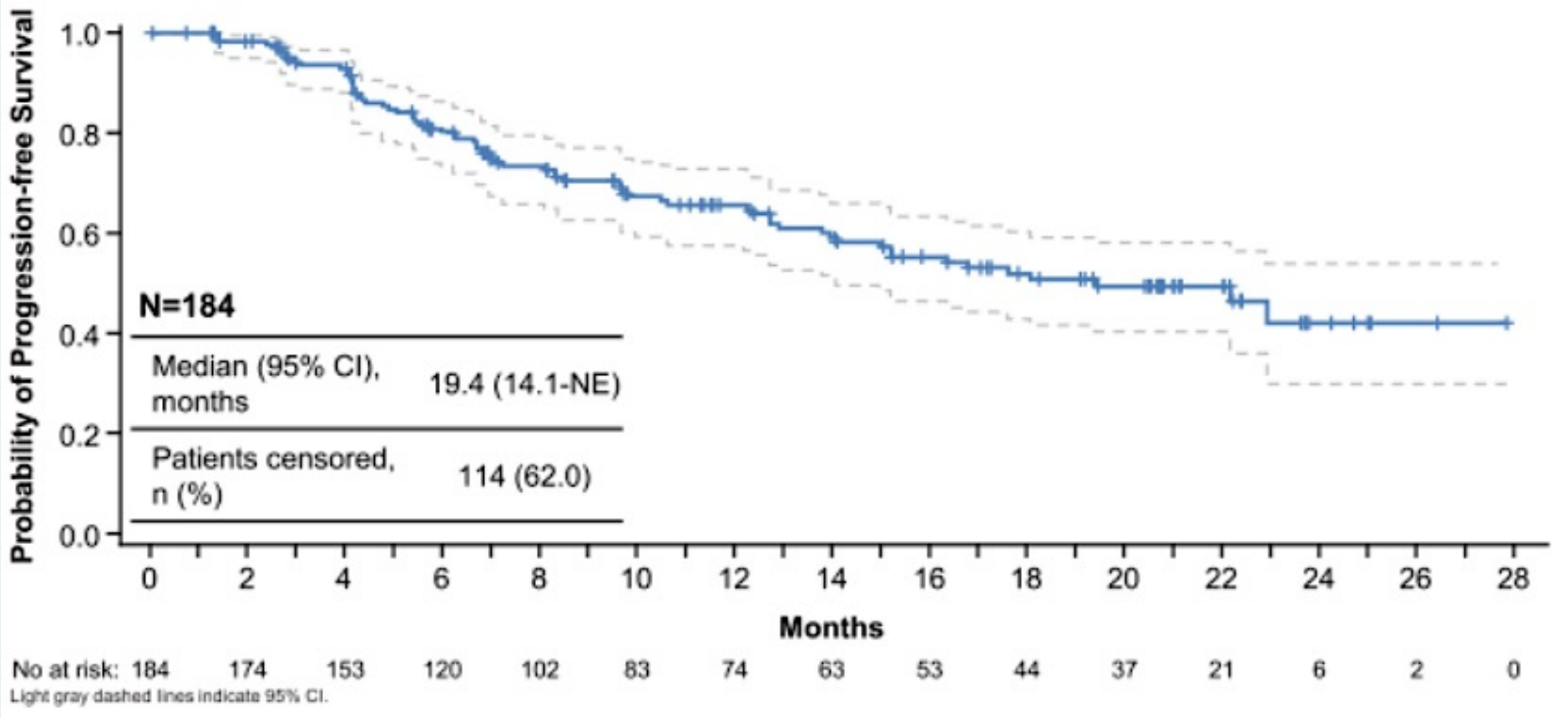
DESTINY-Breast01: Progression-Free Survival



Modi S et al. SABCS 2020;Abstract PD3-06.

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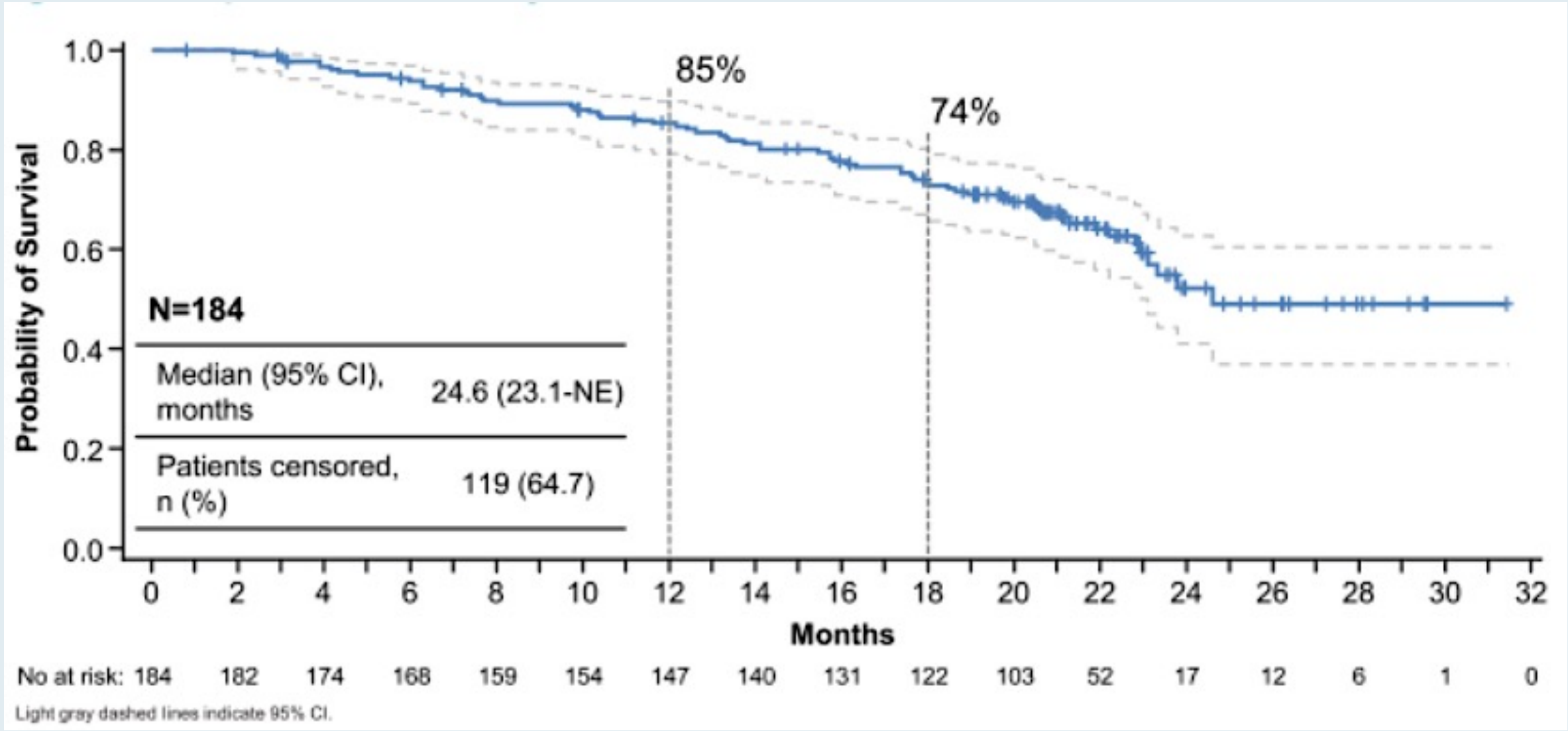
DESTINY-Breast01: Overall Survival



Modi S et al. SABCS 2020;Abstract PD3-06.

