Meet The Professor

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

Hope S Rugo, MD
Professor of Medicine
Director, Breast Oncology and Clinical Trials Education
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center
San Francisco, California

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, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, 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, Merck, Natera Inc, Novartis, 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, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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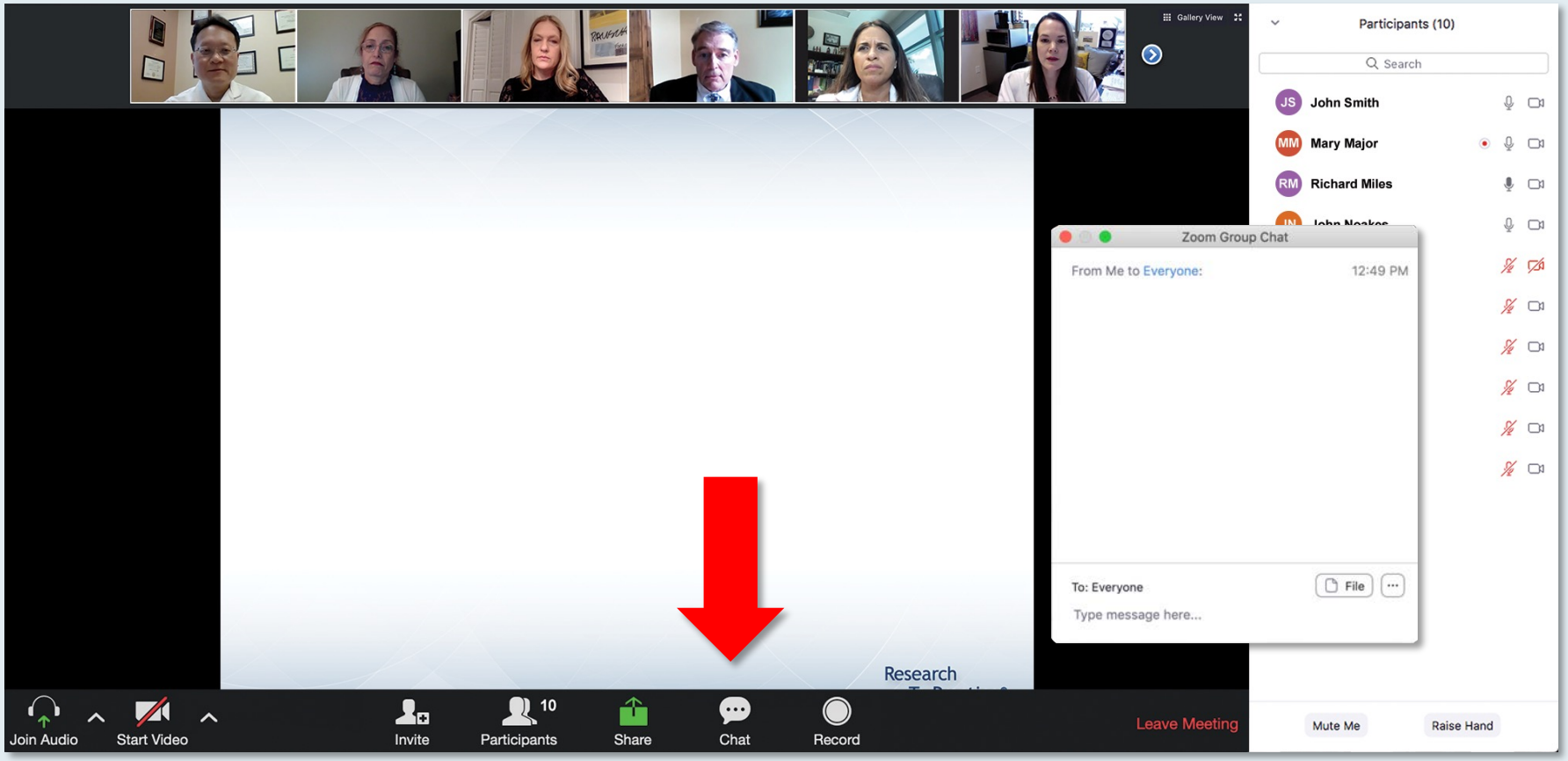
Research To Practice CME Planning Committee Members, Staff and Reviewers

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

Dr Rugo — Disclosures

Consulting Agreement	Samsung Bioepis (limited consulting)
Contracted Research	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Immunomedics Inc, Lilly, MacroGenics Inc, Merck, Novartis, OBI Pharma Inc, Odonate Therapeutics, Pfizer Inc, Seagen Inc, Sermonix Pharmaceuticals
Honoraria	Mylan, Puma Biotechnology Inc
Travel	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, MacroGenics Inc, Merck, Mylan, Novartis, Pfizer Inc

We Encourage Clinicians in Practice to Submit Questions



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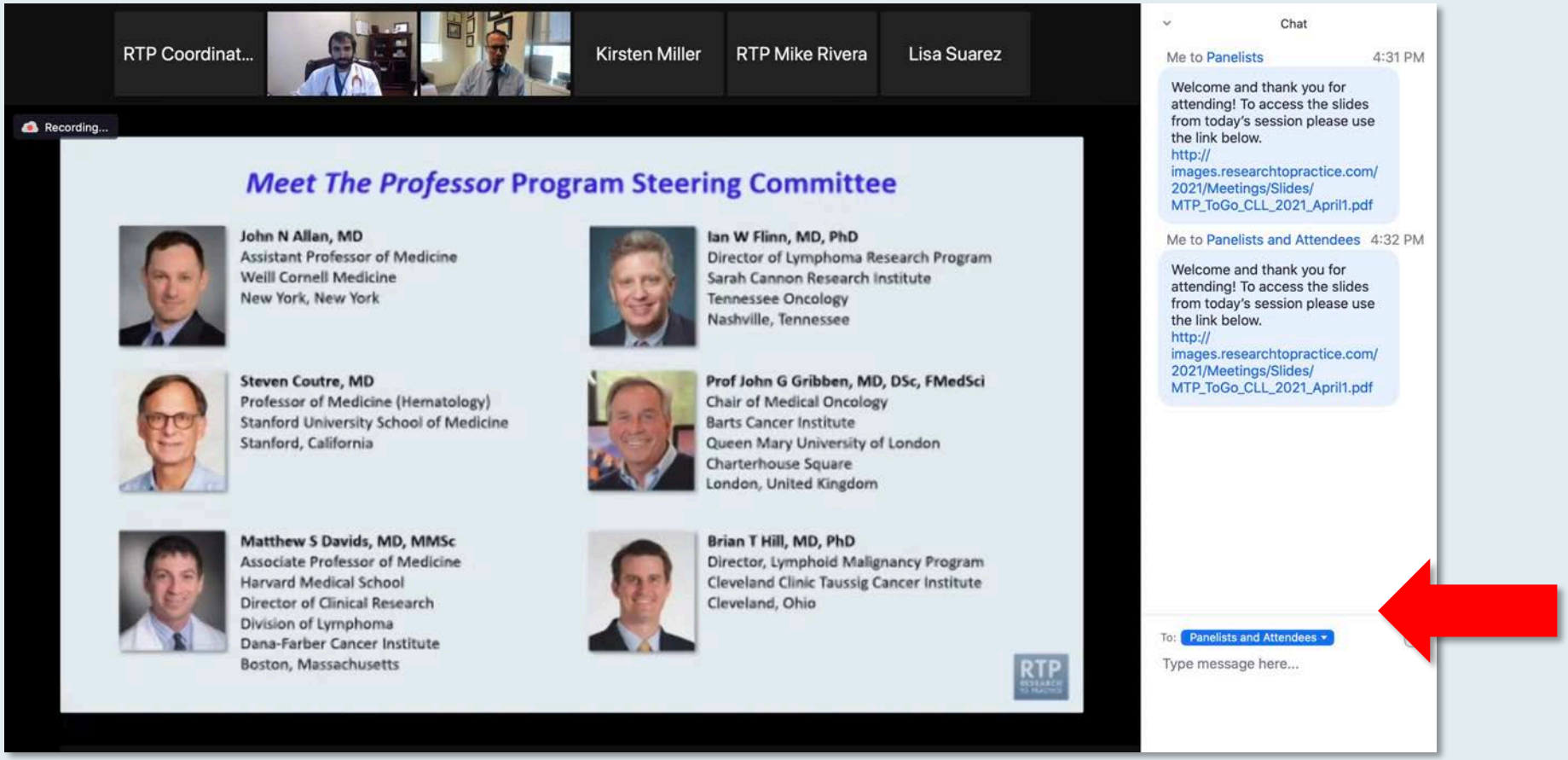

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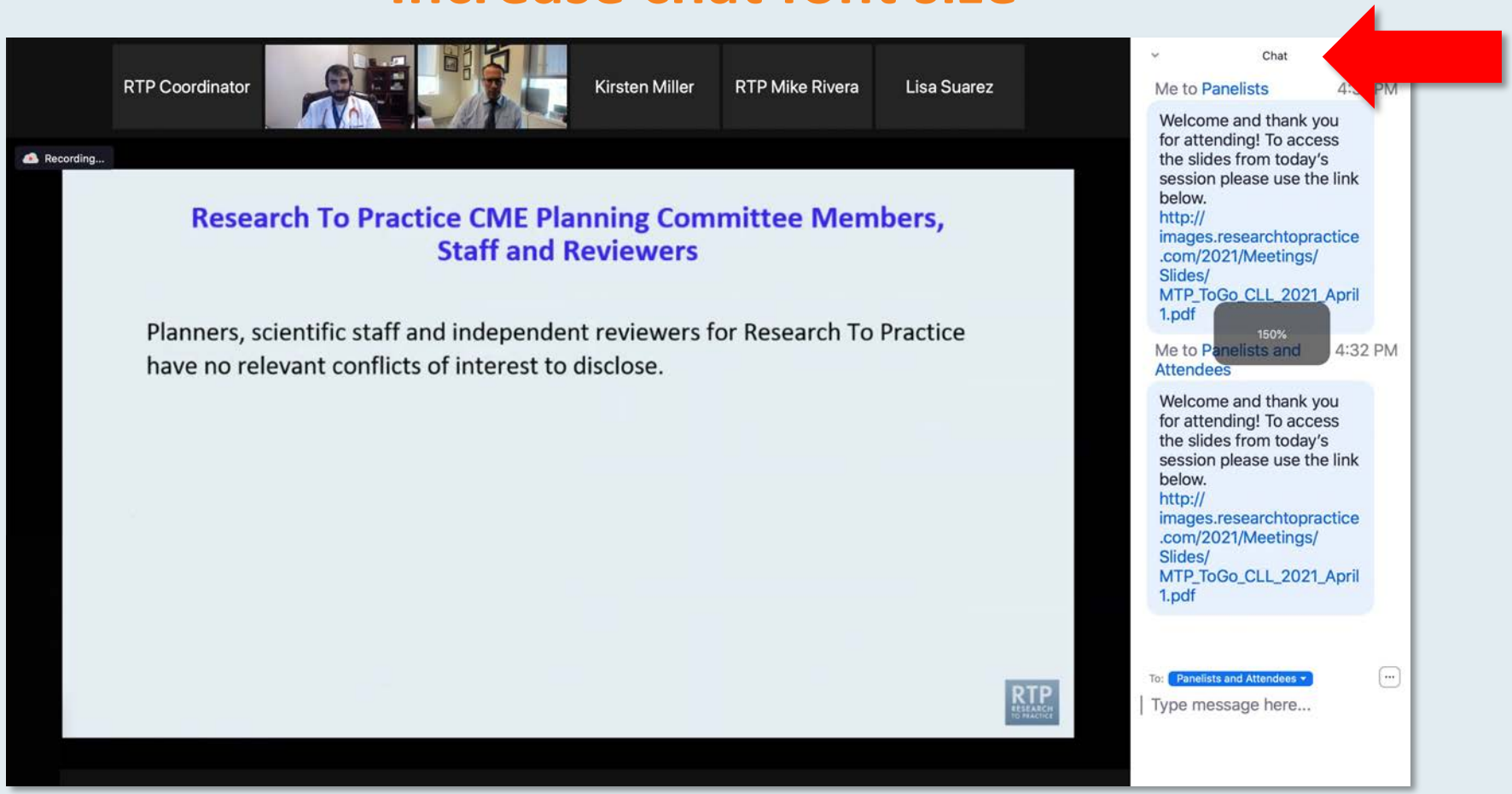

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Management of HER2-Low Breast Cancer

DR IAN KROP

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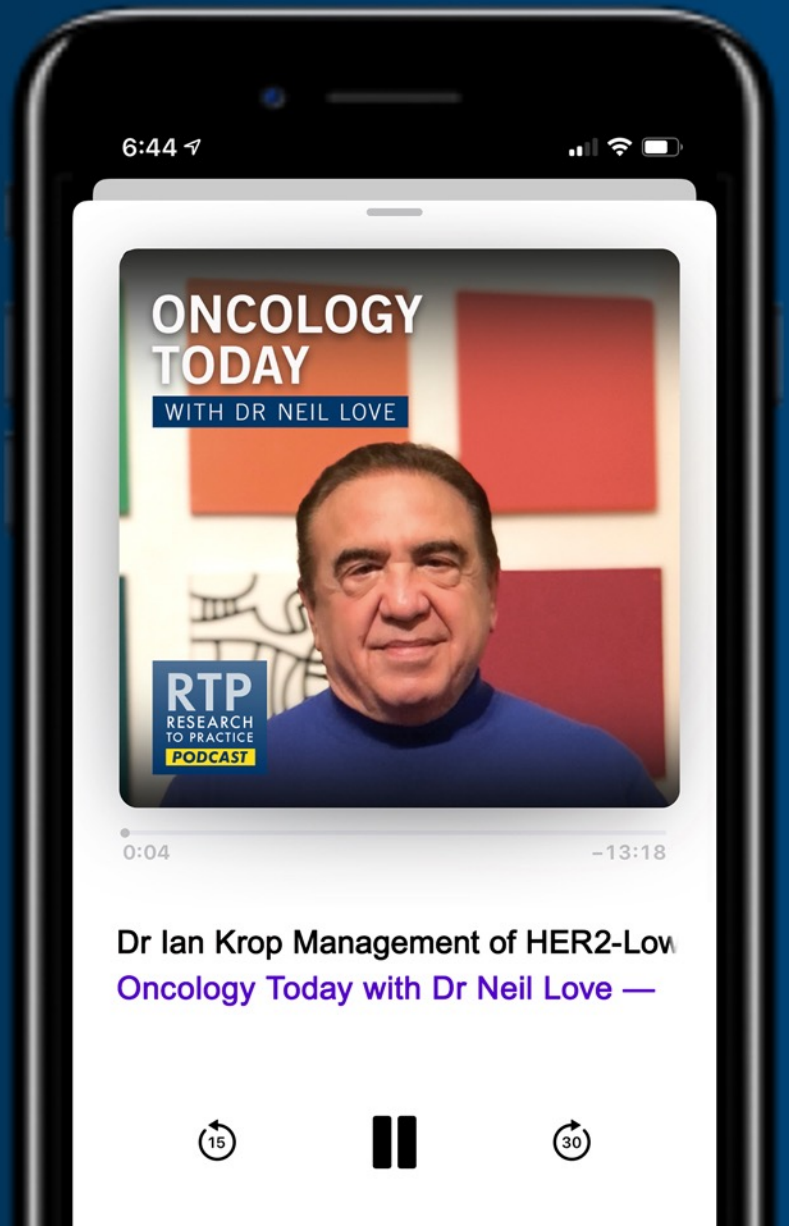

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of ER-Positive Breast Cancer

Tuesday, December 7, 2021
8:00 PM – 9:45 PM ET

Faculty

Aditya Bardia, MD, MPH
Joyce O'Shaughnessy, MD
Kevin Kalinsky, MD, MS

Moderator

Erika Hamilton, MD

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Sara Hurvitz, MD
Ian E Krop, MD, PhD

Moderator

Lisa Carey, MD

RTP RESEARCH TO PRACTICE

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

Thursday, December 9, 2021
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Peter Schmid, FRCP, MD, PhD
Melinda Telli, MD

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Hope S Rugo, MD

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

Friday, December 10, 2021
7:30 AM – 9:30 AM ET

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Anthony R Mato, MD, MSCE
John M Pagel, MD, PhD
Jennifer Woyach, MD

Moderator

John N Allan, MD

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

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Martin Dreyling, MD, PhD
Loretta J Nastoupil, MD
Gilles Salles, MD, PhD

Moderator

Ann S LaCasce, MD, MMSc

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Naval Daver, MD

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Brian T Hill, MD, PhD

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Thursday, December 16, 2021
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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

Adam M Brufsky, MD, PhD
Professor of Medicine
Co-Director, Comprehensive Breast Cancer Center
UPMC Hillman Cancer Center
Associate Division Chief, Division of Hematology/Oncology
Department of Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

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

Karen A Gelmon, MD
Professor of Medicine
University of British Columbia
Medical Oncologist, BC Cancer
Vancouver, British Columbia, Canada

Sara Hurvitz, MD
Professor of Medicine
David Geffen School of Medicine at UCLA
Director, Breast Cancer Clinical Research Program
Co-Director, Santa Monica-UCLA Outpatient Oncology Practice
Santa Monica, California

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Meet The Professor Program Participating Faculty

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

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

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Neil Love, MD
Research To Practice
Miami, Florida

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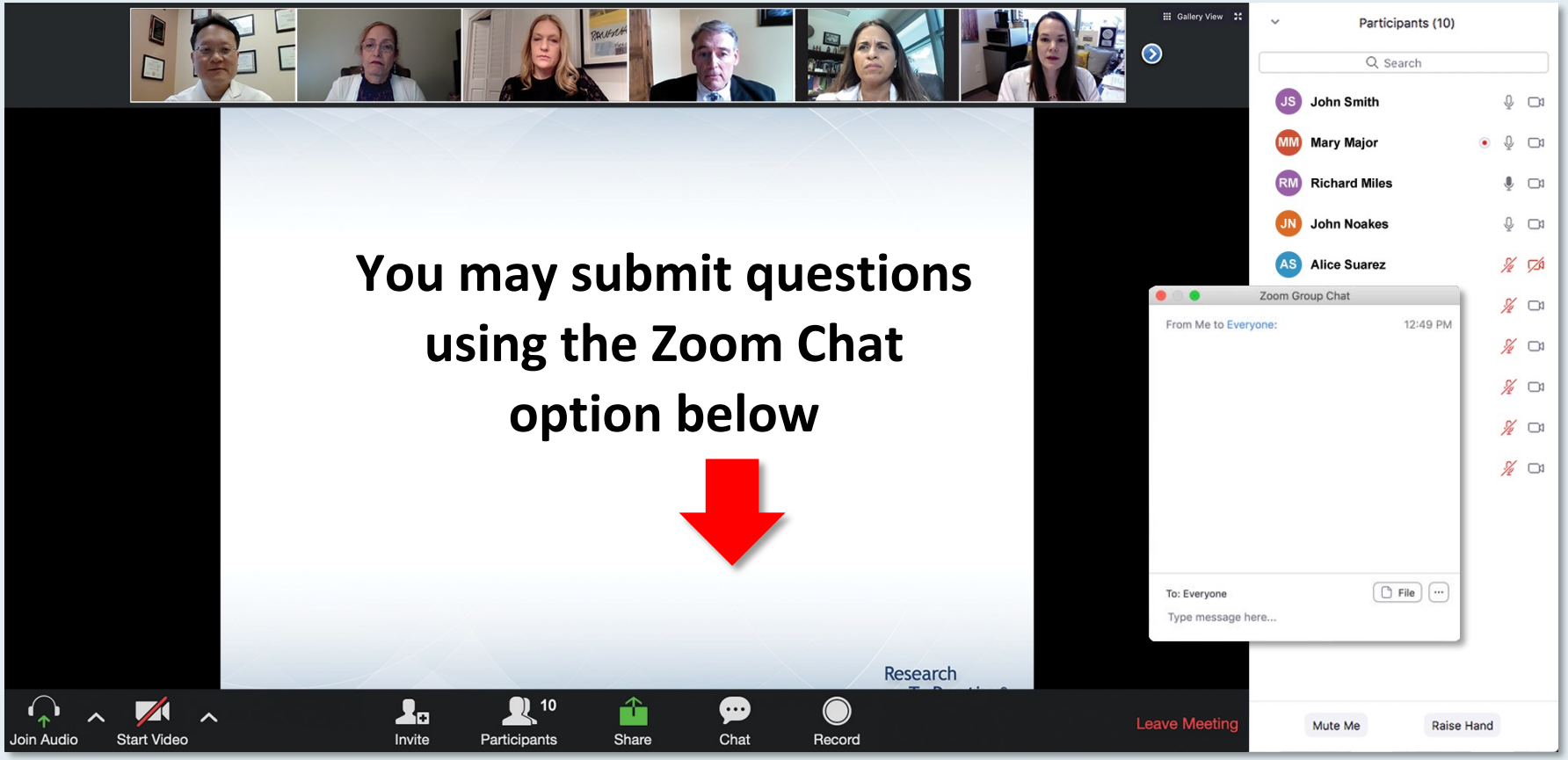

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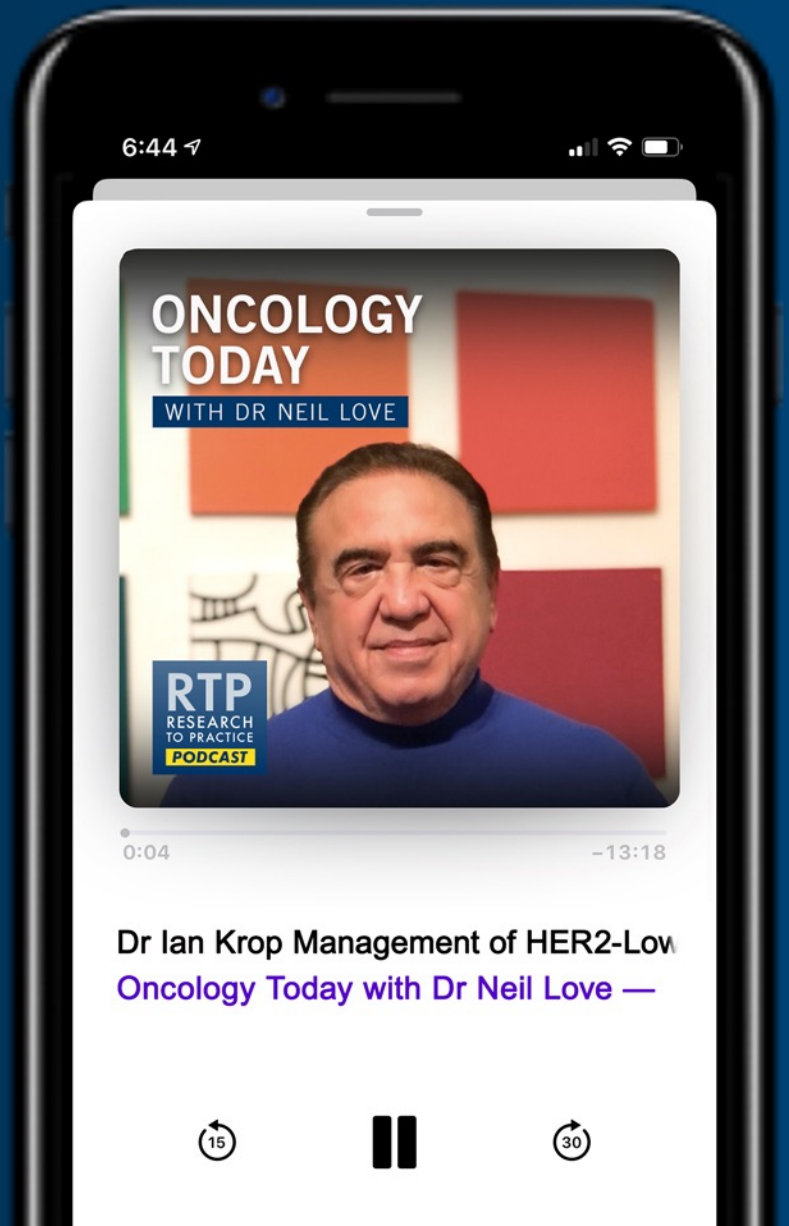

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A 65-year-old woman with an ER-positive, HER2-positive IDC experiences recurrence in the liver and brain 18 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab and postadjuvant neratinib and is receiving adjuvant anastrozole. 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

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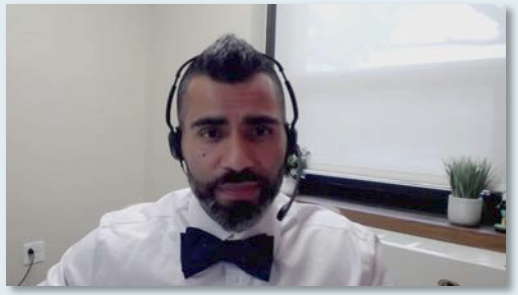
Laila Agrawal, MD
Norton Cancer Institute
Louisville, Kentucky

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



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

Raman Sood, MD
Brooks Memorial Hospital
Dunkirk, New York

Shaachi Gupta, MD, MPH
Florida Cancer Specialists and Research Institute
Lake Worth, Florida

Syed F Zafar, MD
Florida Cancer Specialists and Research Institute
Lee Health
Fort Myers, Florida

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Meet The Professor with Dr Rugo

Introduction: DESTINY Breast03

MODULE 1: Case Presentations

- Dr Sood: A 65-year-old woman with ER/PR-negative, HER2-positive metastatic breast cancer (mBC)
- Dr Gosain: A 67-year-old woman with ER/PR-negative, HER2-positive, ROS1-positive mBC
- Dr Agrawal: A 56-year-old woman with ER/PR-positive, HER2-positive mBC with brain metastases
- Dr Zafar: A 33-year-old woman with triple-positive mBC and possible mosaicism of TP53 mutation
- Dr Peswani: A 37-year-old woman with triple-positive, node-negative localized breast cancer
- Dr Gupta: A 63-year-old woman with ER/PR-positive, HER2-positive, node-positive IDC

MODULE 2: Journal Club with Dr Rugo and SABCS 2021 Preview

MODULE 3: Appendix of Faculty Survey and Key Data Sets

Meet The Professor with Dr Rugo

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MODULE 3: Appendix of Faculty Survey and Key Data Sets

Jason J Luke, MD

A Oliver Sartor, MD

Andrew H Wei, MBBS, PhD

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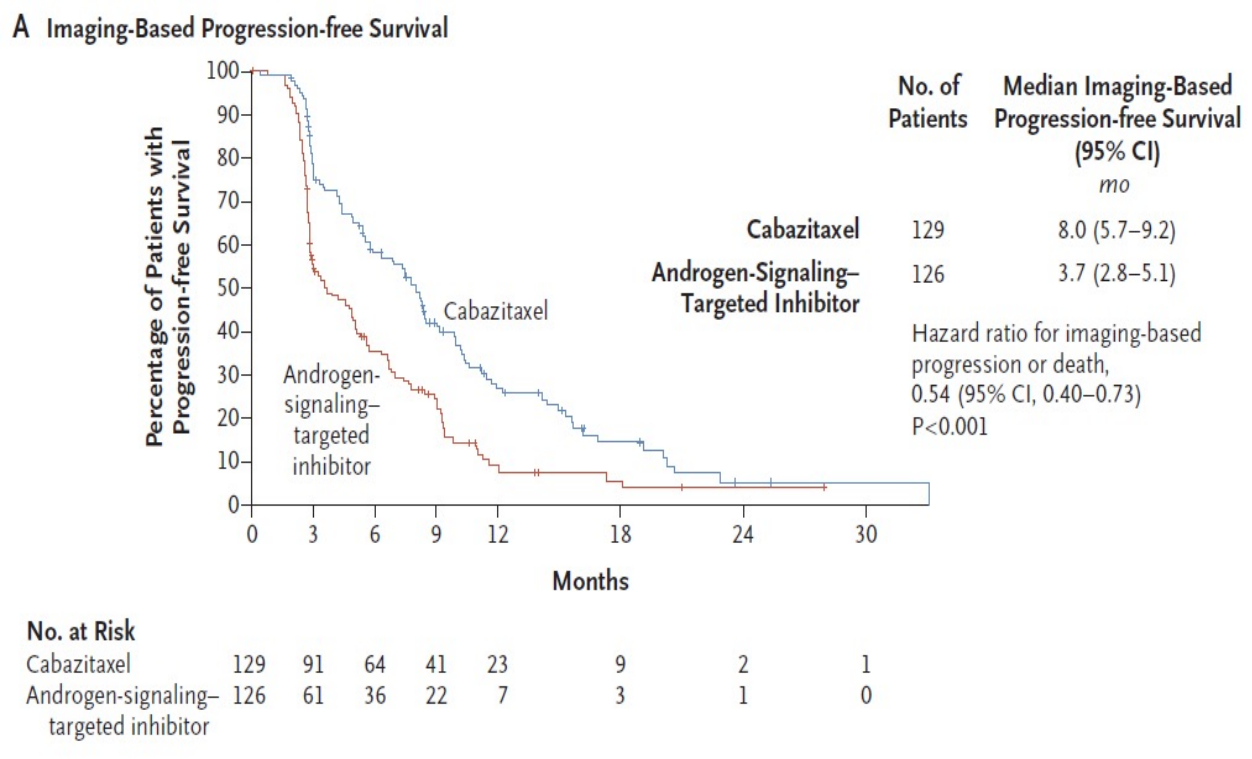
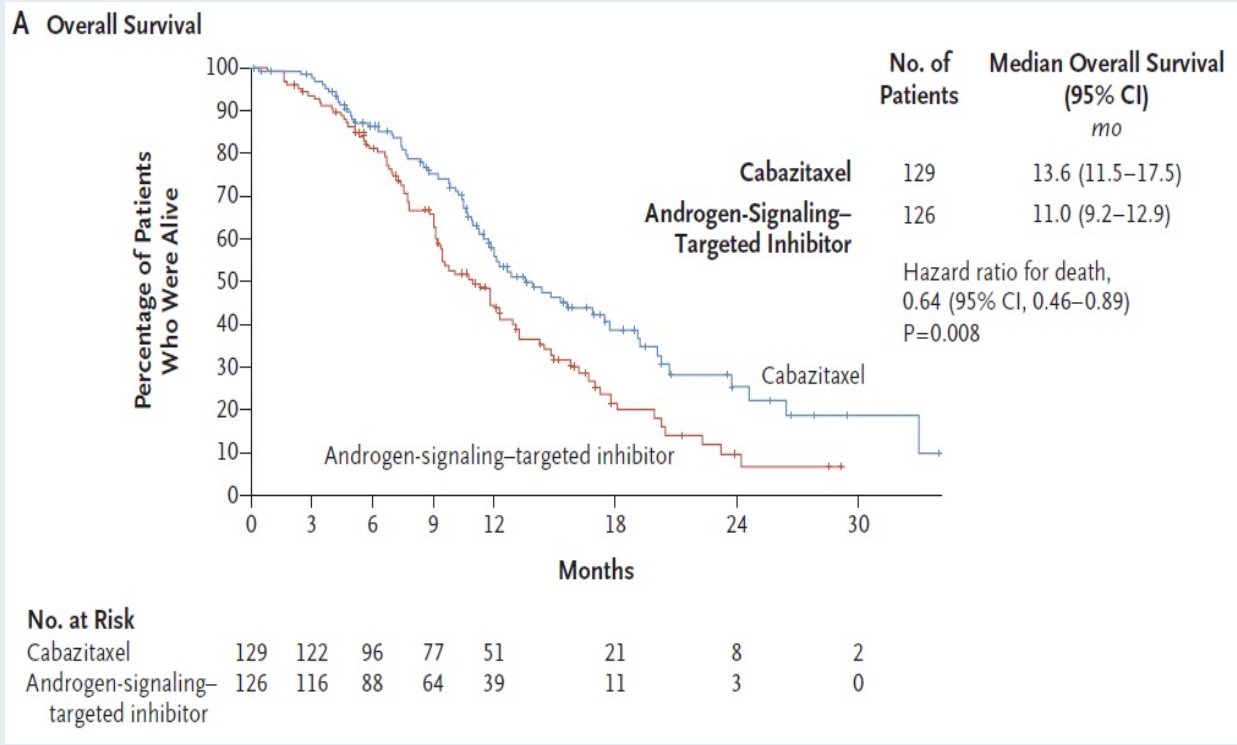
CARD: Imaging-Based PFS and OS with Cabazitaxel versus Abiraterone or Enzalutamide for mCRPC





de Wit R. et al. *NEJM* 2019;381:2506-18.

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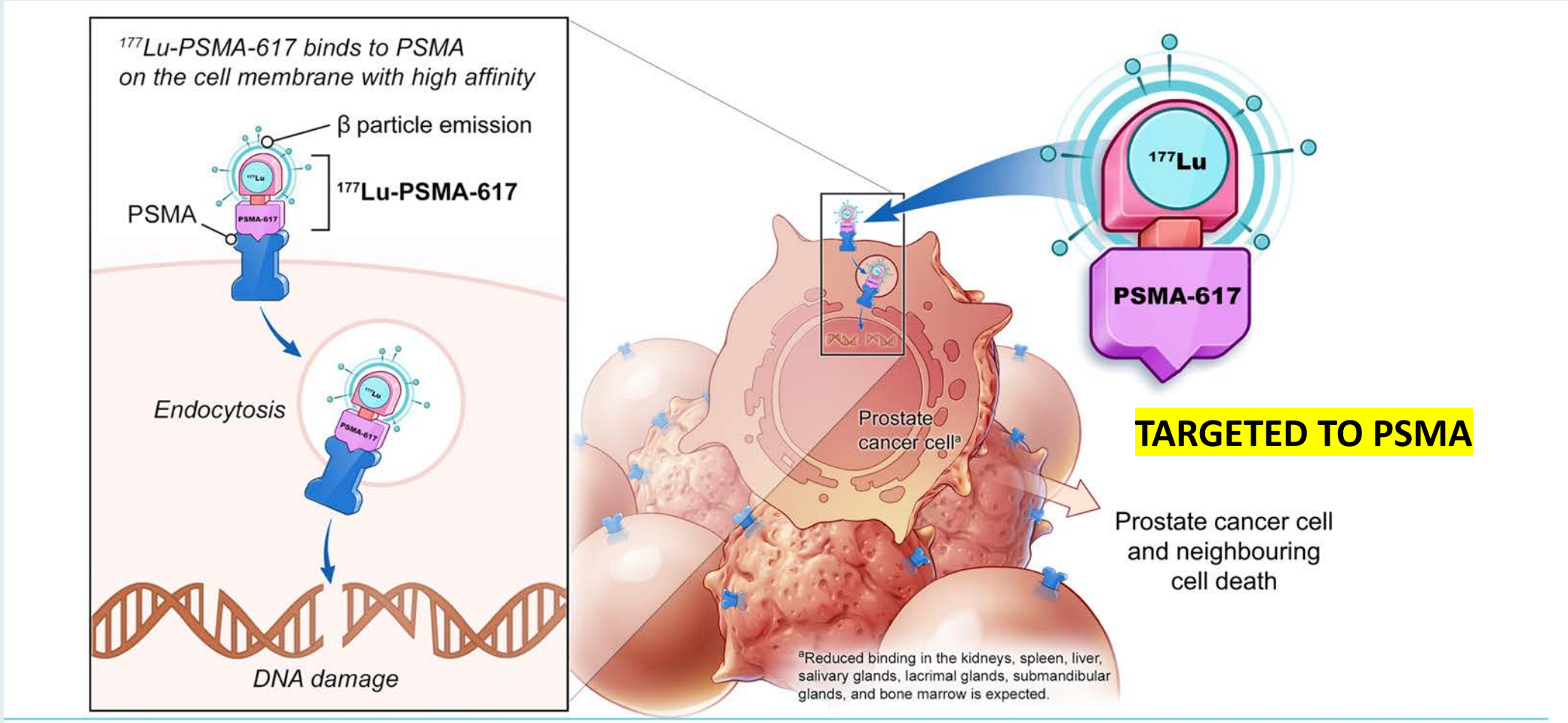
^{177}Lu-PSMA-617: Mechanism of Action



Morris MJ et al. ASCO 2021;Abstract LBA4.