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DESTINY-Breast01: Safety

AEs of special interest (n = 184)	All grades	Grades 3 and 4
Interstitial lung disease	25 (13.6%)	1 (0.5%)
Prolonged QT interval	9 (4.9%)	2 (1.1%)
Infusion-related reaction	4 (2.2%)	0
Decreased left ventricular ejection fraction	3 (1.6%)	1 (0.5%)

- Most common Grade ≥3 AEs were decreased neutrophil count (21%), anemia (9%) and nausea (8%).

Modi S et al. *N Engl J Med* 2020;382(7):610-21.

Trastuzumab Deruxtecan (T-DXd) in Patients with HER2+ Metastatic Breast Cancer with Brain Metastases: A Subgroup Analysis of the DESTINY-Breast01 Trial

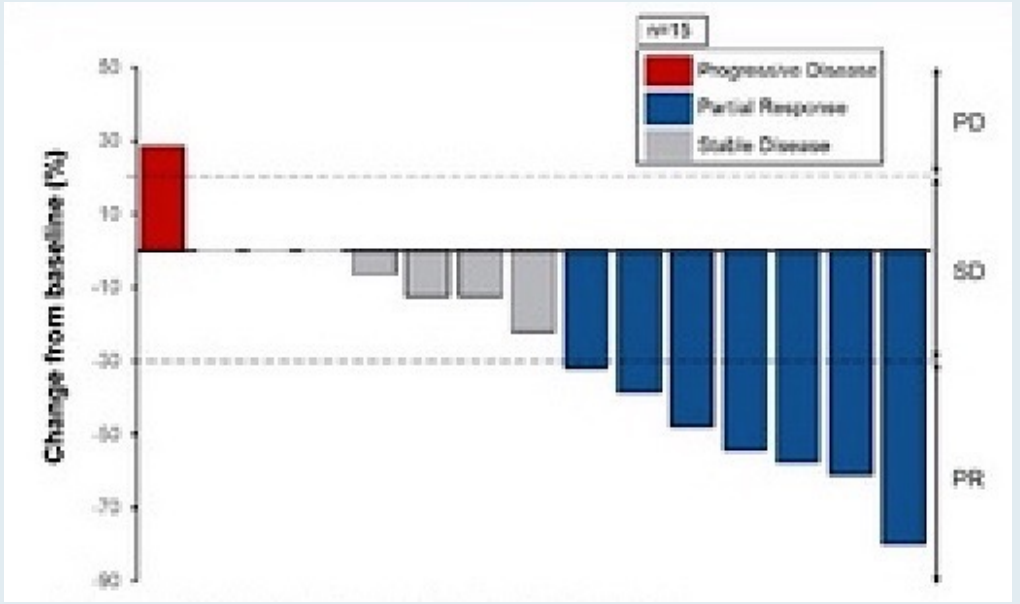
Jerusalem GHM et al.

ASCO 2021;Abstract 526.

DESTINY-Breast01: Clinical Activity Outcomes with Trastuzumab Deruxtecan

Endpoint	CNS Subgroup (n = 24)	All Patients (N = 184)
Confirmed ORR	58.3%	60.9%
Duration of response	16.9 mo	14.8 mo
Progression-free survival	18.1 mo	16.4 mo

Best Response in Brain Lesions in the CNS Subgroup



Jerusalem GHM et al. ASCO 2021;Abstract 526.

RTP RESEARCH TO PRACTICE

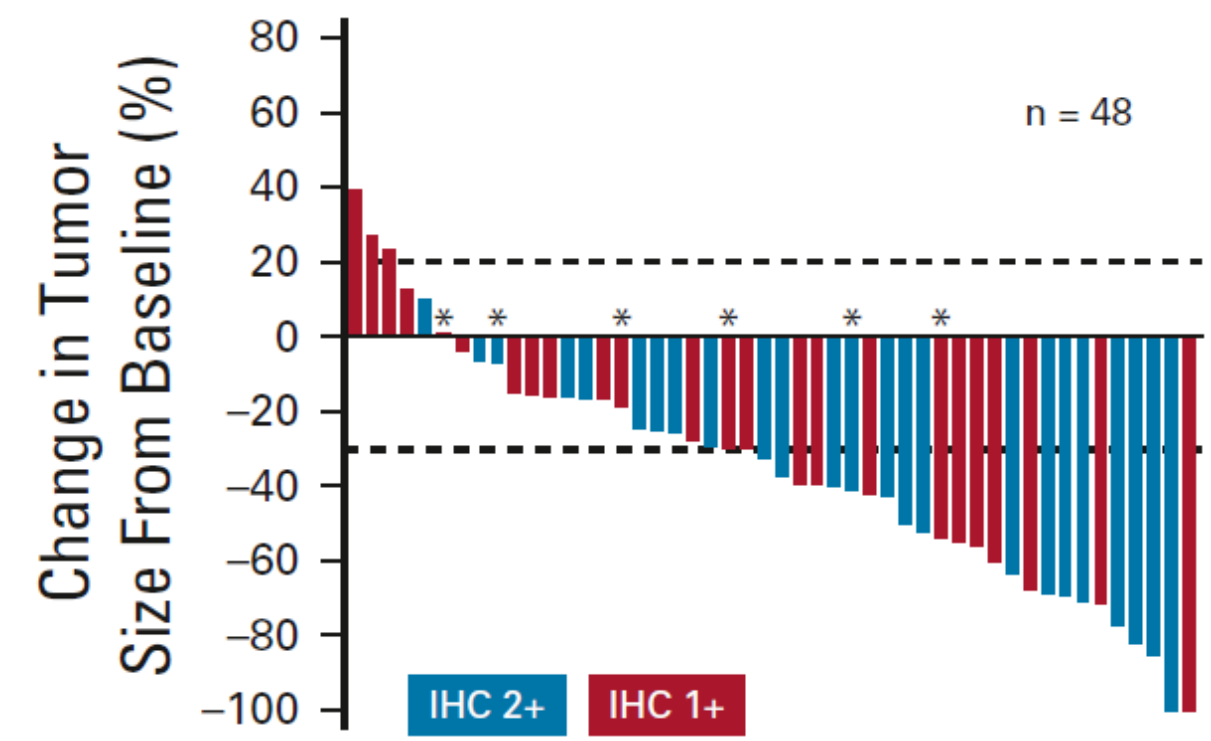
original reports

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD, MBE[3]; Hiroji Iwata, PhD, MD[4]; Kenji Tamura, MD, PhD[5]; Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Doi, MD, PhD[8]; Yasuaki Sagara, MD[9]; Charles Redfern, MD[10]; Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, MS[13]; Masahiro Sugihara, PhD[13]; Lin Zhang, MD, PhD[12]; Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]

J Clin Oncol 2020;38(17):1887-96.

Effect of Trastuzumab Deruxtecan in Heavily Pretreated* HER2-Low Metastatic Breast Cancer



Clinical activity (by independent review)

ORR		
	Overall	37%
	HER2 2+	39%
	HER2 1+	36%
	ER+	40% (N = 47)
	ER-	14% (N = 7)
PFS		
	Overall	11.1 months

* Median of 7.5 prior regimens

Modi et al. *J Clin Oncol* 2020;38(17):1887-96.

Courtesy of Ian E Krop, MD, PhD

RTP RESEARCH TO PRACTICE

Final Overall Survival Results from the SOPHIA Study for Patients with HER2-Positive Metastatic Breast Cancer Did Not Demonstrate a Statistically Significant Advantage with Margetuximab Over Trastuzumab

Press Release – September 07, 2021

"Final overall survival (OS) results of the SOPHIA Phase 3 study in adult patients with metastatic HER2-positive breast cancer did not demonstrate a statistically significant advantage for margetuximab over trastuzumab.

The final OS analysis of the SOPHIA study was performed after 385 OS events occurred in the intent-to-treat (ITT) population. As per the study protocol, OS was defined as the number of days from randomization to the date of death (from any cause). The final OS analysis for the ITT population did not demonstrate a statistically significant advantage for margetuximab plus chemotherapy compared to that of patients who received trastuzumab plus chemotherapy (hazard ratio [HR]=0.95; 95% Confidence Interval [CI]: 0.77-1.17; P=0.62). In this overall ITT population, the median survival was 21.6 months in patients treated with margetuximab plus chemotherapy (N=266) compared to 21.9 months in patients treated with trastuzumab plus chemotherapy (N=270).

The safety profile at the time of the final OS analysis of SOPHIA was similar to what was previously reported."

https://www.globenewswire.com/news-release/2021/09/07/2292944/0/en/MacroGenics-Announces-Final-Overall-Survival-Results-from-SOPHIA-Study-of-MARGENZA-in-Patients-with-HER2-Positive-Metastatic-Breast-Cancer.html

Research

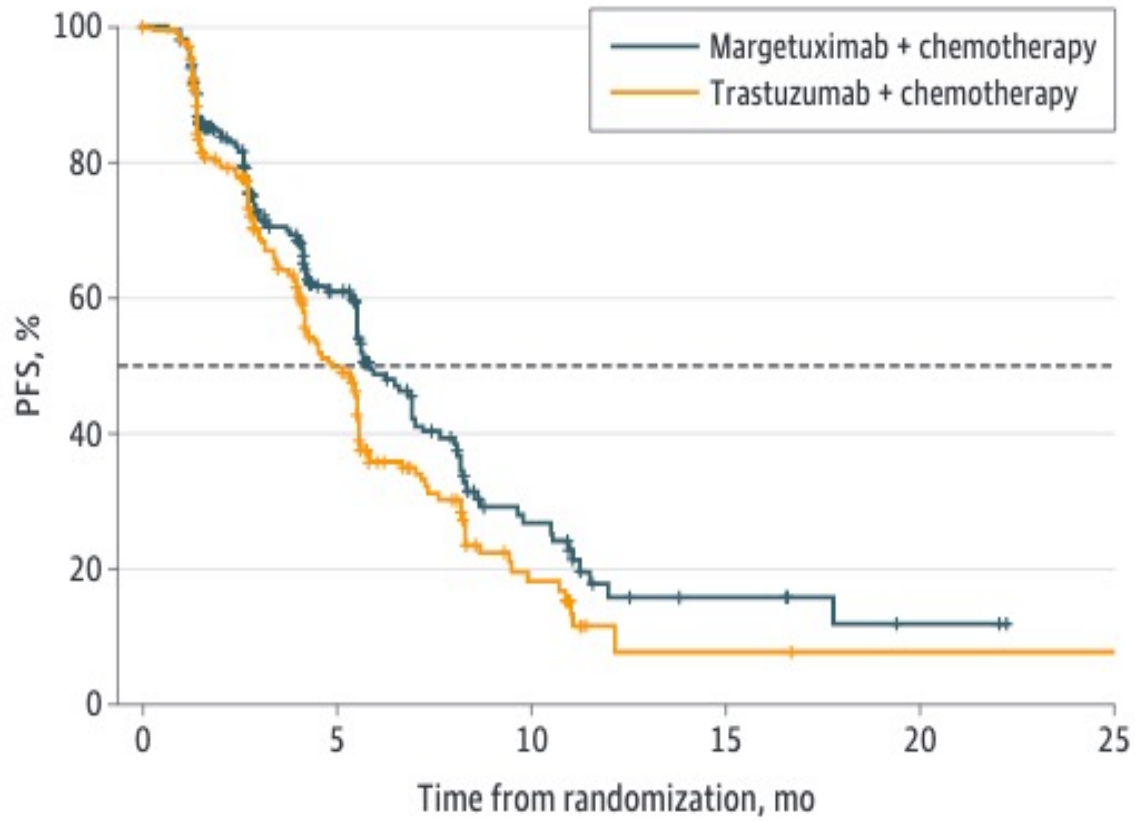
JAMA Oncology | Original Investigation

Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer
A Phase 3 Randomized Clinical Trial

Hope S. Rugo, MD; Seock-Ah Im, MD, PhD; Fatima Cardoso, MD; Javier Cortés, MD, PhD; Giuseppe Curigliano, MD, PhD; Antonino Musolino, MD, PhD, MSc; Mark D. Pegram, MD; Gail S. Wright, MD; Cristina Saura, MD, PhD; Santiago Escrivá-de-Romaní, MD; Michelino De Laurentiis, MD, PhD; Christelle Levy, MD; Ursa Brown-Glaberman, MD; Jean-Marc Ferrero, MD; Maaike de Boer, MD, PhD; Sung-Bae Kim, MD, PhD; Katarína Petráková, MD, PhD; Denise A. Yardley, MD; Orit Freedman, MD, MSc; Erik H. Jakobsen, MD; Bella Kaufman, MD; Rinat Yerushalmi, MD; Peter A. Fasching, MD; Jeffrey L. Nordstrom, PhD; Ezio Bonvini, MD; Scott Koenig, MD, PhD; Sutton Edlich, MS, PA; Shengyan Hong, PhD; Edwin P. Rock, MD, PhD; William J. Gradishar, MD; for the SOPHIA Study Group

JAMA Oncol 2021;[Online ahead of print].

SOPHIA: PFS by Central Blinded Analysis (ITT Population)