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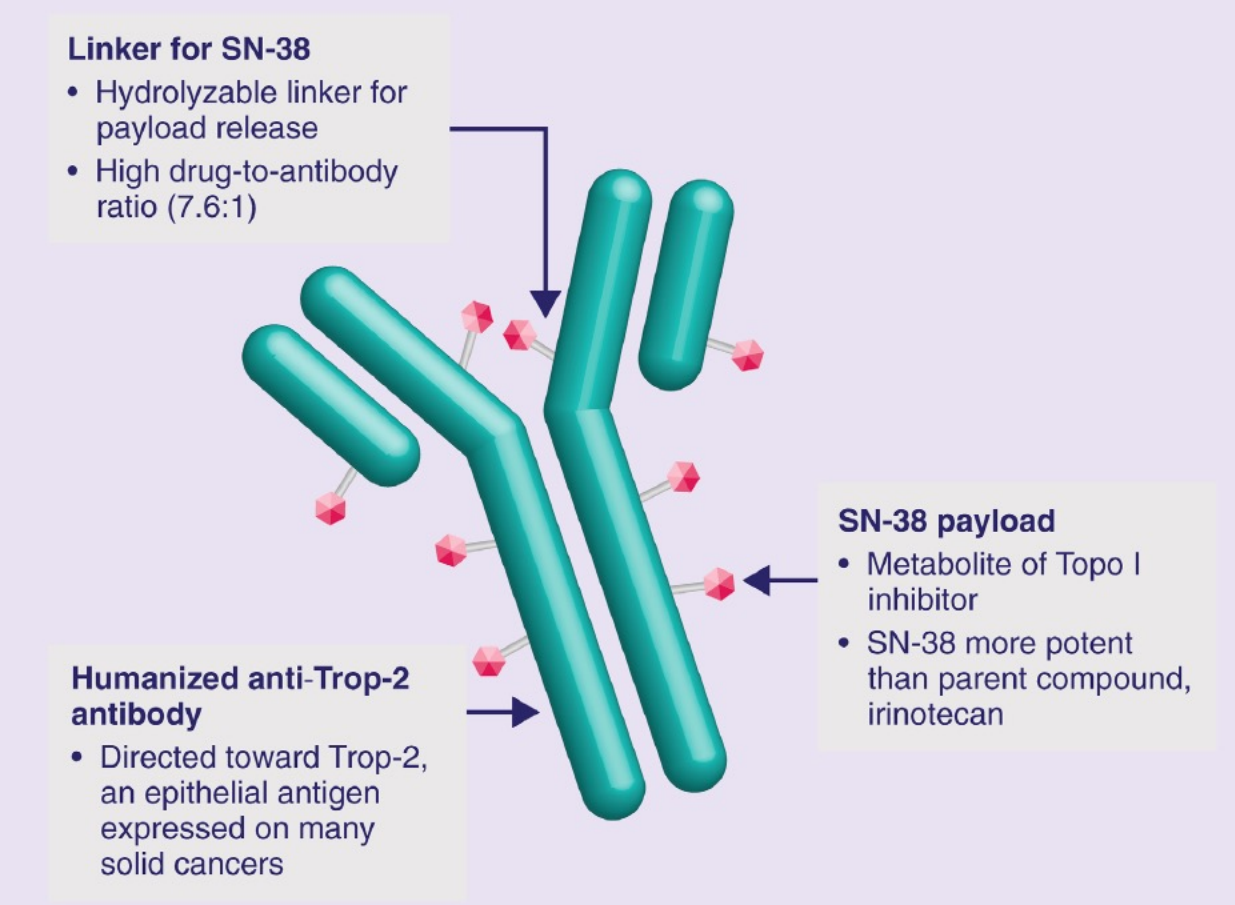
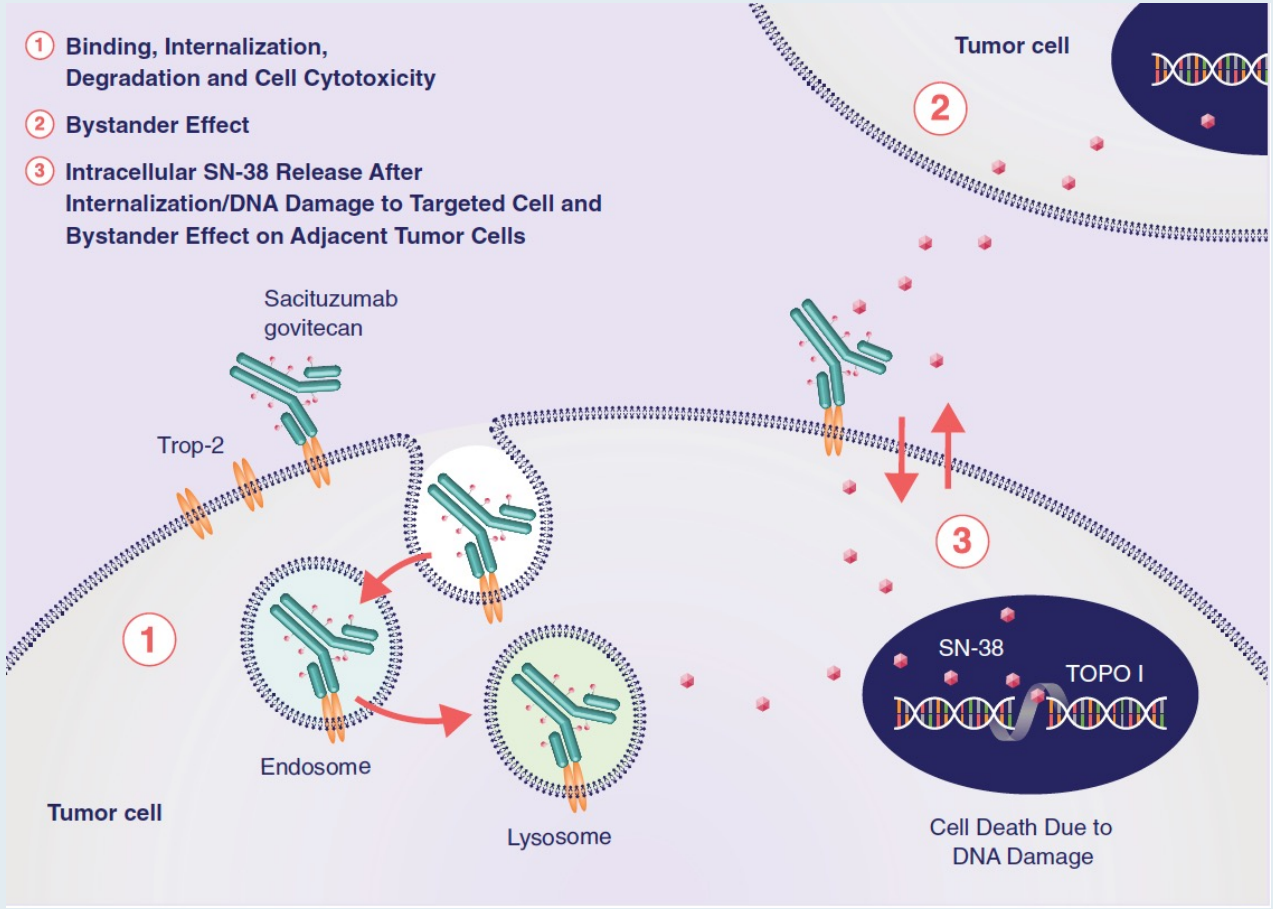
Sacituzumab Govitecan Is a First-in-Class TROP-2-Directed Antibody-Drug Conjugate





Rugo H et al. *Future Oncol* 2020;16(12):705-15.

Elacestrant, an Oral Selective Estrogen Receptor Degrader (SERD), vs Investigator's Choice of Endocrine Monotherapy for ER+/HER2- Advanced/Metastatic Breast Cancer (mBC) Following Progression on Prior Endocrine and CDK4/6 Inhibitor Therapy: Results of EMERALD Phase 3 Trial

Bardia A et al.

SABCS 2021;Abstract GS2-02.

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."

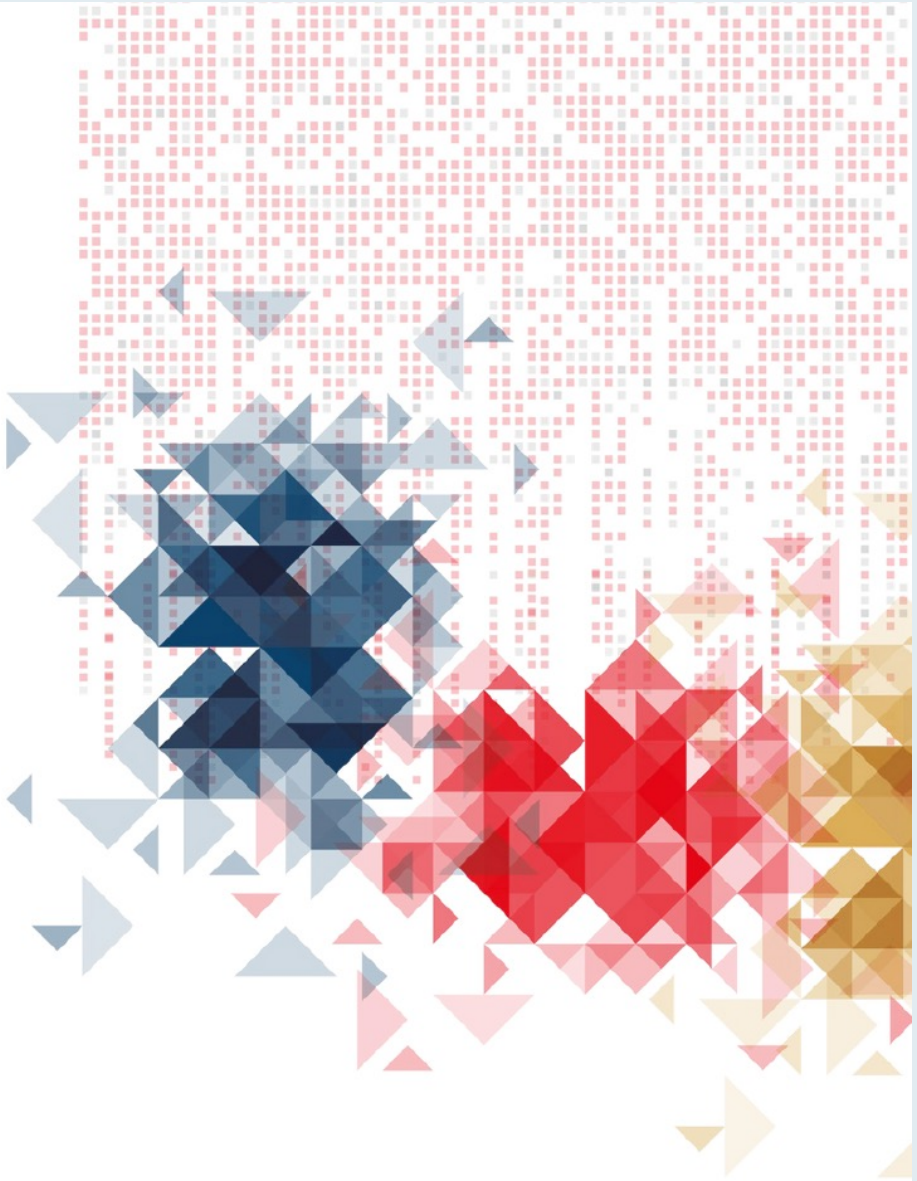
https://www.cancernetwork.com/view/trastuzumab-deruxtecan-significantly-improved-pfs-over-tdm-1-for-her2-metastatic-breast-cancer

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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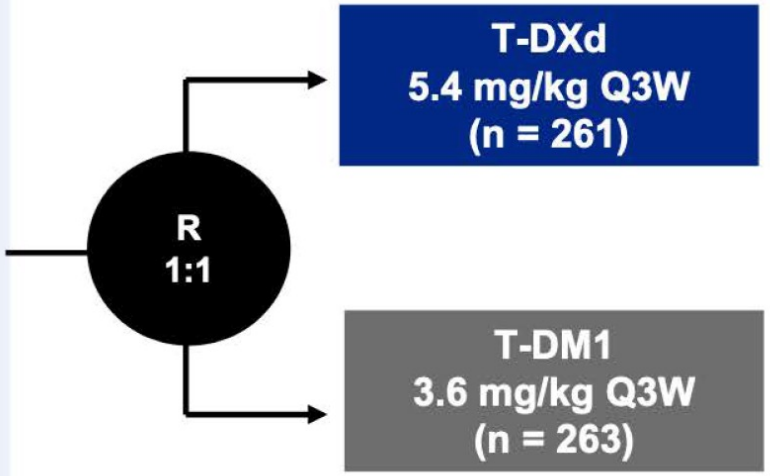
DESTINY-Breast03 Phase III Trial Schema

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

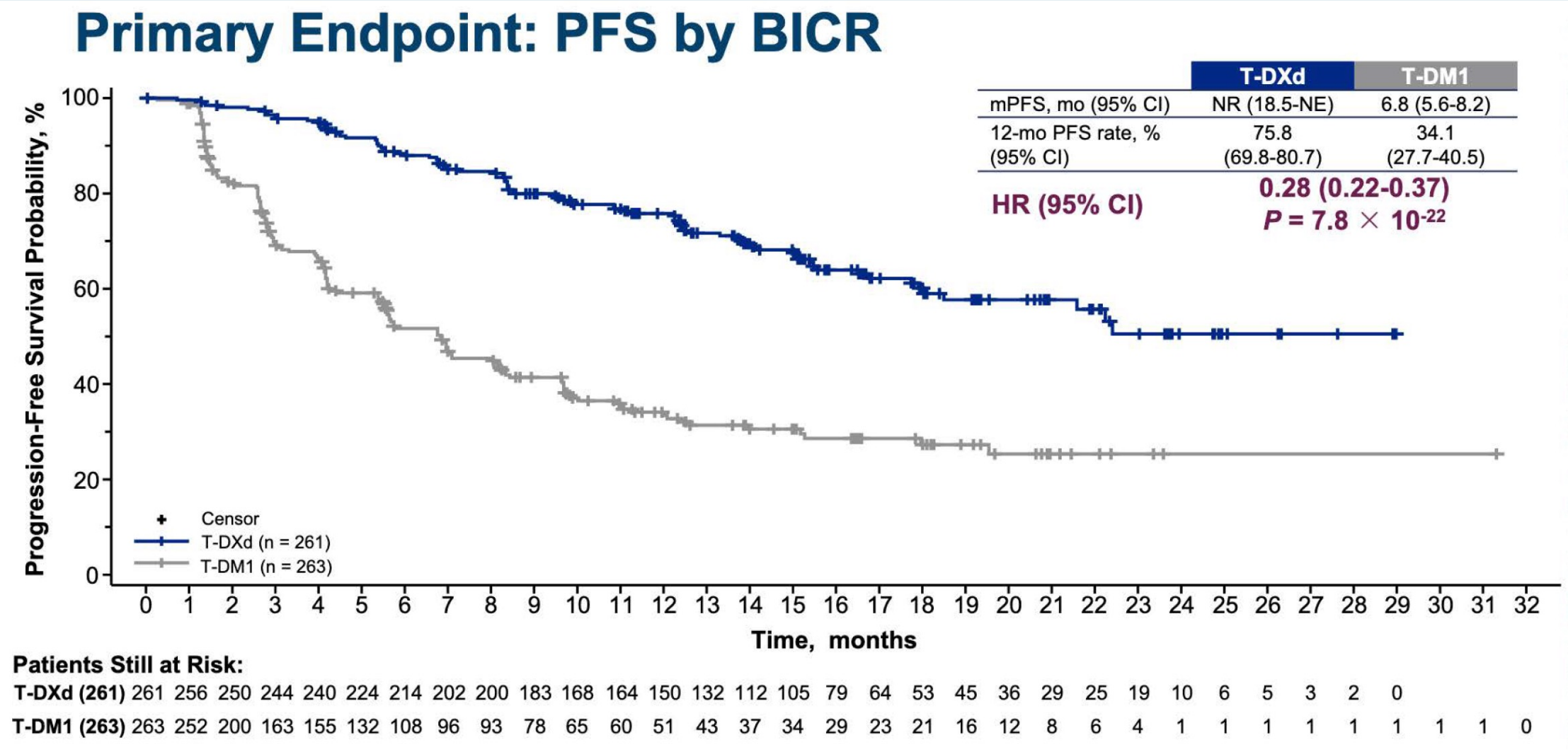
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

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.

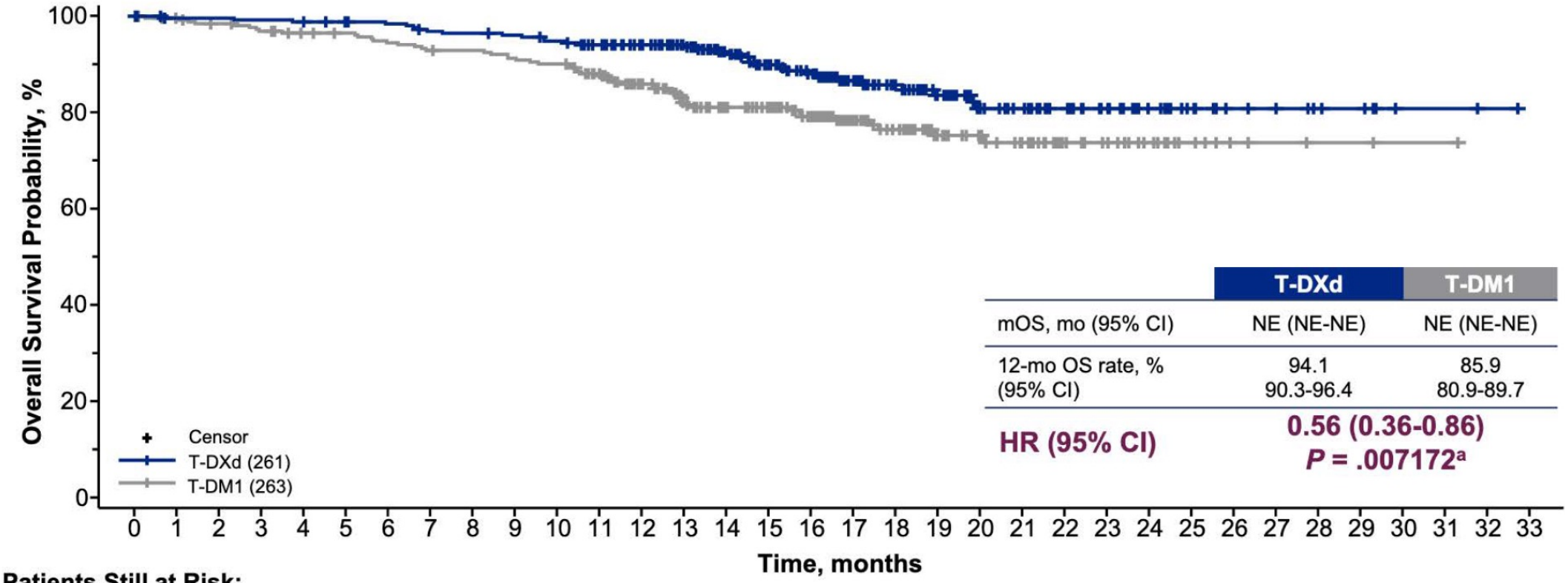
DESTINY-Breast03: Progression-Free Survival by BICR



Cortés J et al. ESMO 2021;Abstract LBA1.

DESTINY-Breast03: Overall Survival 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.

RTP RESEARCH TO PRACTICE

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.

DESTINY Breast03: PFS and ORR with T-DXd versus T-DM1 by Subgroup

	PFS by BICR, HR (95% CI)	Absolute ORR difference T-DXd, T-DM1 (95% CI)
All patients (N = 524)	0.28 (0.22-0.37)	45.5 (37.6-53.4)
Hormone receptor		
Positive (n = 272)	0.32 (0.22-0.46)	47.3 (36.1-58.4)
Negative (n = 248)	0.30 (0.20-0.44)	43.2 (31.5-55.0)
Prior pertuzumab		
Yes (n = 320)	0.31 (0.22-0.43)	46.7 (36.5-56.9)
No (n = 204)	0.30 (0.19-0.47)	43.6 (30.5-56.7)
Prior lines of therapy		
0-1 (n = 258)	0.33 (0.23-0.48)	39.3 (27.3-51.2)
≥2 (n = 266)	0.28 (0.19-0.41)	51.6 (40.9-62.4)
Visceral disease		
Yes (n = 384)	0.28 (0.21-0.38)	48.3 (39.1-57.6)
No (n = 140)	0.32 (0.17-0.58)	39.1 (23.6-54.6)
Brain metastases at baseline		
Yes (n = 82)	0.25 (0.13-0.45)	46.9 (25.6-68.3)
No (n = 442)	0.30 (0.22-0.40)	45.5 (36.9-54.1)

Hurvitz S et al. SABCS 2021;Abstract GS3-01.

Meet The Professor with Dr Rugo

Introduction: DESTINY Breast03

MODULE 1: Case Presentations

- Dr Sood: A 65-year-old woman with ER/PR-negative, HER2-positive mBC
- Dr Gosain: A 67-year-old woman with ER/PR-negative, HER2-positive, ROS1-positive mBC
- Dr Agrawal: A 56-year-old woman with ER/PR-positive, HER2-positive mBC with brain metastases
- Dr Zafar: A 33-year-old woman with triple-positive mBC and possible mosaicism of TP53 mutation
- Dr Peswani: A 37-year-old woman with triple-positive, node-negative localized breast cancer
- Dr Gupta: A 63-year-old woman with ER/PR-positive, HER2-positive, node-positive IDC

MODULE 2: Journal Club with Dr Rugo and SABCS 2021 Preview

MODULE 3: Appendix of Faculty Survey and Key Data Sets

Case Presentation – Dr Sood: A 65-year-old woman with ER/PR-negative, HER2-positive mBC

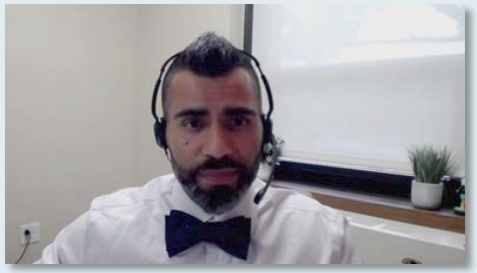
Dr Raman Sood

- 2008: Presented with right-sided inflammatory breast cancer (ER/PR-negative, HER2 3+)
- Neoadjuvant TCH → mastectomy → large residual tumor with multiple positive nodes
- RT with continued trastuzumab monotherapy
- Developed biopsy-confirmed pulmonary metastases
- Received multiple chemotherapy combinations with trastuzumab without much activity
- June 2010: Received lapatinib with stable disease but discontinued due to hepatotoxicity
- Jan 2013: Pertuzumab with vinorelbine added, but vinorelbine discontinued after 6 months
- Trastuzumab and pertuzumab continued since 2013 without any disease progression

Question

- Should we consider this patient to be cured?

Case Presentation – Dr Gosain: A 67-year-old woman with ER/PR-negative, HER2-positive, ROS1-positive mBC



Dr Rohit Gosain

- 5-cm ER/PR-negative, HER2-positive, ROS1-positive BC
- CT CAP: Multiple lung and liver lesions, biopsy-confirmed HER2-positive BC
- Paclitaxel/trastuzumab/pertuzumab (THP) → PD after 9 months → T-DM1
- Altered mental status after 6 months
- MRI: Multiple sub-centimeter brain lesions; Increase in size of lung and liver lesions

Questions

- What treatment would you recommend for third-line therapy?
- Would you continue with SRS for the brain metastases?

Case Presentation – Dr Agrawal: A 56-year-old woman with ER/PR-positive, HER2-positive mBC with brain metastases

Dr Laila Agrawal

- Initially presented with a 4-cm IDC, ER/PR-positive, HER2-positive with axillary metastasis
- She declined the recommended neoadjuvant chemotherapy and HER2 targeted treatment in favor of alternative therapies
- She returned 3 years later with a fungating breast mass, bone metastases, pleural effusions and a brain metastasis
- Taxane/trastuzumab/pertuzumab; brain metastasis treated with SRS
- After 12 months, she had PD systemically and new brain metastases amenable to additional SRS
- Tucatinib/capecitabine/trastuzumab → GI tolerability issues

Questions

- For patients who have asymptomatic progression of brain metastases who will be treated with tucatinib, would you recommend the radiation oncologist to proceed with SRS or attempt to control with systemic therapy? If the patient had leptomeningeal carcinomatosis would your answer change? What would be your preferred treatment in that case?
- How would you manage the toxicities associated with tucatinib/capecitabine/trastuzumab?

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Case Presentation – Dr Zafar: A 33-year-old woman with triple-positive mBC and possible mosaicism of TP53 mutation

Dr Syed Zafar

- Bilateral breast masses and LAD
  - Right: 6-cm, Grade III, ER/PR/HER2-positive
  - Left: 3-cm, Grade III, ER/PR-positive, HER2-negative
- Solitary 1.7-cm right hepatic metastasis, biopsy-confirmed ER/PR/HER2-positive
- Germline testing: BRCA wildtype, possible mosaicism of TP53 mutation
- OFS + trastuzumab/pertuzumab/docetaxel, with good response (6-mm residual liver lesion, SBRT)
- Maintenance trastuzumab/pertuzumab + OFS/AI and bisphosphonate
- Stereotactic radiotherapy to liver

Question

What would you recommend for her primary tumor?

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

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 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

UNC | LINEBERGER COMPREHENSIVE CANCER CENTER

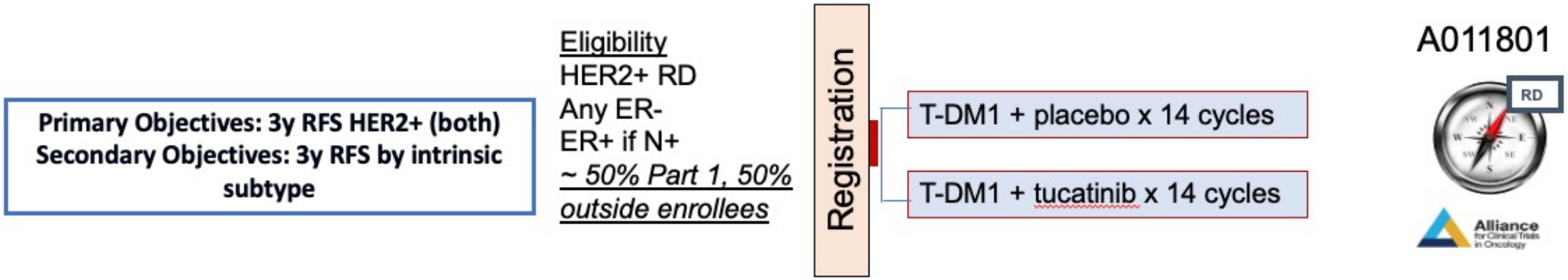
UNC CANCER CARE

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer

Lisa A. Carey MD, ScM
University of North Carolina
Lineberger Comprehensive Cancer Center
December, 2021

Ongoing Challenge of CNS Metastasis

- **KATHERINE did not see a difference with T-DM1 in incidence of CNS relapse (~ 5% both arms)**
- **Small molecule inhibitors may be key**
  - **Post-hoc subset analysis of ExteNET HR+ suggest 59% reduction in risk of CNS relapse**
  - **Tucatinib added to trastuzumab + capecitabine in MBC found 68% improvement in CNS PFS**
- **Being tested in COMPASS-RD:**



Chan A et al, Clin Breast Cancer 2021; Lin NU et al, JCO 2021

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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]

Ann Oncol 2021;32(8):1005-14

KATHERINE: Central Nervous System Recurrence Events

	T-DM1 (n = 743)	Trastuzumab (n = 743)
Patients with CNS recurrence	45 (6.1%)	40 (5.4%)
At first IDFS event[a]	44 (5.9%)	32 (4.3%)
After first IDFS event[b]	1 (0.1%)	8 (1.1)
Patients with CNS as only event[c]	36 (4.8%)	21 (2.8%)
Median time to CNS recurrence	17.5 months	11.9 months

T-DM1 = trastuzumab emtansine; CNS = central nervous system; IDFS = invasive disease-free survival
CNS recurrence [a]within or [b]after 61 days of first IDFS event or at [c]any time

Mamounas EP et al. *Ann Oncol* 2021;32(8):1005-14.

Case Presentation – Dr Peswani: A 37-year-old woman with triple-positive, node-negative localized breast cancer

Dr Namrata Peswani

- 2-cm cT2N0M0 ER/PR/HER2-positive IDC of the right breast
- Neoadjuvant TCHP

Question

- Should age be taken into consideration when deciding whether or not to use an anthracycline-containing regimen?

Case Presentation – Dr Gupta: A 63-year-old woman with ER/PR-positive, HER2-positive, node-positive IDC

Dr Shaachi Gupta

- PMH: HSV type II, mild COPD, former smoker, HRT
- February 2021: Screening mammogram showed dense breasts, a spiculated 1 cm mass UOQ in the right breast, confirmed by diagnostic mammogram
- Core biopsy: Poorly differentiated IDC, ER 90%, PR 40%, HER2 3+
- April 2021: Right partial mastectomy/SLNB → pathology revealed 1.8-cm, Grade 3 IDC/Grade 2 DCIS, 3/3 SLNs positive for carcinoma (restaging PET confirms NED)
- Right ALND showed 6/12 lymph nodes involved by carcinoma upstaging her to N2a disease (total of 9 lymph nodes positive)
- Plan to administer adjuvant TCHP x 6 cycles and empirically switch to T-DM1 for a year

Questions

- Is this treatment plan reasonable? What are your thoughts of giving her neratinib? Enrollment on a clinical trial of abemaciclib in the HER2-positive setting?
- What is more important, continued HER2 blockade or HR pathway blockade?

Meet The Professor with Dr Rugo

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MODULE 2: Journal Club with Dr Rugo and SABCS 2021 Preview

MODULE 3: Appendix of Faculty Survey and Key Data Sets

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Research

JAMA Oncol 2021;7(11):1654-63

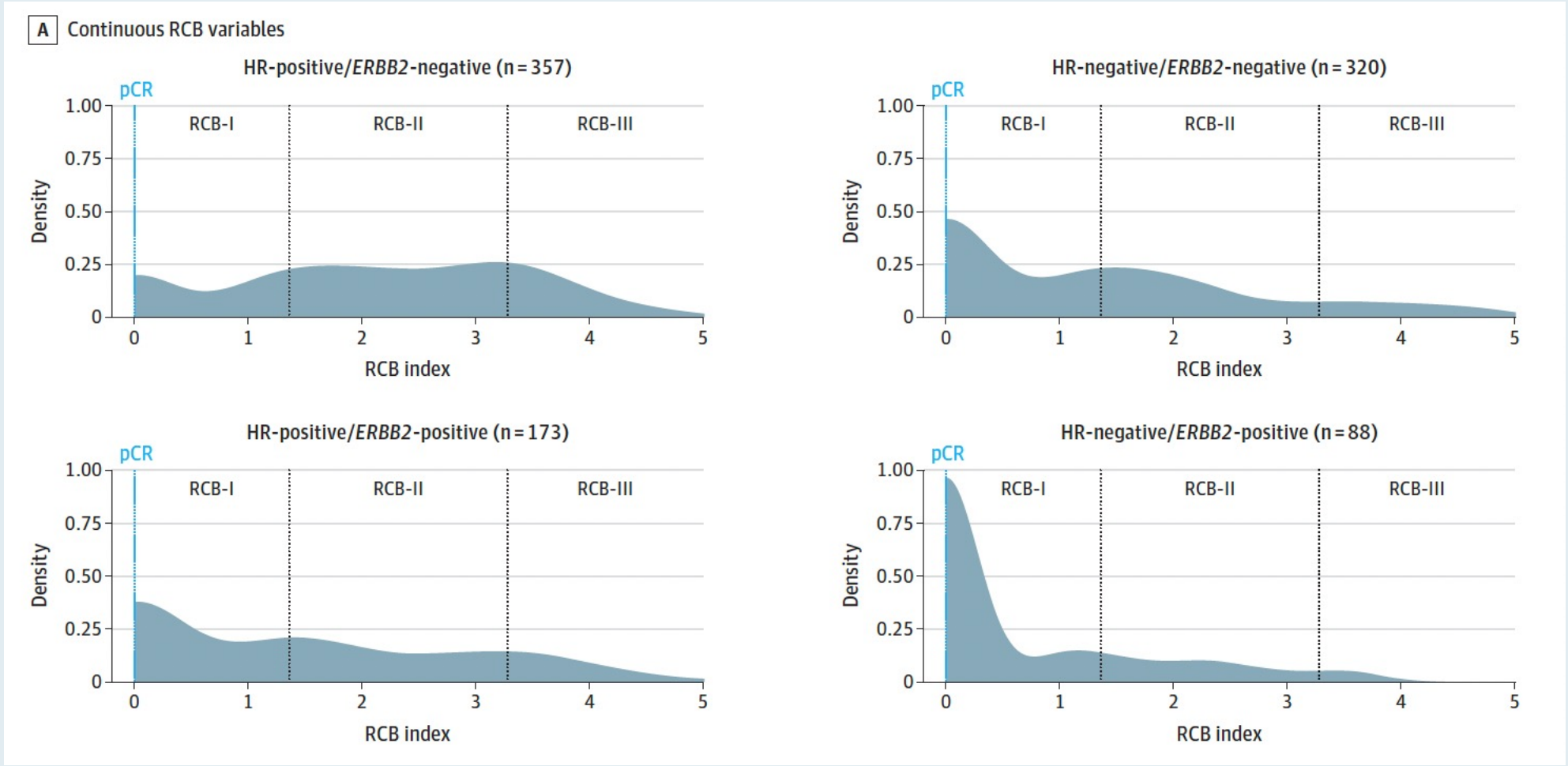
JAMA Oncology | Original Investigation

Assessment of Residual Cancer Burden and Event-Free Survival in Neoadjuvant Treatment for High-risk Breast Cancer

An Analysis of Data From the I-SPY2 Randomized Clinical Trial

W. Fraser Symmans, MD; Christina Yau, PhD; Yunn-Yi Chen, MD; Ron Balassanian, MD; Molly E. Klein, MD; Lajos Pusztai, MD; Rita Nanda, MD; Barbara A. Parker, MD; Brian Datnow, MD; Gregor Krings, MD; Shi Wei, MD; Michael D. Feldman, MD; Xiuzhen Duan, MD; Beiyun Chen, MD; Husain Sattar, MD; Laila Khazai, MD; Jay C. Zeck, MD; Sharon Sams, MD; Paulette Mhawech-Fauceglia, MD; Mara Rendi, MD; Sunati Sahoo, MD; Idris Tolgay Ocal, MD; Fang Fan, MD; Lauren Grasso LeBeau, MD; Tuyethoa Vinh, MD; Megan L. Troxell, MD; A. Jo Chien, MD; Anne M. Wallace, MD; Andres Forero-Torres, MD; Erin Ellis, MD; Kathy S. Albain, MD; Rashmi K. Murthy, MD; Judy C. Boughey, MD; Minetta C. Liu, MD; Barbara B. Haley, MD; Anthony D. Elias, MD; Amy S. Clark, MD; Kathleen Kemmer, MD; Claudine Isaacs, MD; Julie E. Lang, MD; Hyo S. Han, MD; Kirsten Edmiston, MD; Rebecca K. Viscusi, MD; Donald W. Northfelt, MD; Qamar J. Khan, MD; Brian Leyland-Jones, MD; Sara J. Venters, PhD; Sonal Shad, BS; Jeffrey B. Matthews, PhD; Smita M. Asare, BS; Meredith Buxton, PhD; Adam L. Asare, PhD; Hope S. Rugo, MD; Richard B. Schwab, MD; Teresa Helsten, MD; Nola M. Hylton, MD; Laura van 't Veer, PhD; Jane Perlmutter, PhD; Angela M. DeMichele, MD; Douglas Yee, MD; Donald A. Berry, PhD; Laura J. Esserman, MD

Distribution of Residual Cancer Burden (RCB) within Each Phenotypic Subtype as Landscape Plots of Continuous RCB Values



Symmans WF et al. *JAMA Oncol* 2021;7(11):1654-63.