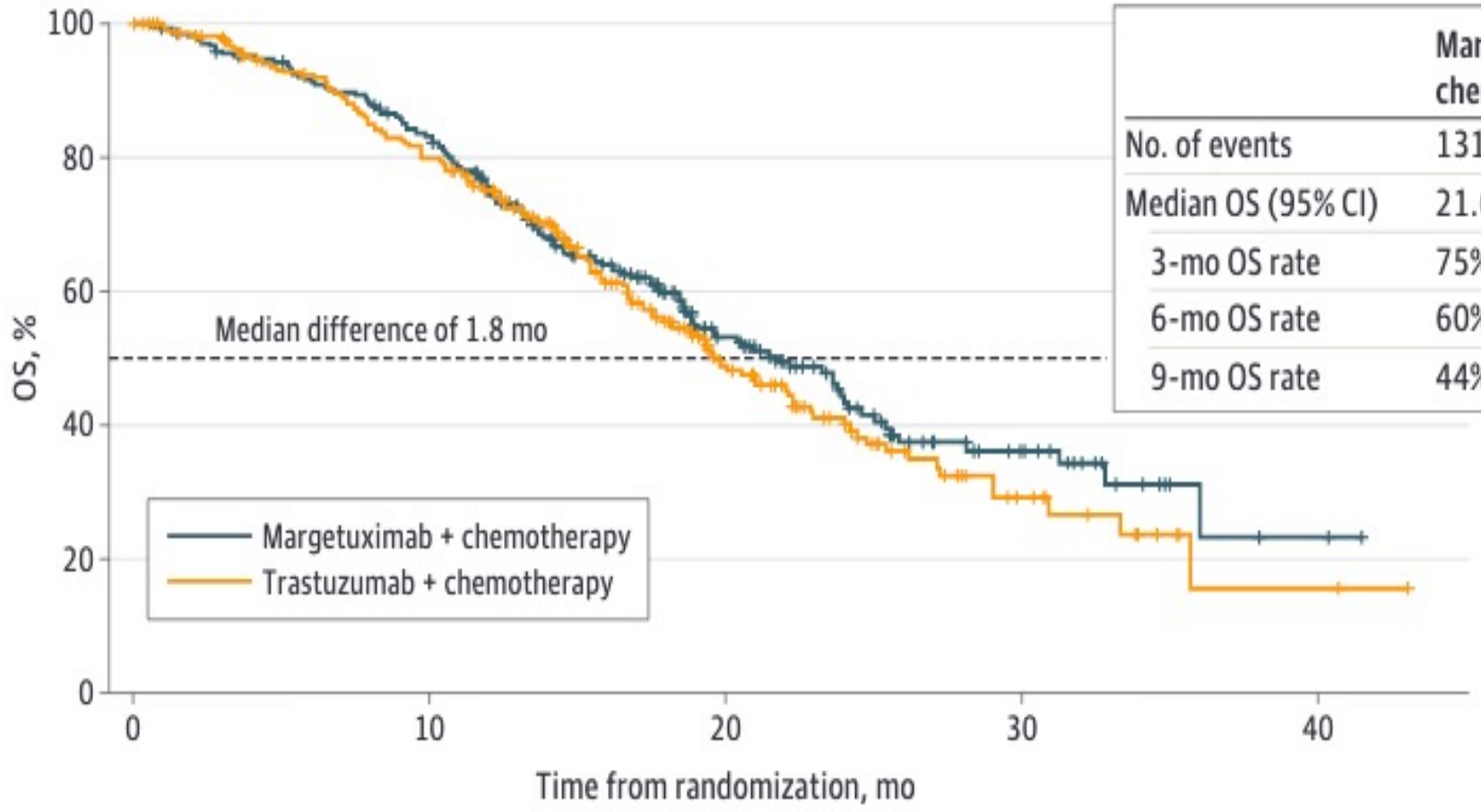


	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)
Stratified log-rank $P = .03$
24% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

Rugo HS et al. *JAMA Oncol* 2021;[Online ahead of print].

SOPHIA: OS Analysis (ITT Population)



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86-24.05)	19.8 mo (17.54-22.28)
3-mo OS rate	75% (70%-80%)	75% (70%-80%)
6-mo OS rate	60% (53%-66%)	56% (49%-62%)
9-mo OS rate	44% (36%-51%)	40% (33%-48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69-1.13)
Stratified log-rank $P = .33$
Median follow-up, 15.6 mo

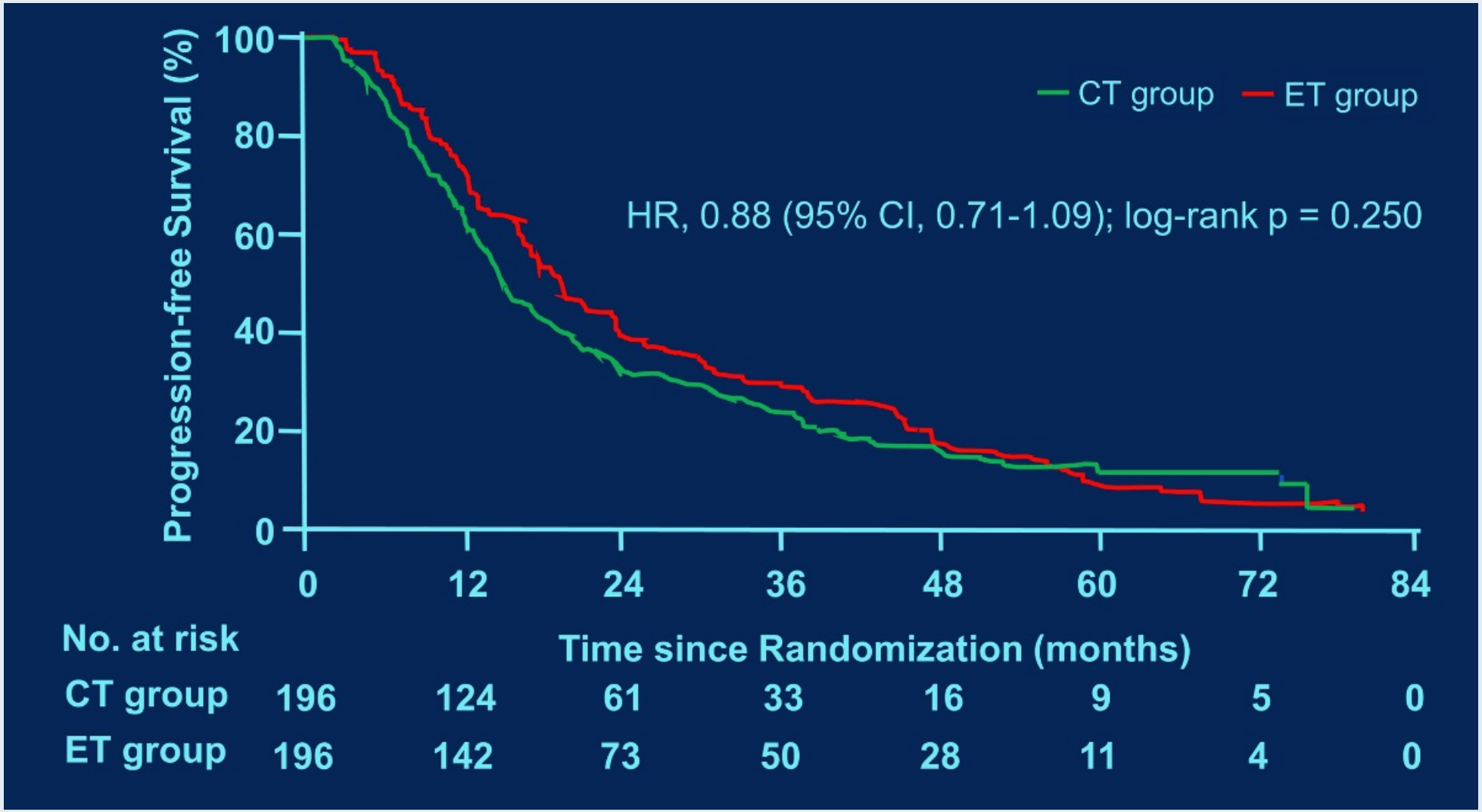
Rugo HS et al. *JAMA Oncol* 2021;[Online ahead of print].

Trastuzumab plus Endocrine Therapy or Chemotherapy as First-Line Treatment for Metastatic Breast Cancer with Hormone Receptor-Positive and HER2-Positive: The SYSUCC-002 Randomized Clinical Trial

Yuan Z et al.

ASCO 2021;Abstract 1003.

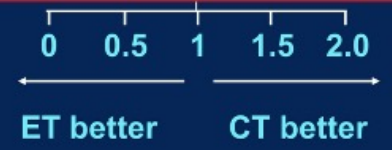
SYSUCC-002: Progression-Free Survival (Primary Endpoint)



Yuan Z et al. ASCO 2021;Abstract 1003.

SYSUCC-002: Subgroup Analysis of PFS

Subgroup	ET group (events/ n)	CT group (events/ n)	Hazard Ratio (95% CI)	p value
Age, years				0.146
≤ 40	29/31	30/42	1.14 (0.67, 1.91)	
> 40	151/165	135/154	0.80 (0.63, 1.00)	
Receptor status				0.099
ER and PR positive	143/157	128/157	0.90 (0.71, 1.15)	
ER or PR positive	37/39	37/39	0.76 (0.48, 1.20)	
Visceral involvement				0.487
Yes	106/114	103/119	0.95 (0.72, 1.25)	
No	74/82	62/77	0.80 (0.57, 1.12)	
Previous adjuvant endocrine therapy				0.904
AIs	74/83	66/83	0.98 (0.69, 1.15)	
ORMs	56/59	51/59	0.97 (0.70, 1.36)	
Metastasis number				0.851
< 2	127/140	111/139	0.89 (0.69, 1.15)	
≥ 2	53/56	54/57	0.86 (0.59, 1.27)	
Disease-free interval				0.016
≤ 24 months	59/64	64/78	1.39 (0.97, 1.98)	
> 24 months	71/78	53/64	0.77 (0.53, 1.10)	



Yuan Z et al. ASCO 2021;Abstract 1003.

Primary Outcome of the Phase III SYD985.002/TULIP Trial Comparing [vic-]Trastuzumab Duocarmazine to Physician's Choice Treatment in Patients with Pre-treated HER2-Positive Locally Advanced or Metastatic Breast Cancer

Manich E et al.

ESMO 2021;Abstract LBA15.

Conclusions: Treatment with [vic-]trastuzumab duocarmazine significantly improved PFS in comparison with standard physician's choice chemotherapy and may provide a new treatment option for patients with pre-treated locally advanced or metastatic HER2-positive breast cancer.

Select Ongoing Phase III Trials in Metastatic HER2-Positive Breast Cancer

Trial identifier	Estimated enrollment	Setting	Regimens	Estimated completion date
DESTINY-Breast09 (NCT04784715)	1,134	First line	• Trastuzumab deruxtecan • Trastuzumab deruxtecan + pertuzumab • Trastuzumab + pertuzumab + taxane	2029
HER2CLIMB-02 (NCT03975647)	460	Second line	• T-DM1 + tucatinib • Placebo + T-DM1	2024
DESTINY-Breast02 (NCT03523585)	600	Third line	• Trastuzumab deruxtecan • Physician's choice of capecitabine/trastuzumab or capecitabine/lapatinib	2024
DESTINY-Breast12	500	≤2 lines of therapy, presence or absence of BM	• Trastuzumab deruxtecan	2024

BM = brain metastases

www.clinicaltrials.gov. Accessed September 2021.

RTP RESEARCH TO PRACTICE

Localized HER2-Positive Breast Cancer

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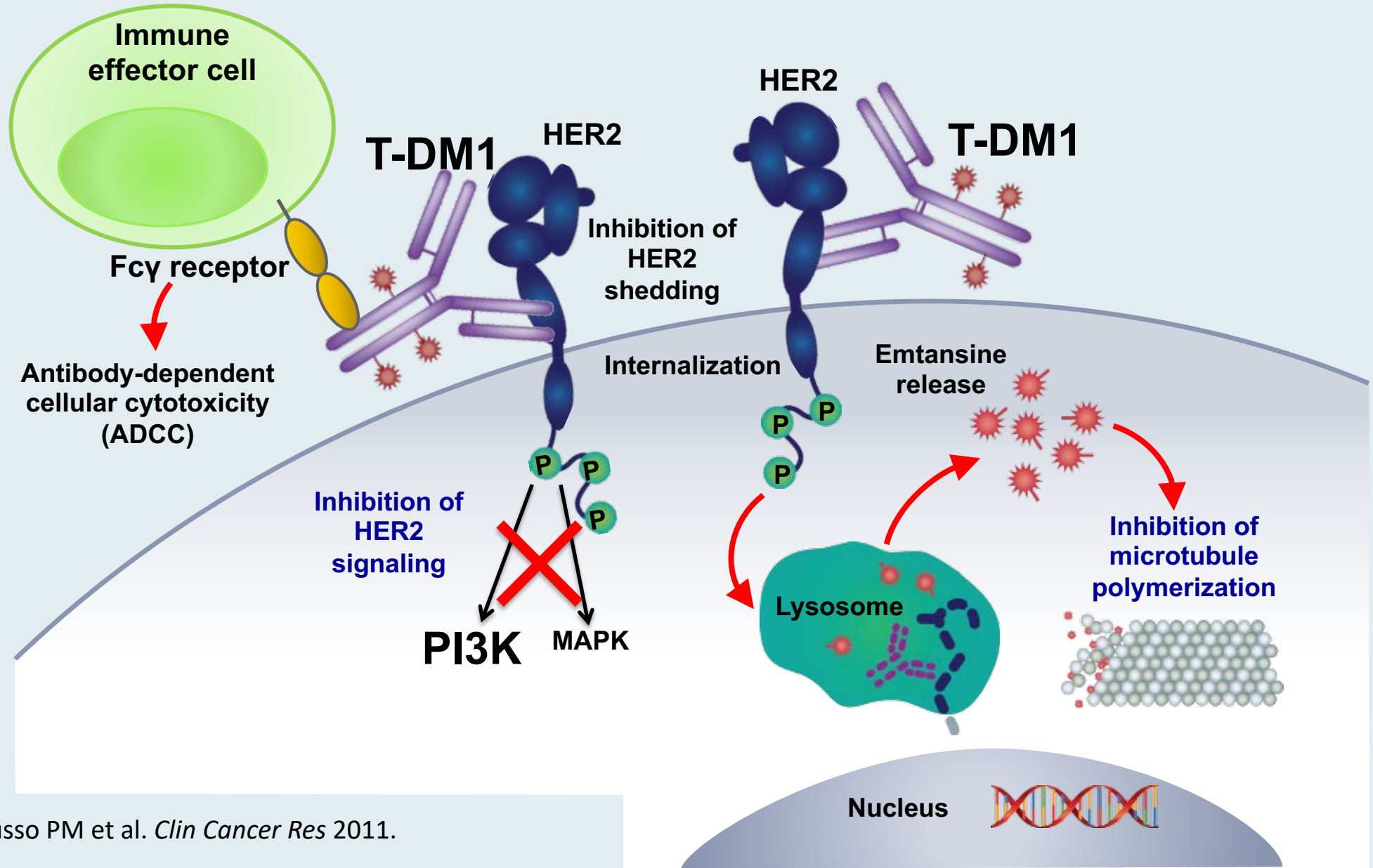
FDA-Approved Agents for Early-Stage HER2-Positive Breast Cancer

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

AC-H = doxorubicin, cyclophosphamide, and trastuzumab; AC-T, doxorubicin, cyclophosphamide, and paclitaxel; AC-T-H, doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab; H, trastuzumab; PD, pertuzumab and docetaxel; PT, trastuzumab and pertuzumab; PTD, pertuzumab, trastuzumab, and docetaxel; TC, docetaxel and cyclophosphamide; TC-H, docetaxel, cyclophosphamide, and trastuzumab; TD, trastuzumab and docetaxel; THP, docetaxel, trastuzumab, and pertuzumab

Choong GM et al. *CA Cancer J Clin* 2020;70:355-374.

Trastuzumab Emtansine (T-DM1): Mechanisms of Action



Adapted from LoRusso PM et al. *Clin Cancer Res* 2011.