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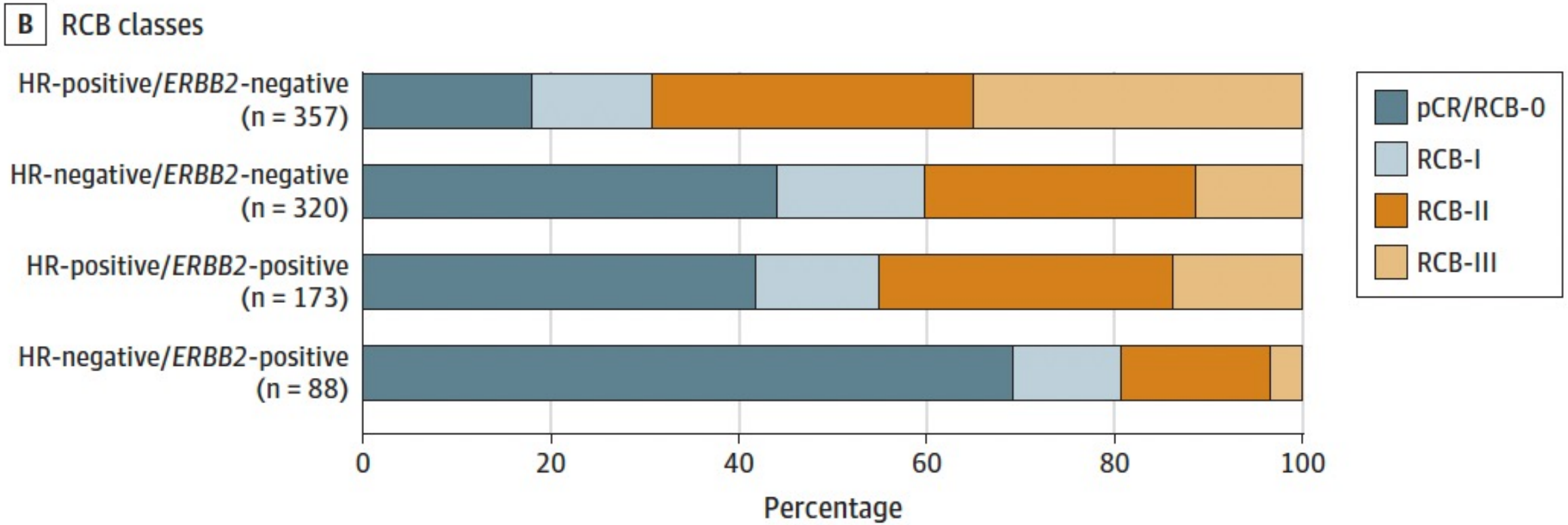
Distribution of Residual Cancer Burden (RCB) within Each Phenotypic Subtype as Mosaic Plots of RCB Classes



Symmans WF et al. *JAMA Oncol* 2021;7(11):1654-63.

RTP RESEARCH TO PRACTICE

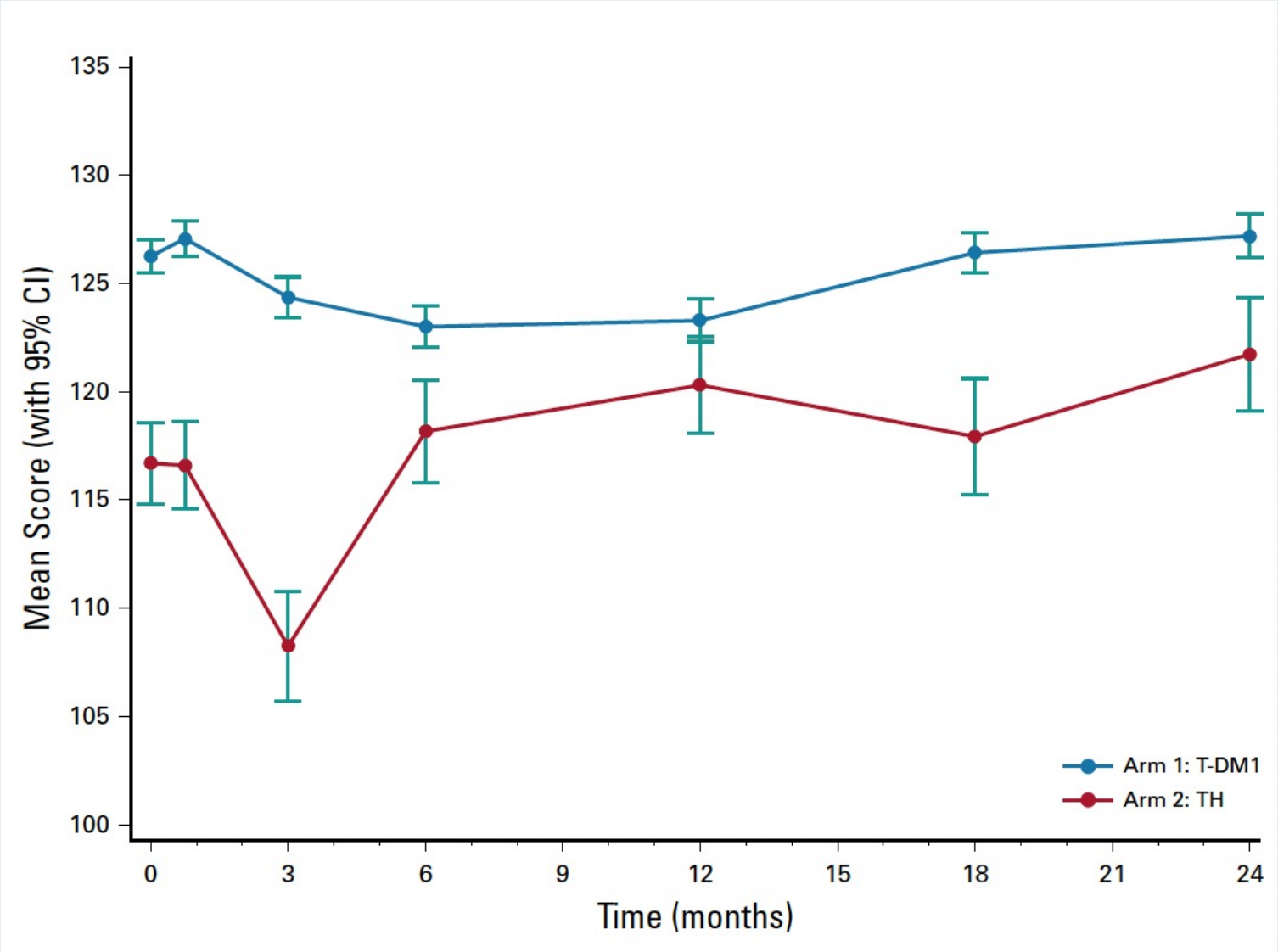
J Clin Oncol 2021;39(21):2375-85

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]

Overall QOL Over Time as Reported by Patients in FACT-B



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

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Breast Cancer Research and Treatment (2021) 189:103–110
https://doi.org/10.1007/s10549-021-06267-8

CLINICAL TRIAL

Chemotherapy-related amenorrhea (CRA) after adjuvant ado-trastuzumab emtansine (T-DM1) compared to paclitaxel in combination with trastuzumab (TH) (TBCRC033: ATEMPT Trial)

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

Journal Club with Dr Rugo

- Vidal GA et al. **The Neat-HER virtual registry: Updated results on HER2+ breast cancer patients receiving neratinib as extended adjuvant therapy.** ASCO 2021;Abstract e13565.
- Vidula N et al. **Evaluation of disseminated tumor cells and circulating tumor cells in patients with breast cancer receiving adjuvant zoledronic acid.** *NPJ Breast Cancer* 2021;7(1):113.

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SABCS 2021 Preview

- Hurvitz S et al. **Trastuzumab deruxtecan vs trastuzumab emtansine in patients with HER2+ metastatic breast cancer: Results of the randomized phase 3 study DESTINY-Breast03.** Abstract GS3-01.
- Rugo H et al. **Phase 3 SOPHIA study of margetuximab (M) + chemotherapy (CTX) vs trastuzumab (T) + CTX in patients (pts) with HER2+ metastatic breast cancer (MBC) after prior anti-HER2 therapies: Final overall survival (OS) analysis.** Abstract PD8-03.
- Xu B et al. **Updated overall survival (OS) results from the phase 3 PHOEBE trial of pyrotinib versus lapatinib in combination with capecitabine in patients with HER2-positive metastatic breast cancer.** Abstract GS3-02.
- Jhaveri K et al. **Neratinib + fulvestrant + trastuzumab for hormone receptor-positive, HER2-mutant metastatic breast cancer and neratinib + trastuzumab for triple-negative disease: Latest updates from the SUMMIT trial.** Abstract GS4-10.
- Ferraro E et al. **Genomic analysis of 733 HER2+ breast cancers identifies recurrent pathways alterations associated with anti-HER2 resistance and new therapeutic vulnerabilities.** Abstract GS3-03.

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Meet The Professor with Dr Rugo

Introduction: DESTINY Breast03

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MODULE 2: Journal Club with Dr Rugo and SABCS 2021 Preview

MODULE 3: Appendix of Faculty Survey and Key Data Sets

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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 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 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 and brain 18 months after completing neoadjuvant TCHP followed by adjuvant trastuzumab/pertuzumab. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

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 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

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 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

RTP
RESEARCH
TO PRACTICE

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

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

Management of Metastatic HER2-Positive Breast Cancer

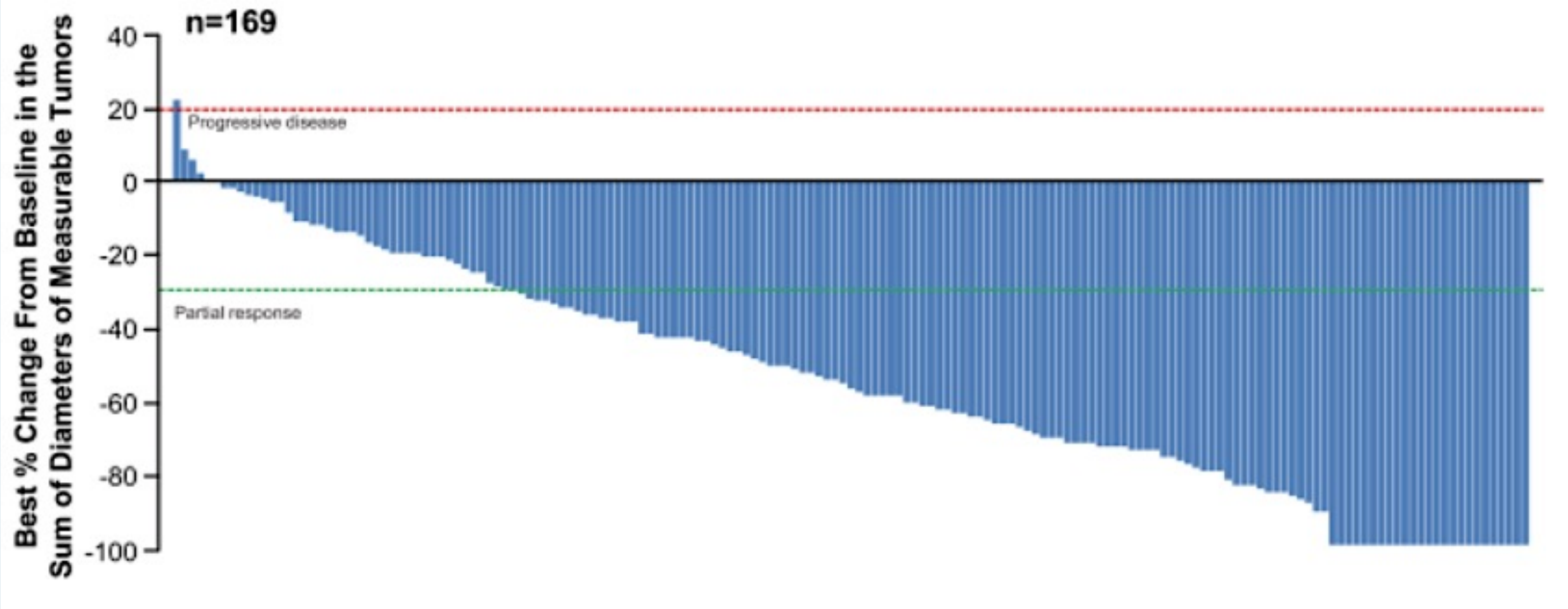
RTP
RESEARCH
TO PRACTICE

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.

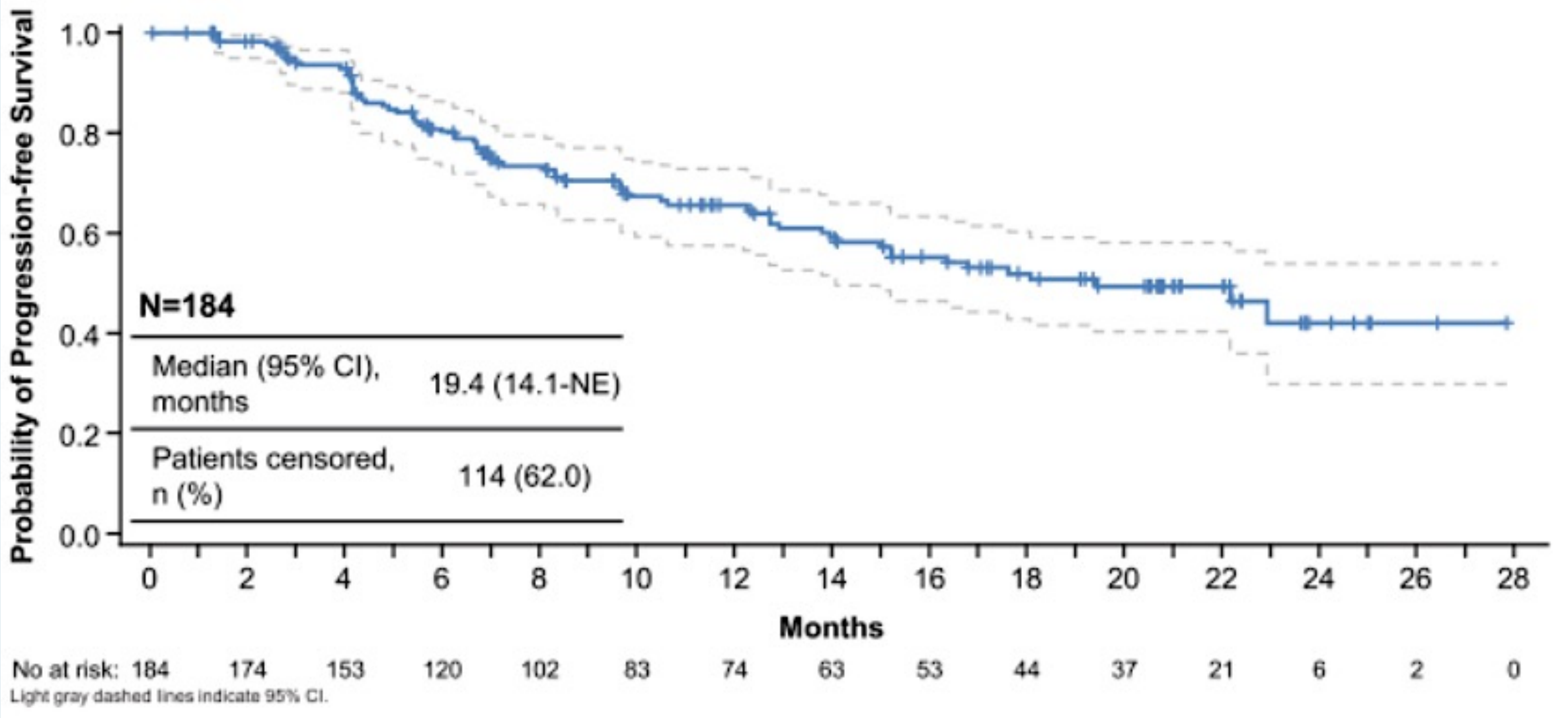
DESTINY-Breast01: Best Percent Change in Tumor Size from Baseline



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

RTP RESEARCH TO PRACTICE

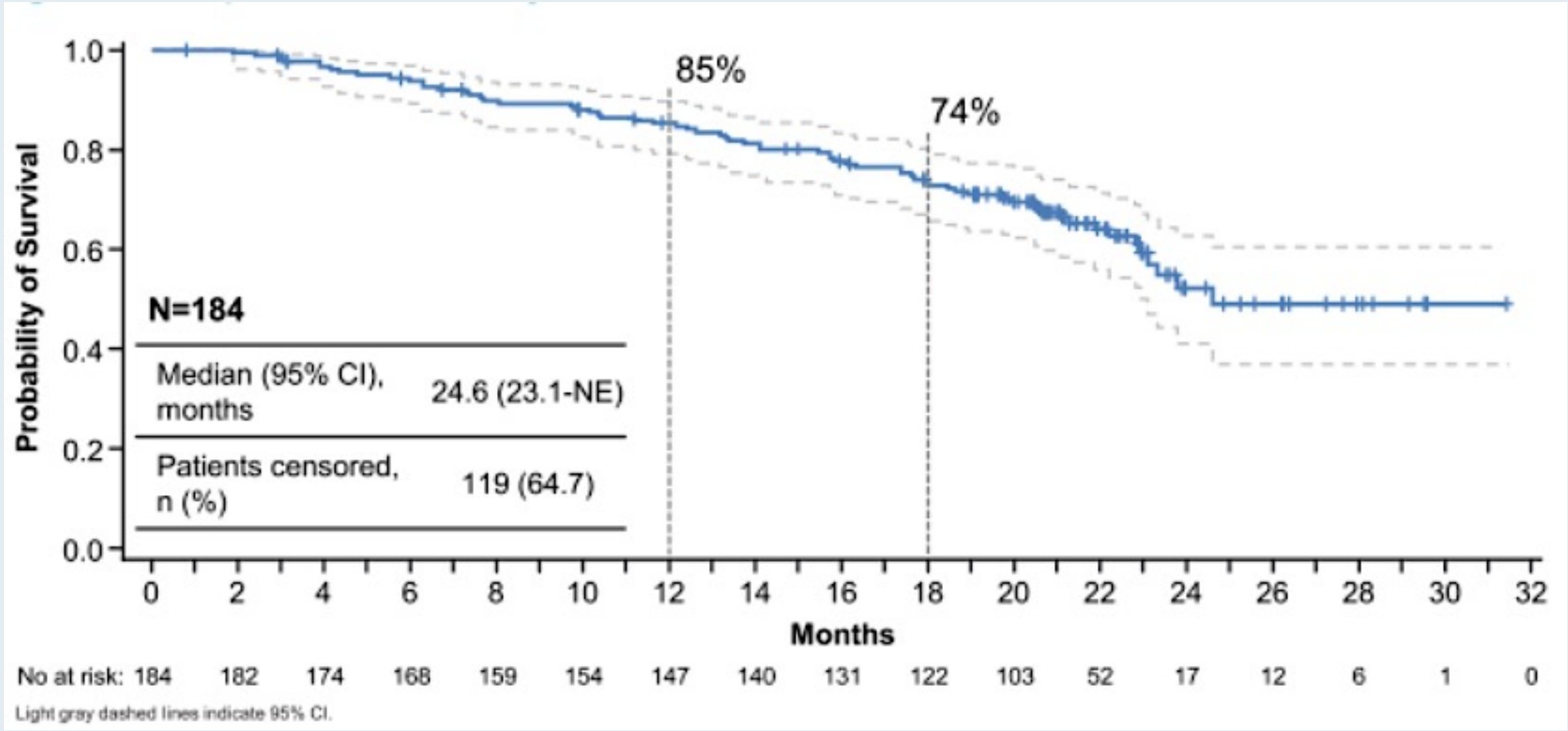
DESTINY-Breast01: Progression-Free Survival



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

RTP RESEARCH TO PRACTICE

DESTINY-Breast01: Overall Survival



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

RTP RESEARCH TO PRACTICE

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

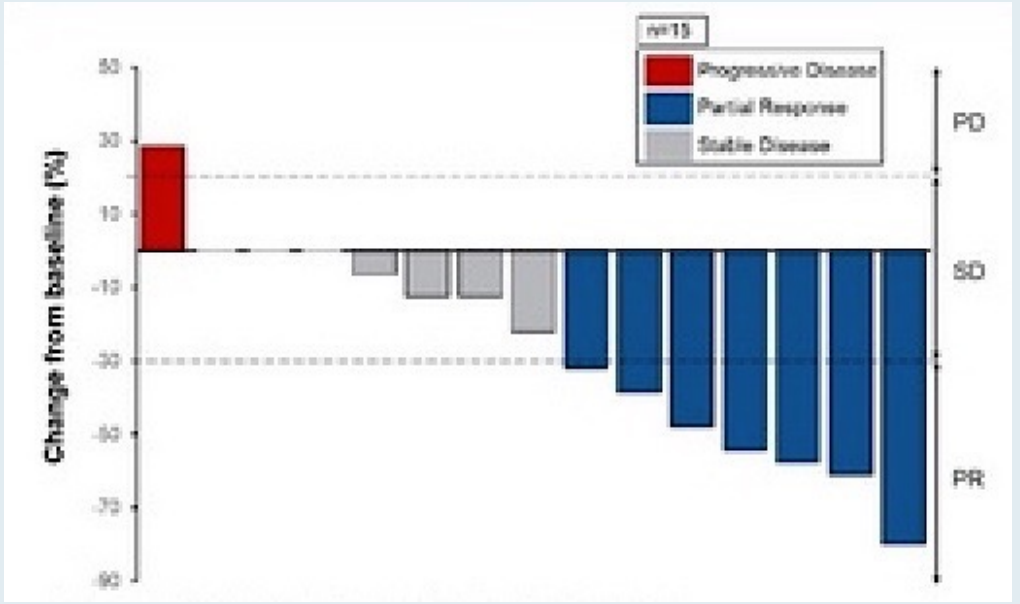
Jerusalem GHM et al.

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

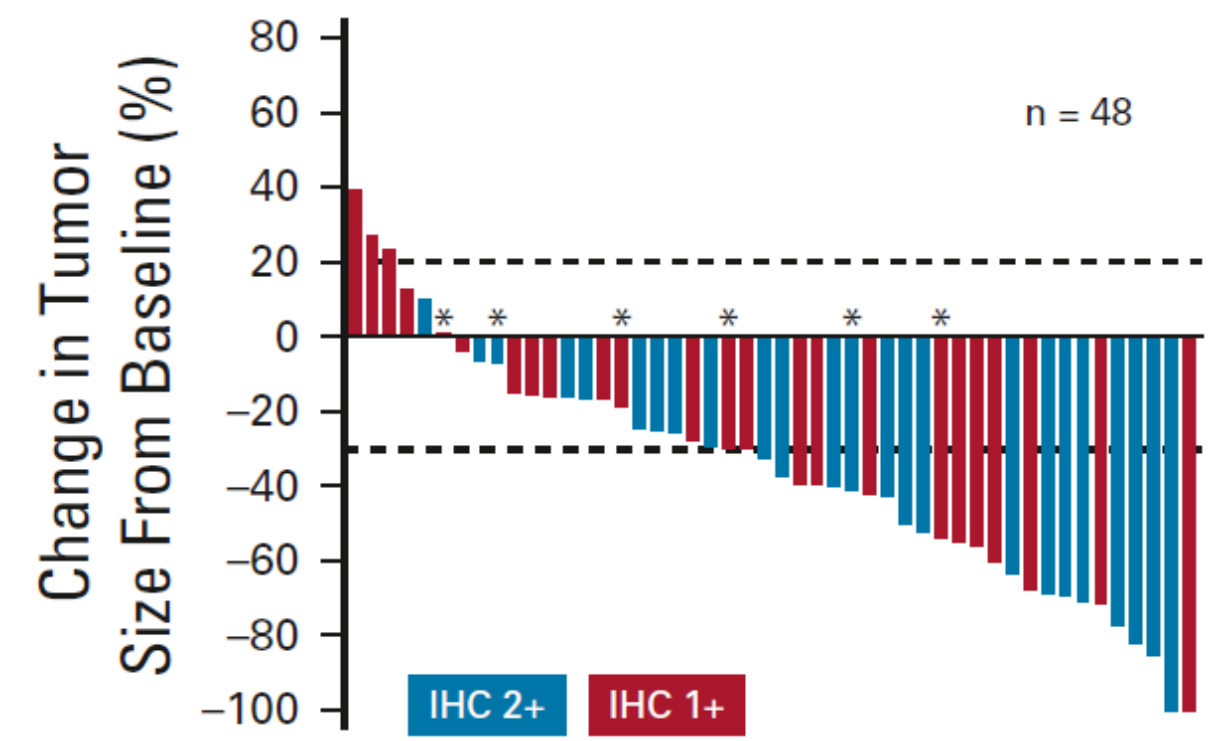
original reports

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

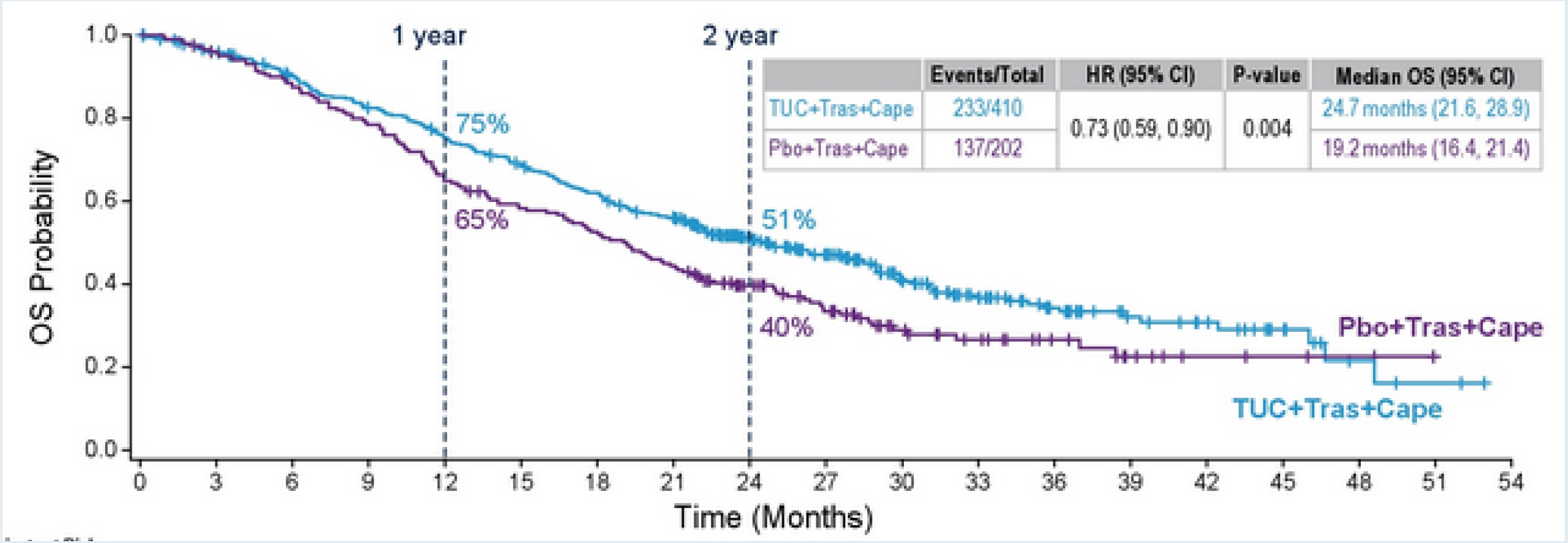
RTP RESEARCH TO PRACTICE

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

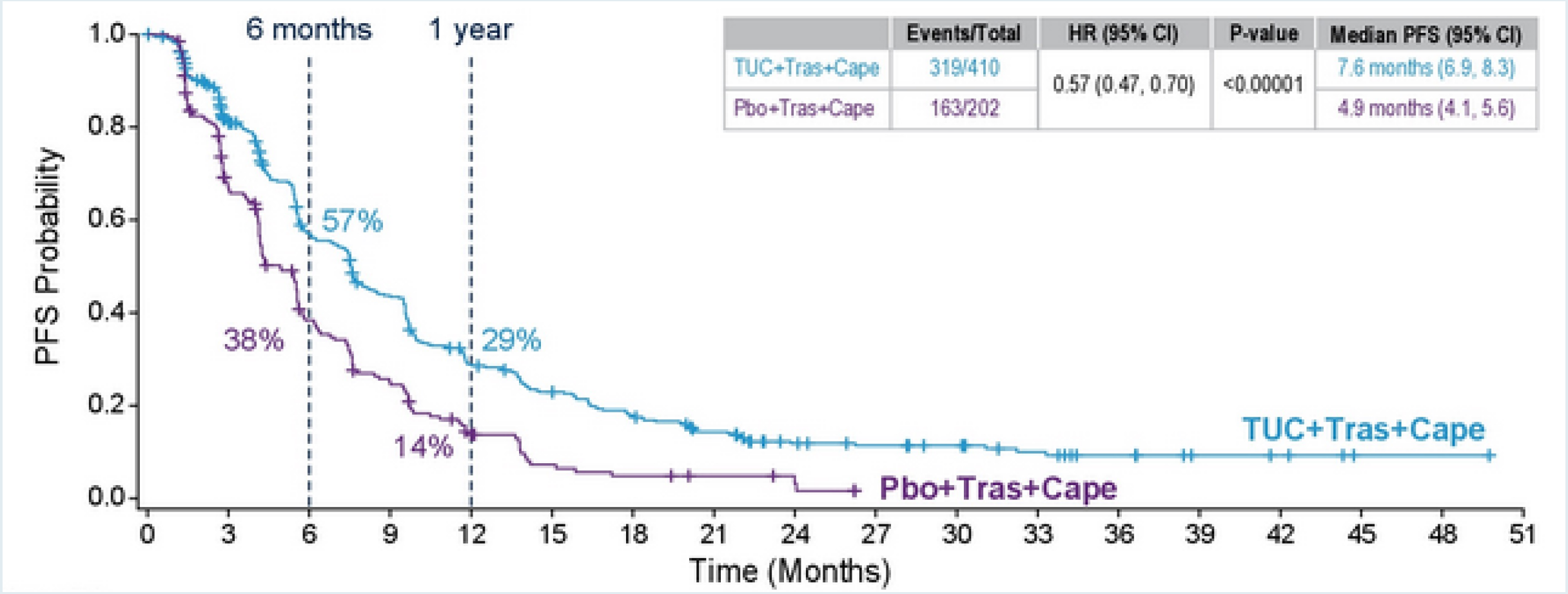


	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	233/410	0.73 (0.59, 0.90)	0.004	24.7 months (21.6, 28.9)
Pbo+Tras+Cape	137/202			19.2 months (16.4, 21.4)

Curigliano G et al. ASCO 2021;Abstract 1043.

RTP RESEARCH TO PRACTICE

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

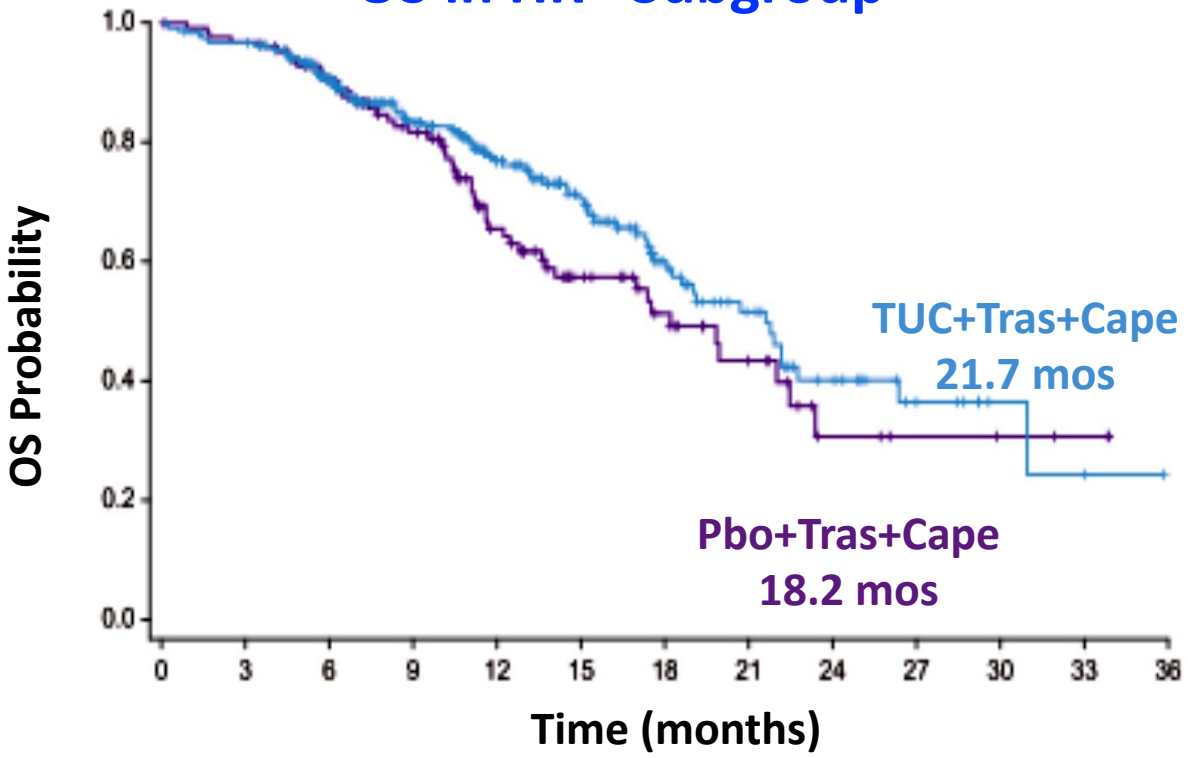
Hamilton E et al.

SABCS 2020;Abstract PD3-08.

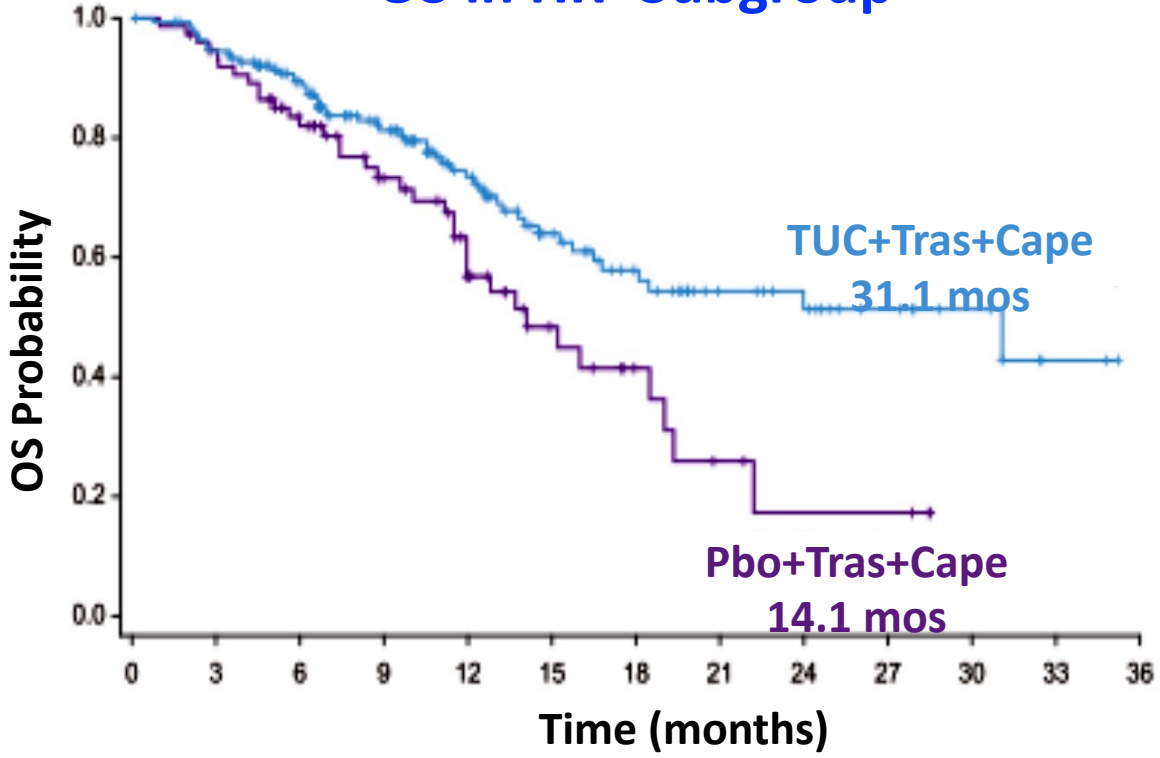
OS by HR Status in the Total Study Population

- 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.

RTP RESEARCH TO PRACTICE

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.