ARTICLE IN PRESS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Ann Oncol 2021;[Online ahead of print]

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Adjuvant T-DM1 versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analyses from KATHERINE

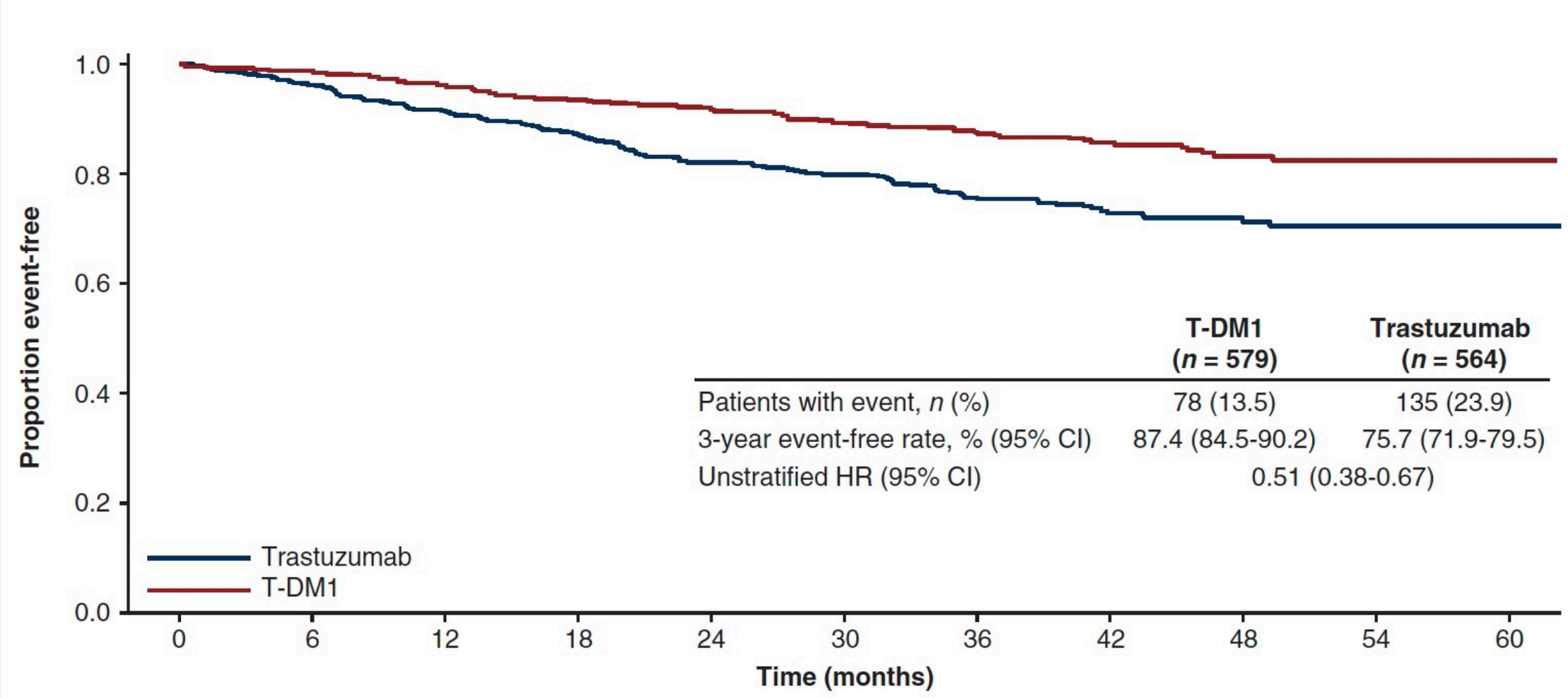
E. P. Mamounas[1,2*], M. Untch[3], M. S. Mano[4], C.-S. Huang[5], C. E. Geyer Jr[1,6], G. von Minckwitz[7], N. Wolmark[1,8], X. Pivot[9], S. Kuemmel[10,11], M. P. DiGiovanna[12], B. Kaufman[13], G. Kunz[7,14], A. K. Conlin[1,15], J. C. Alcedo[16], T. Kuehn[17], I. Wapnir[1,18], A. Fontana[19], J. Hackmann[7,20], J. Polikoff[1,21], M. Saghatchian[22], A. Brufsky[1,23], Y. Yang[24], M. Zimovjanova[25], T. Boulet[26], H. Liu[27], D. Tesarowski[28], L. H. Lam[28], C. Song[28], M. Smitt[28,29] & S. Loibl[7,30]

KATHERINE: Summary of Adverse Events Associated with T-DM1

Event	Trastuzumab (N = 720)	T-DM1 (N = 740)
Grade ≥3 adverse event	15.4%	25.7%
AE leading to drug discontinuation	2.1%	18.1%
Selected Grade ≥3 adverse event		
Decreased platelet count	0.3%	5.7%
Hypertension	1.2%	2.0%
Peripheral sensory neuropathy	0	1.4%
Decreased neutrophil count	0.7%	1.2%
Hypokalemia	0.1%	1.2%
Fatigue	0.1%	1.1%
Anemia	0.1%	1.1%

Von Minckwitz G et al. *N Engl J Med* 2019;380(7):617-28.

Time to First Invasive Disease-Free Survival Event for Patients Who Received Anthracycline-Based Neoadjuvant Therapy