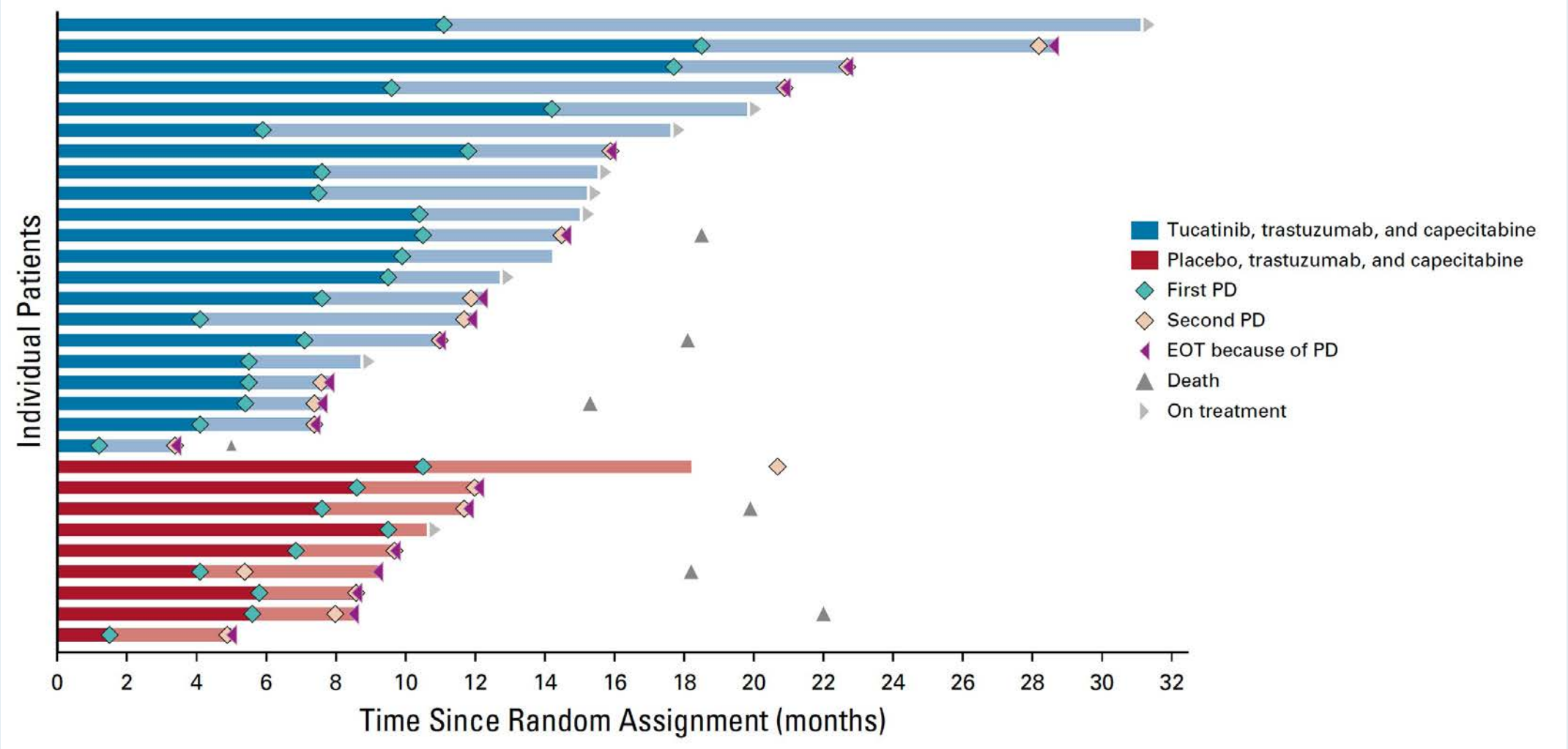
rapid communications

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]

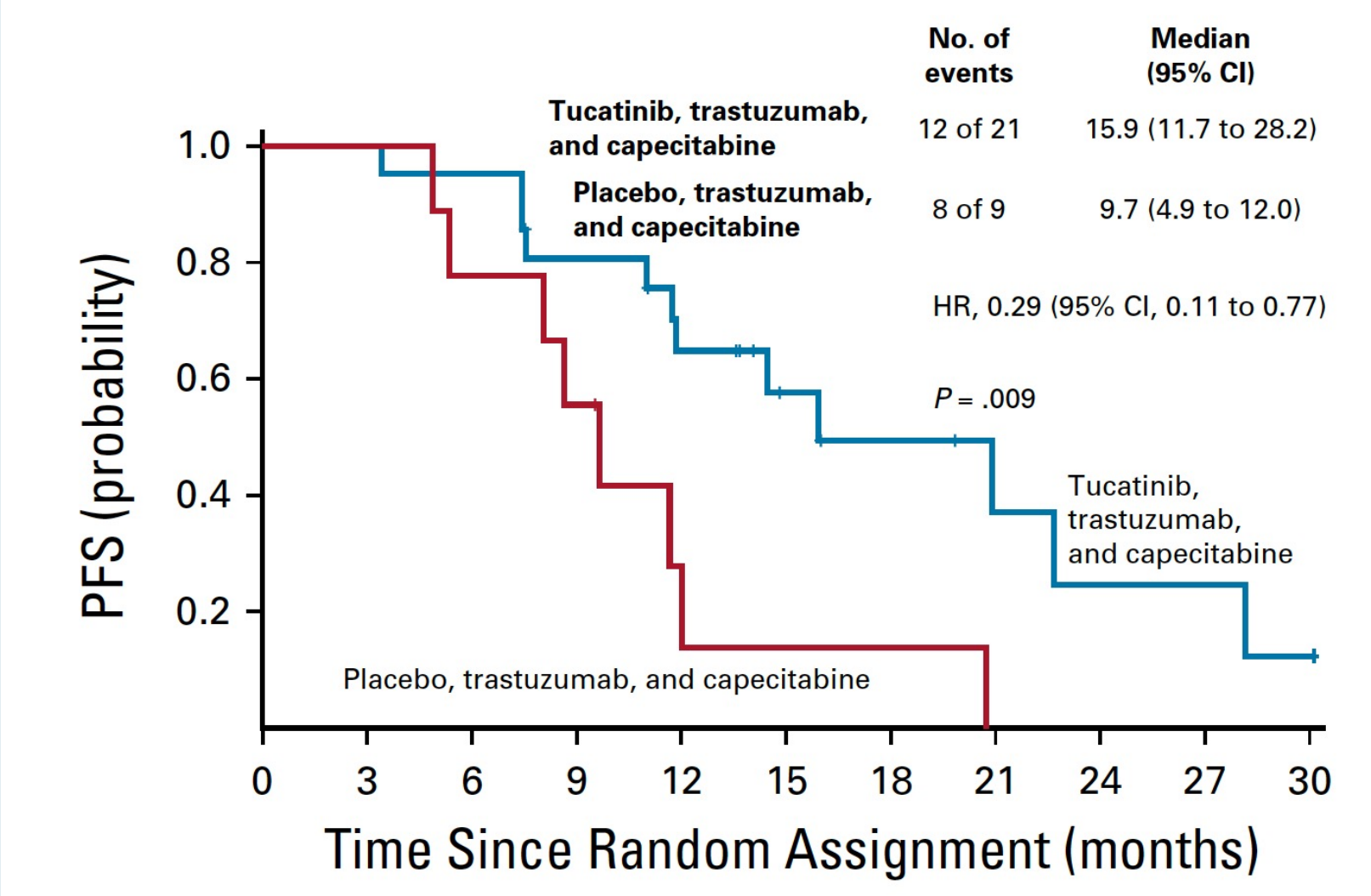
J Clin Oncol 2020;38(23):2610-9.

Duration of Treatment



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

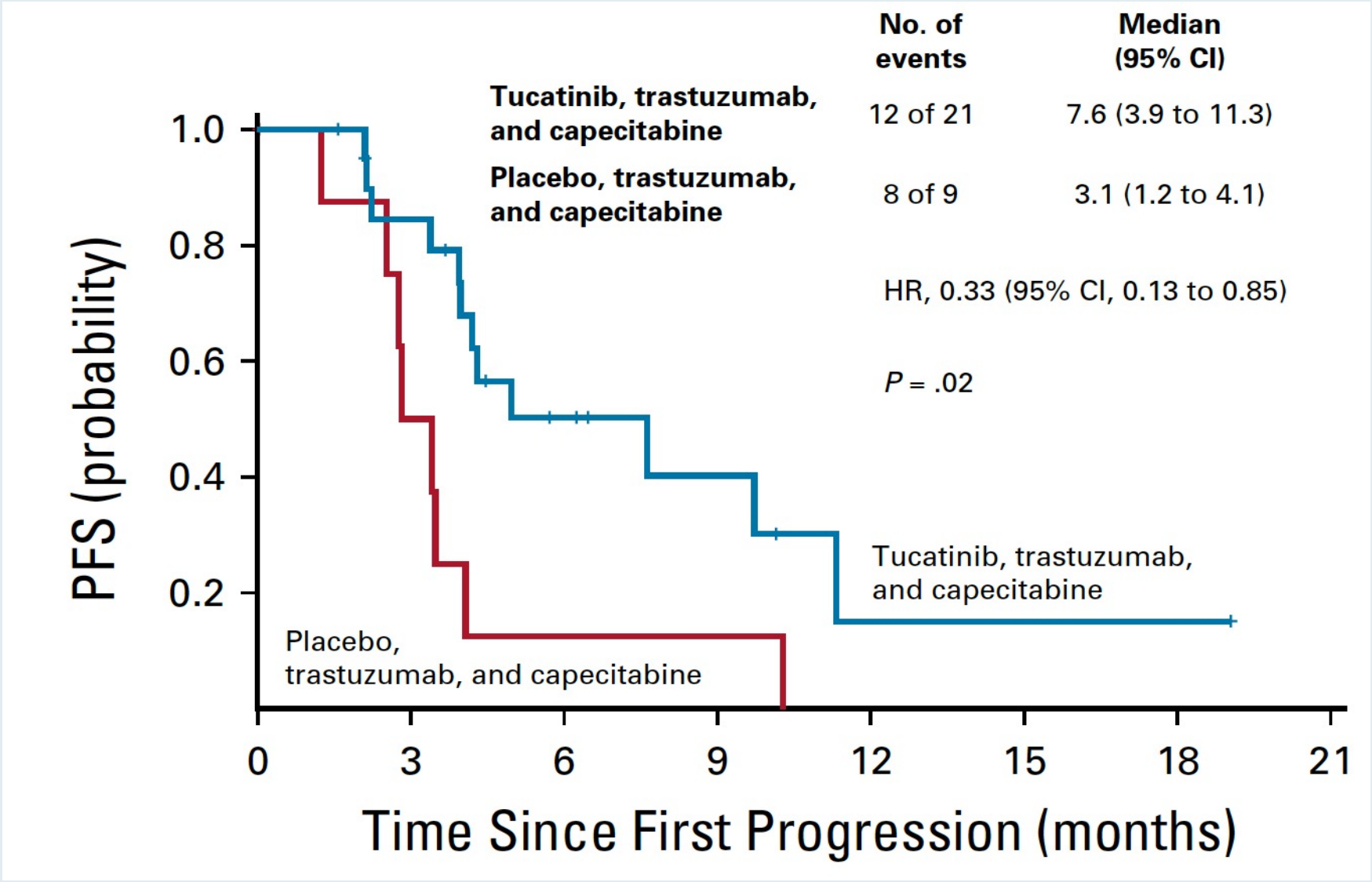
Time from Random Assignment to Second Disease Progression by Investigator Assessment or Death



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.

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

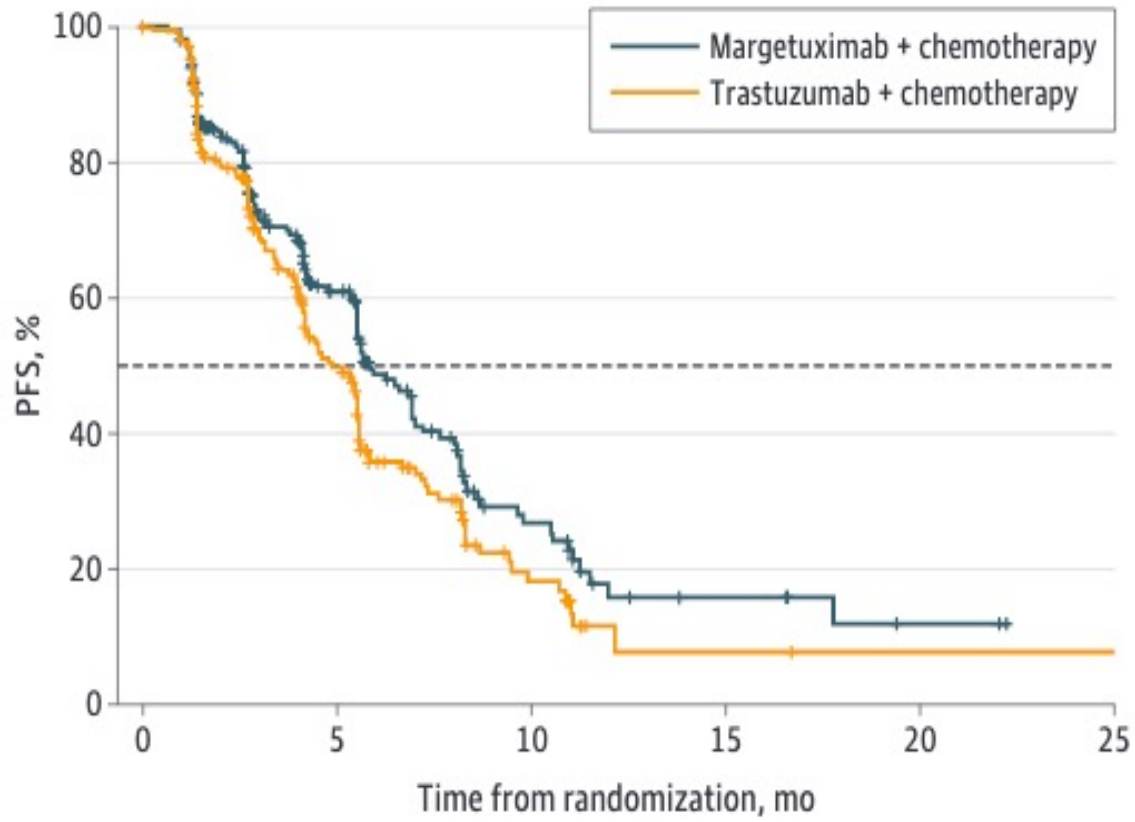
JAMA Oncology | Original Investigation

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)

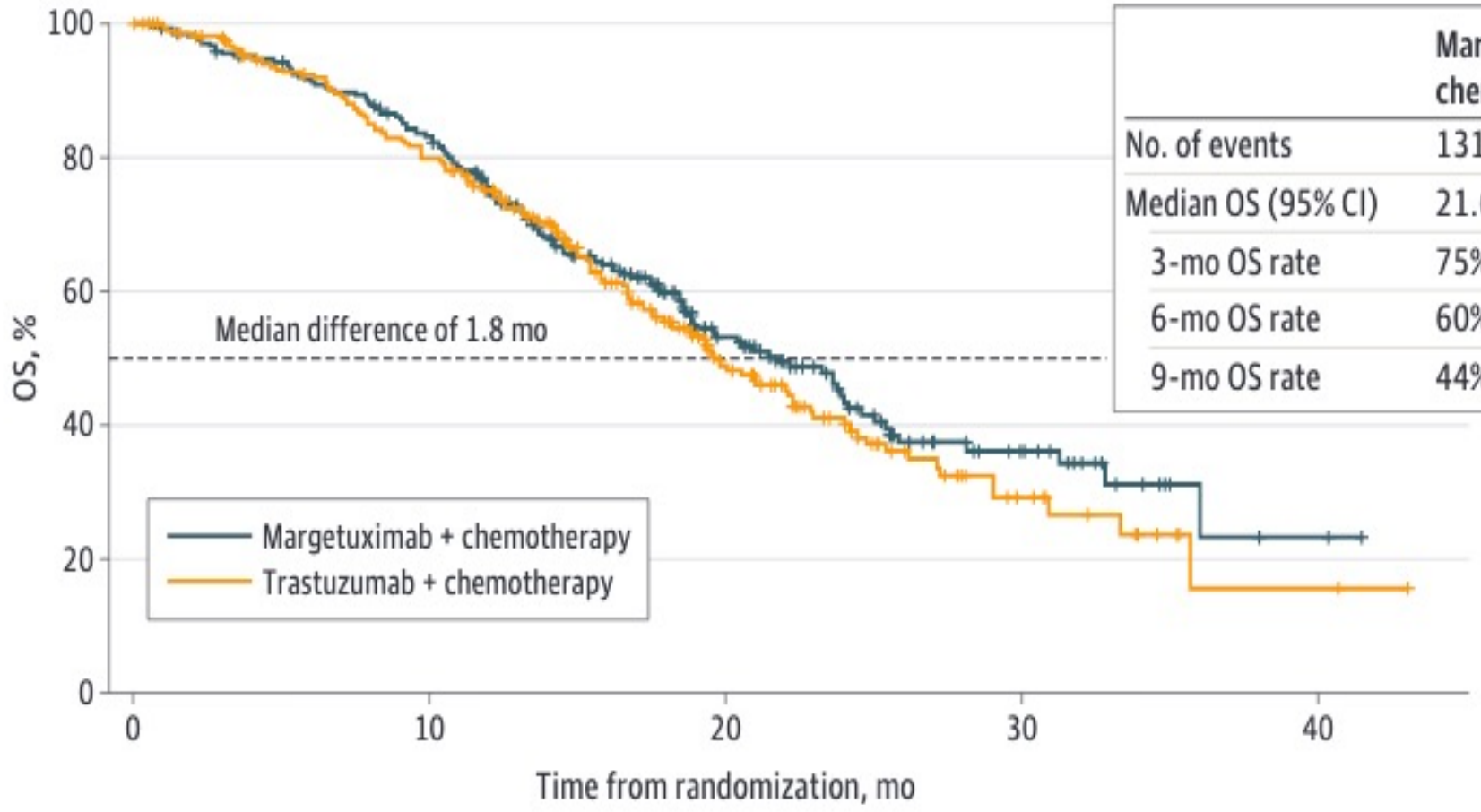


	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

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

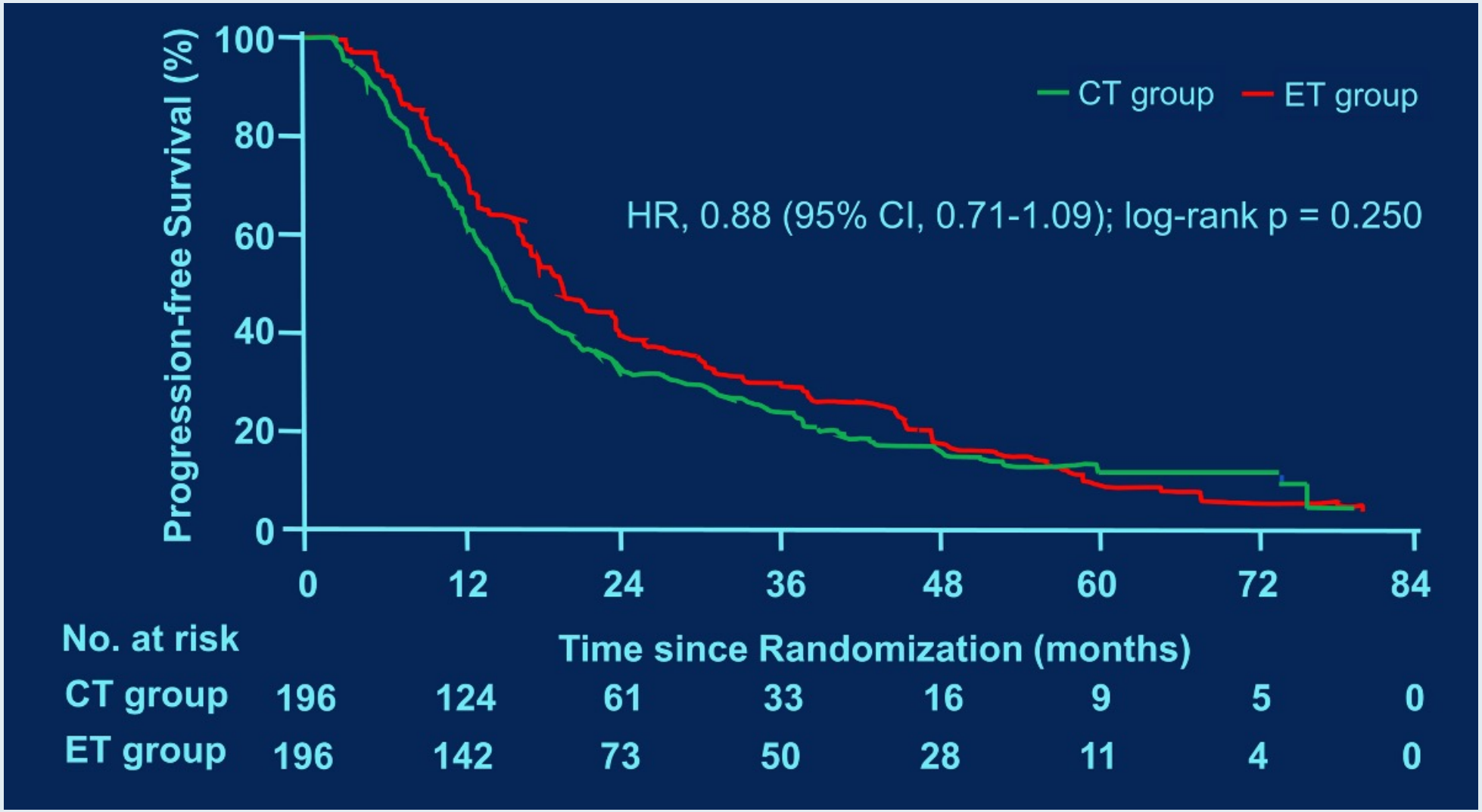
Rugo HS et al. *JAMA Oncol* 2021;[Online ahead of print].