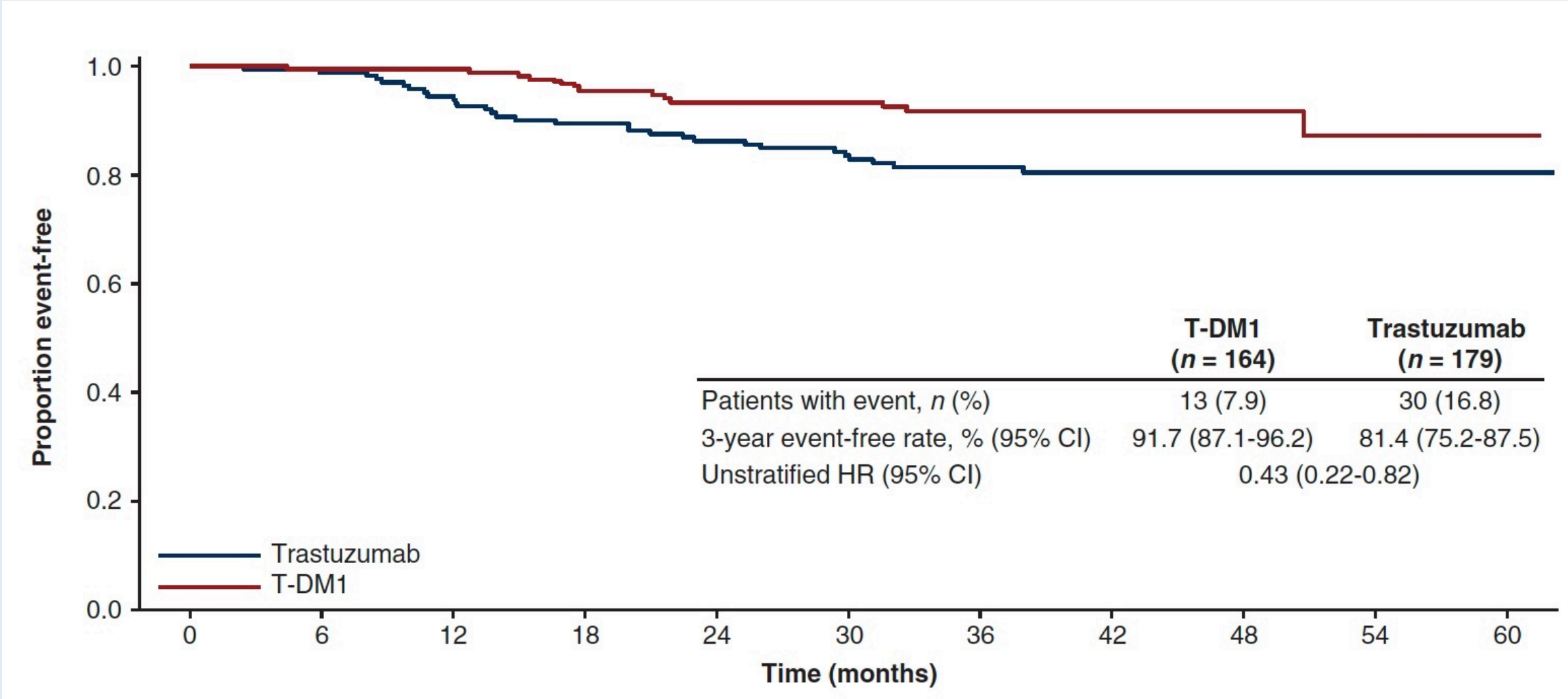


	T-DM1 (*n* = 579)	Trastuzumab (*n* = 564)
Patients with event, *n* (%)	78 (13.5)	135 (23.9)
3-year event-free rate, % (95% CI)	87.4 (84.5-90.2)	75.7 (71.9-79.5)
Unstratified HR (95% CI)	0.51 (0.38-0.67)	

Mamounas EP et al. *Ann Oncol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Time to First Invasive Disease-Free Survival Event for Patients Who Received Non-Anthracycline-Based Neoadjuvant Therapy



Mamounas EP et al. *Ann Oncol* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

original reports

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

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

J Clin Oncol 2021;[Online ahead of print]

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

Outcome	T-DM1 (n = 383)	TH (n = 114)
Three-year iDFS	97.8%	93.4%
Three-year RFI	99.2%	94.3%

Tolaney SM et al. *J Clin Oncol* 2021;[Online ahead of print].

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;[Online ahead of print].

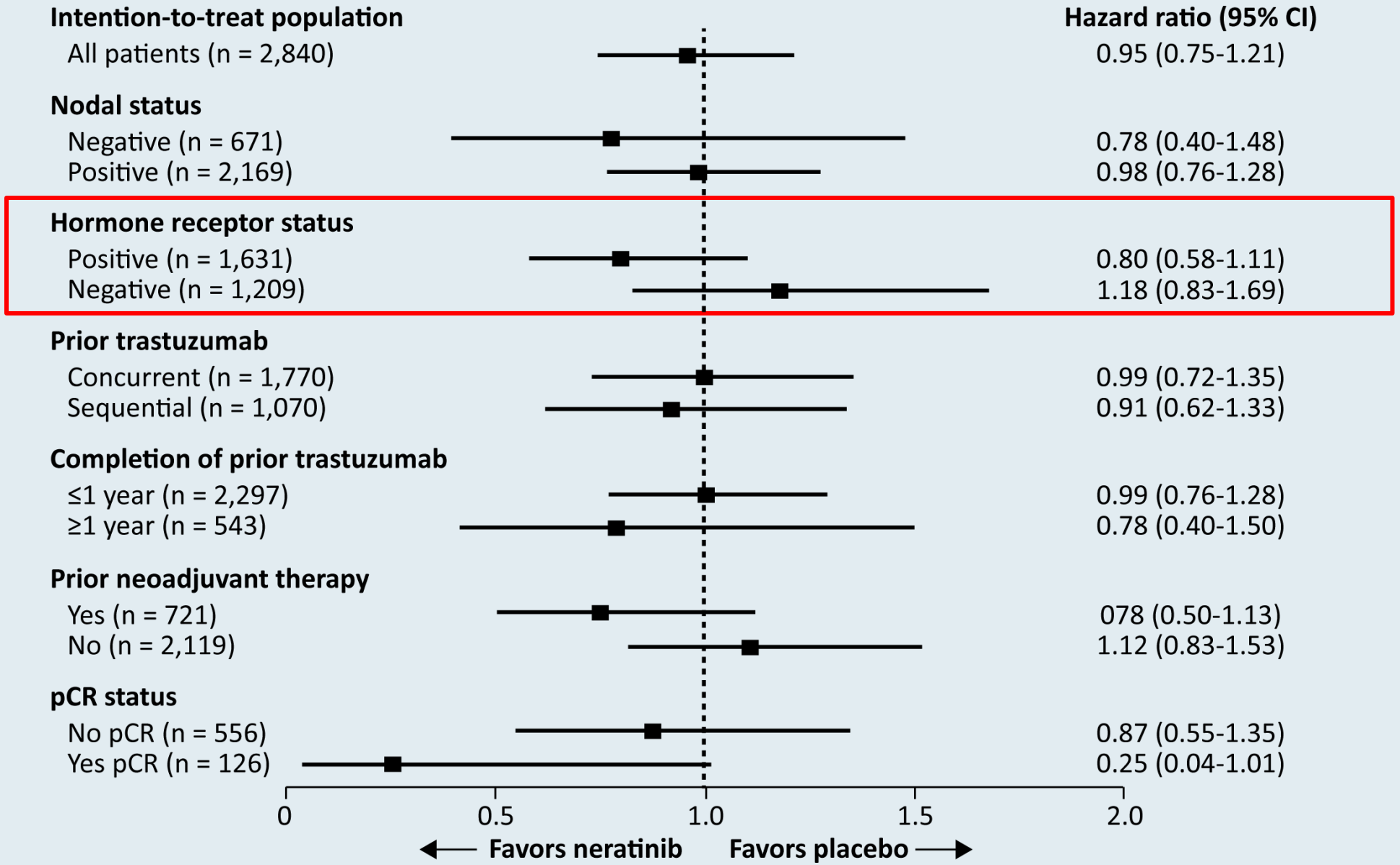
RTP RESEARCH TO PRACTICE

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



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

ExteNET: Cumulative Incidence of CNS Recurrences

Population or subgroup	Events, n		Cumulative incidence of CNS recurrences, % (95% CI)	
	Neratinib	Placebo	Neratinib	Placebo
Intention-to-treat population (n = 2,840)	16	23	1.3 (0.8-2.1)	1.8 (1.2-2.7)
HR+/≤1-year population (EU indication) (n = 1,334)	4	12	0.7 (0.2-1.7)	2.1 (1.1-3.5)
Prior neoadjuvant therapy (n = 1,334)				
No (n = 980)	3	6	0.7 (0.2-2.0)	1.5 (0.6-3.0)
Yes (n = 354)	1	6	0.7 (0.1-3.3)	3.7 (1.5-7.4)
pCR status (n = 354)				
No (n = 295)	1	5	0.8 (0.1-4.0)	3.6 (1.3-7.8)
Yes (n = 38)	0	1	0 (NE)	5.0 (0.3-21.2)

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

ExteNET: CNS Disease-Free Survival at 5 Years

Population or subgroup	Events, n		Kaplan-Meier estimate at 5 years %, (95% CI)		Hazard ratio
	Neratinib	Placebo	Neratinib	Placebo	
Intention-to-treat population (n = 2,840)	29	42	97.5 (96-4-98.3)	96.4 (95.2-97.4)	0.73
HR+/≤1-year population (EU indication) (n = 1,334)	9	23	98.4 (96.8-99.1)	95.7 (93.6-97.2)	0.41
Prior neoadjuvant therapy (n = 1,334)					
No (n = 980)	7	10	98.2 (96.3-99.2)	97.5 (95.3-98.6)	0.70
Yes (n = 354)	2	13	98.7 (94.8-99.7)	91.2 (85.1-94.8)	0.18
pCR status (n = 354)					
No (n = 295)	2	10	98.4 (93.6-99.6)	92.0 (85.6-95.7)	0.24
Yes (n = 38)	0	3	100 (100-100)	81.9 (53.1-93.9)	0