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.

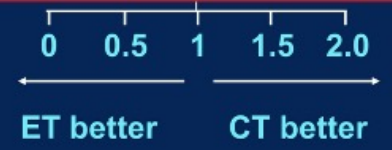
SYSUCC-002: Progression-Free Survival (Primary Endpoint)



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

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

Localized HER2-Positive Breast Cancer

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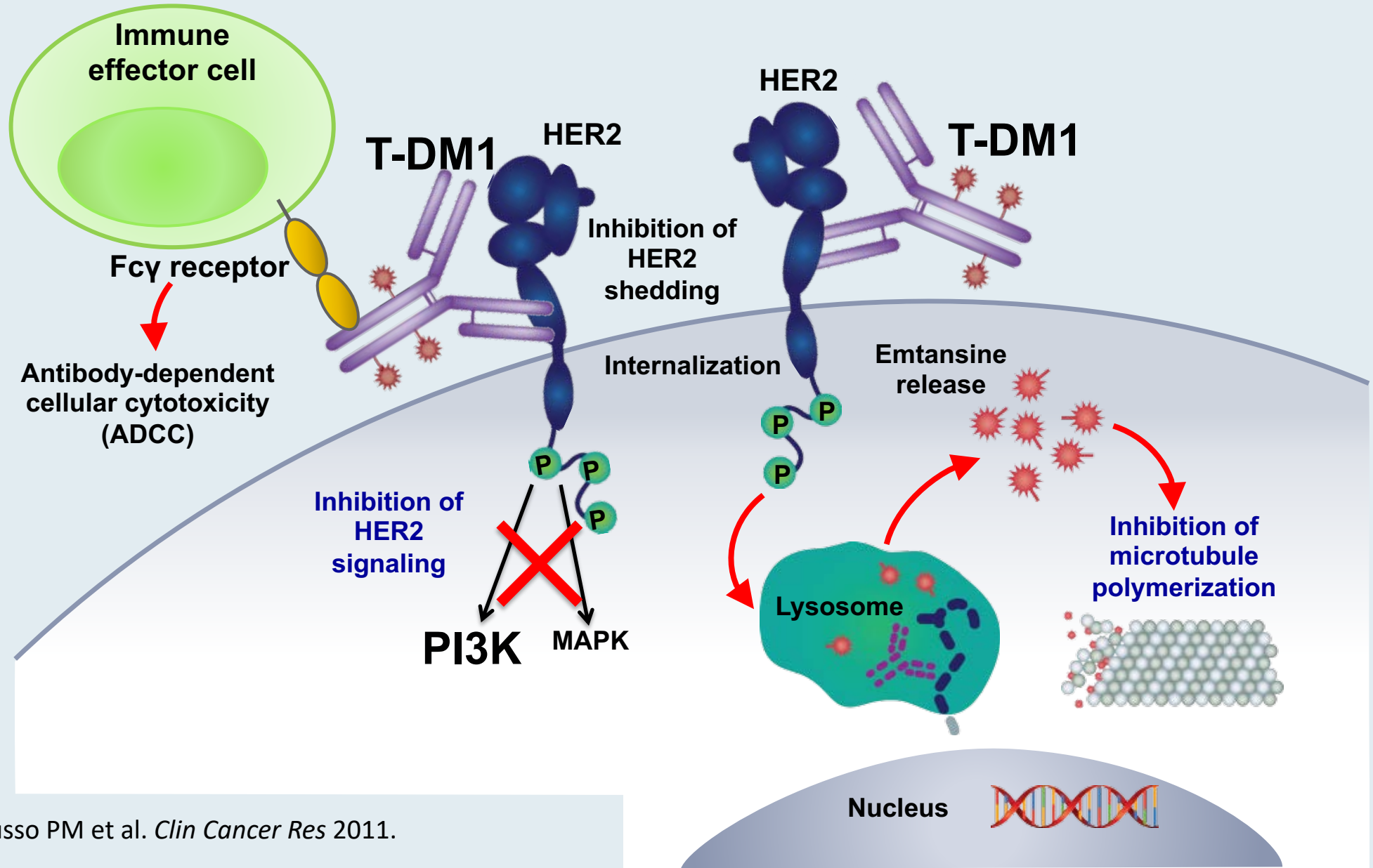
FDA-Approved Agents for Early-Stage HER2-Positive Breast Cancer

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

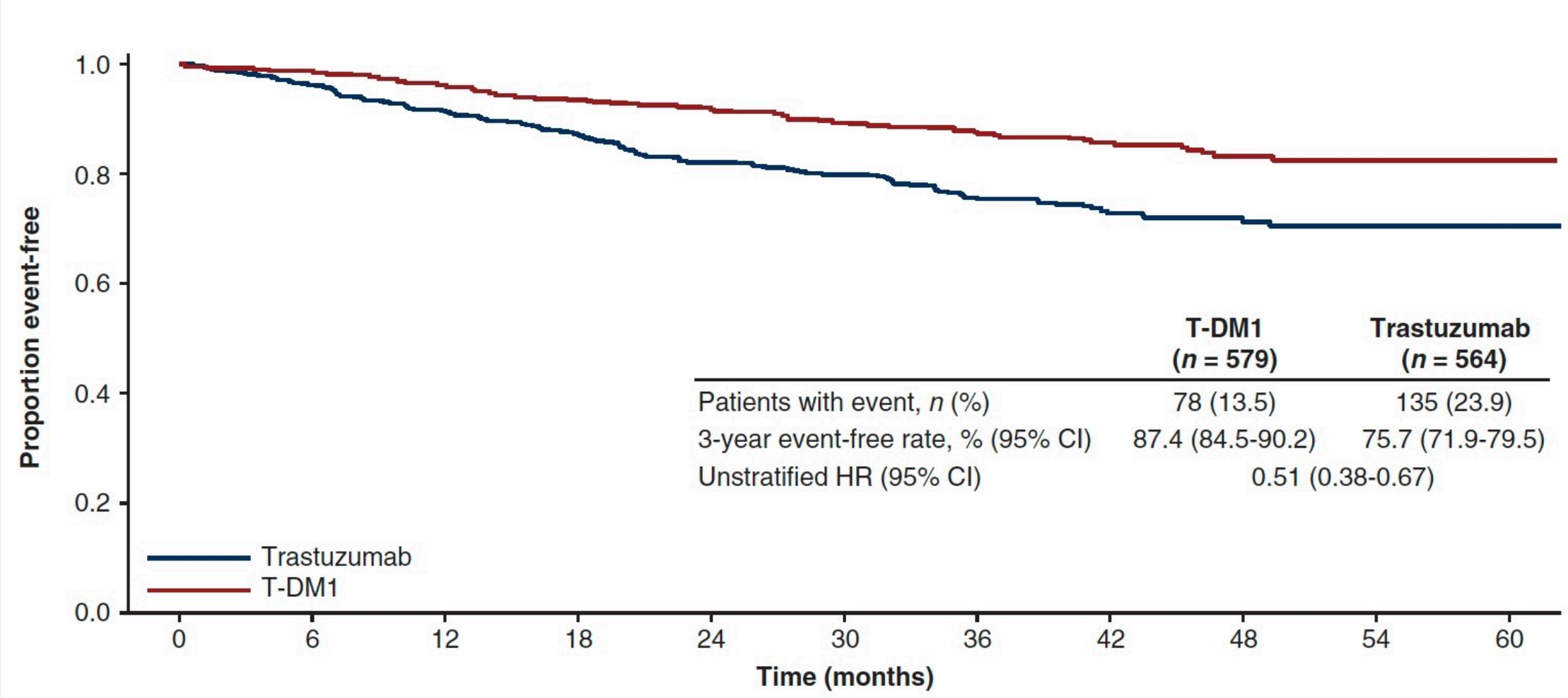
E. P. Mamounas[1,2*], M. Untch[3], M. S. Mano[4], C.-S. Huang[5], C. E. Geyer Jr[1,6], G. von Minckwitz[7], N. Wolmark[1,8], X. Pivot[9], S. Kuemmel[10,11], M. P. DiGiovanna[12], B. Kaufman[13], G. Kunz[7,14], A. K. Conlin[1,15], J. C. Alcedo[16], T. Kuehn[17], I. Wapnir[1,18], A. Fontana[19], J. Hackmann[7,20], 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].

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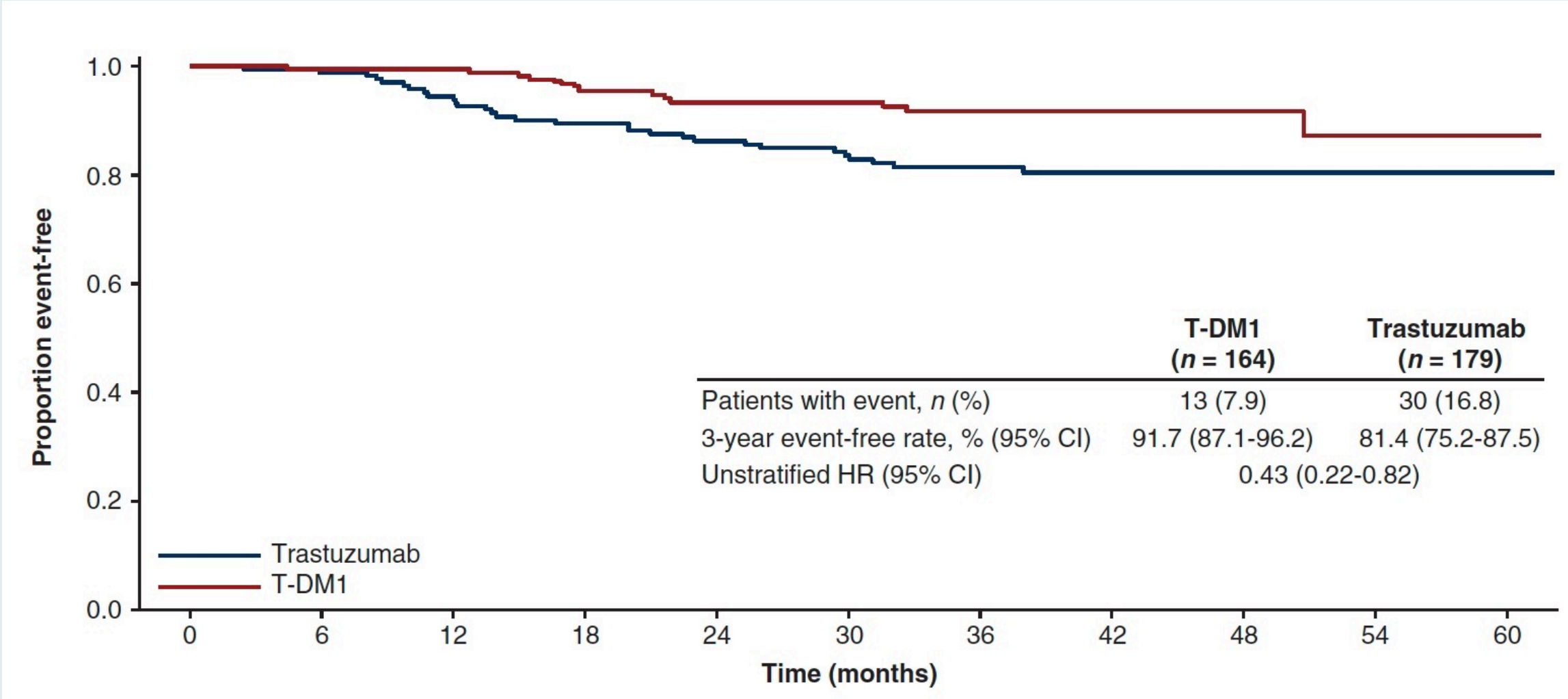
Time to First Invasive Disease-Free Survival Event for Patients Who Received Non-Anthracycline-Based Neoadjuvant Therapy



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

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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].

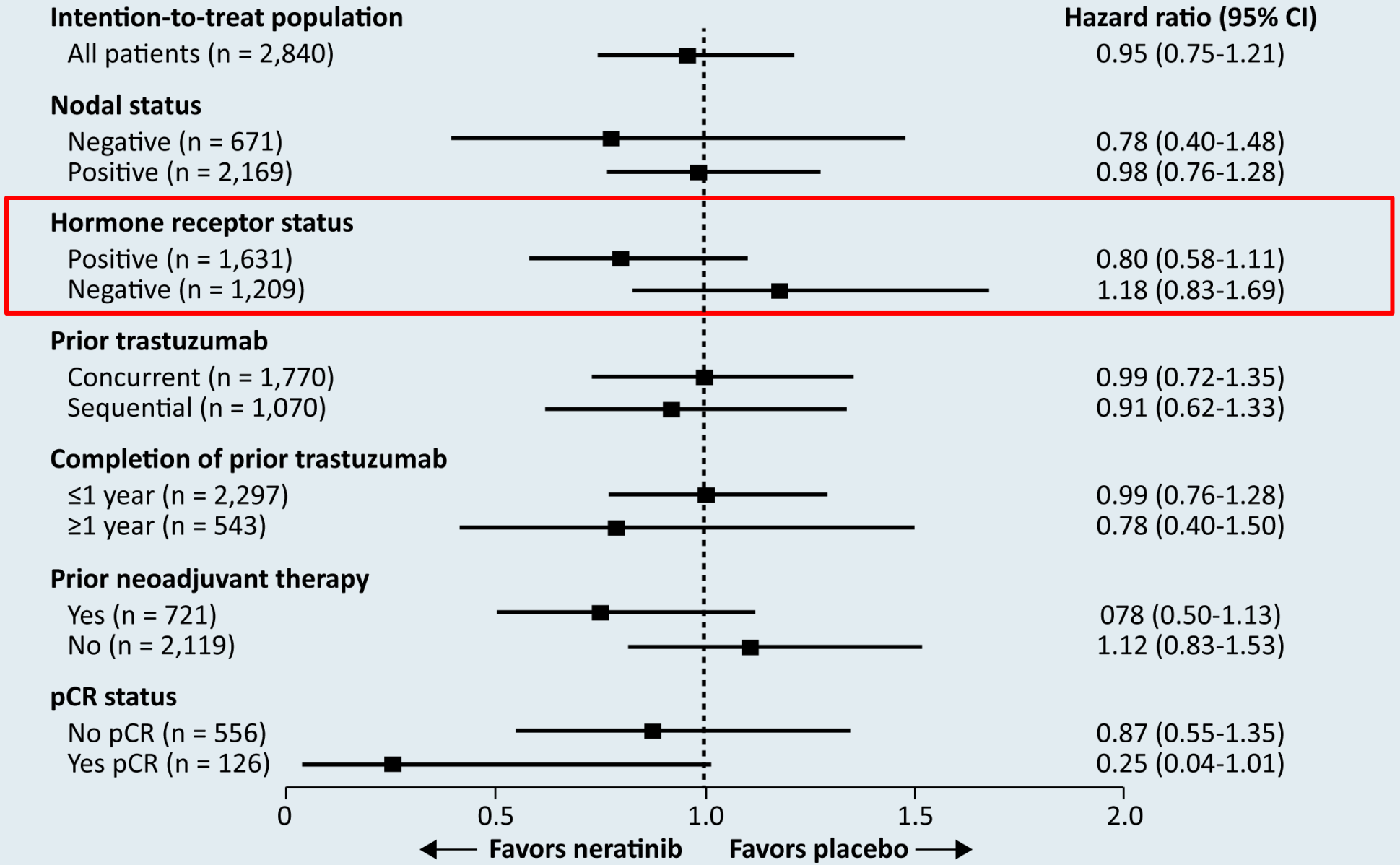
RTP RESEARCH TO PRACTICE

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

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

Tuesday, December 7, 2021
8:00 PM – 9:45 PM ET

Faculty

Aditya Bardia, MD, MPH
Joyce O'Shaughnessy, MD
Kevin Kalinsky, MD, MS

Moderator

Erika Hamilton, 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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