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

RTP RESEARCH TO PRACTICE

CONTROL Trial: Strategies to Improve Neratinib Tolerability

Background: Neratinib is approved for extended adjuvant therapy in HER2-positive BC

- Neratinib poorly tolerated in ExteNET
  - Discontinuation rate: 17%
  - Grade 3 diarrhea: 40%

Objective: Improve GI tolerability of neratinib

Methods: **Sequential single arm interventions in patients treated with adjuvant therapy**

- Cohort 1 (L): Loperamide (n = 137)
- Cohort 2 (BL): Budesonide + loperamide (n = 64)
- Cohort 3 (CL or CL-PRN): Colestipol + loperamide (n = 136) or colestipol + as needed loperamide (n = 104)
- Cohort 4 (DE): Neratinib dose escalation; ongoing (n = 60)

Barcenas CH et al. *Ann Oncol* 2020;31(9):1223-30.

Treatment-Emergent Diarrhea in the ExteNET and CONTROL Studies

Outcome	ExteNET (*n* = 1408)	L (*n* = 137)	BL (*n* = 64)	CL (*n* = 136)	CL-PRN (*n* = 104)	DE (*n* = 60)
Treatment-emergent diarrhea incidence, *n* (%)						
No diarrhea	65 (5)	28 (20)	9 (14)	23 (17)	5 (5)	1 (2)
Grade 1	323 (23)	33 (24)	16 (25)	38 (28)	34 (33)	25 (42)
Grade 2	458 (33)	34 (25)	21 (33)	47 (35)	32 (31)	25 (42)
Grade 3	561 (40)	42 (31)	18 (28)	28 (21)	33 (32)	9 (15)
Grade 4	1 (<1)	0	0	0	0	0
Action taken, *n* (%)						
Dose hold	477 (34)	20 (15)	12 (19)	22 (16)	15 (14)	7 (12)
Dose reduction	372 (26)	10 (7)	3 (5)	10 (7)	12 (12)	2 (3)
Discontinuation	237 (17)	28 (20)	5 (8)	5 (4)	8 (8)	2 (3)
Hospitalization	20 (1)	2 (1)	0	0	0	0

Barcenas CH et al. *Ann Oncol* 2020;31(9):1223-30.

Select Ongoing Trials in Early-Stage HER2-Positive Breast Cancer

Trial identifier	Phase	Setting	Regimens	Estimated completion date
CompassHER2 pCR (NCT04266249)	II	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	High-risk, residual disease after neoadjuvant chemotherapy	• Trastuzumab deruxtecan • T-DM1	2027

www.clinicaltrials.gov. Accessed August 2021.

RTP RESEARCH TO PRACTICE

Fall Oncology Nursing Series

A Complimentary NCPD-Accredited Virtual Curriculum

Chronic Lymphocytic Leukemia

Thursday, October 14, 2021
5:00 PM – 6:00 PM ET

Faculty

Anthony R Mato, MD, MSCE
Corinne Hoffman, MS, APRN-CNP, AOCNP

Moderator

Neil Love, MD

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Recent Advances and Future Directions in Oncology: A Daylong Multitumor Educational Webinar in Partnership with Florida Cancer Specialists

A CME-MOC/NCPD Accredited Virtual Event

Saturday, October 23, 2021
9:30 AM – 4:30 PM ET

Faculty

Neeraj Agarwal, MD
Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Brad S Kahl, MD
Mark Levis, MD, PhD
Ann Partridge, MD, MPH
Mark D Pegram, MD
Daniel P Petrylak, MD
Noopur Raje, MD
David Sallman, MD
Lecia V Sequist, MD, MPH
David R Spigel, MD
Saad Zafar Usmani, MD, MBA
Andrew D Zelenetz, MD, PhD

Moderator

Neil Love, MD

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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of HER2-Low Breast Cancer

DR IAN KROP

DANA-FARBER CANCER INSTITUTE

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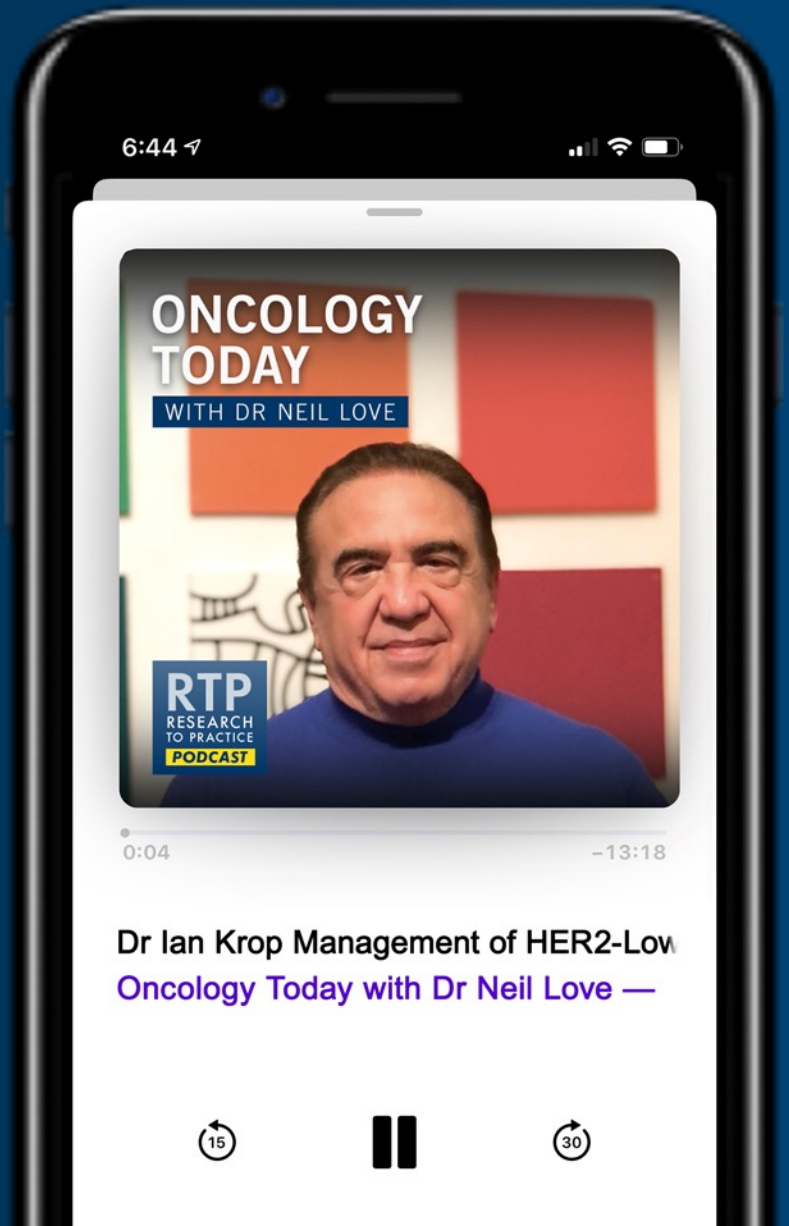

Thank you for joining us!

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

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