Dissecting the Decision: Clinical and Nursing Investigators Provide Practical Perspectives on Key Issues in Cancer Care

Part 2 — HER2-Positive Breast Cancer

Thursday, March 18, 2021
5:00 PM – 6:00 PM ET

Faculty

Jamie Carroll, APRN, MSN, CNP
Sara Hurvitz, MD

Moderator

Neil Love, MD

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Faculty

Jamie Carroll, APRN, MSN, CNP
Mayo Clinic
Rochester, Minnesota

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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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc and Puma Biotechnology 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 and NCPD activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies Corporation, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Biodesix Inc, bioTheranostics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Guardant Health, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lexicon Pharmaceuticals Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seagen Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Teva Oncology, Tokai Pharmaceuticals Inc and Verastem Inc.

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Dr Carroll — Disclosures

No relevant conflicts of interest to disclose.

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Dr Hurvitz — Disclosures

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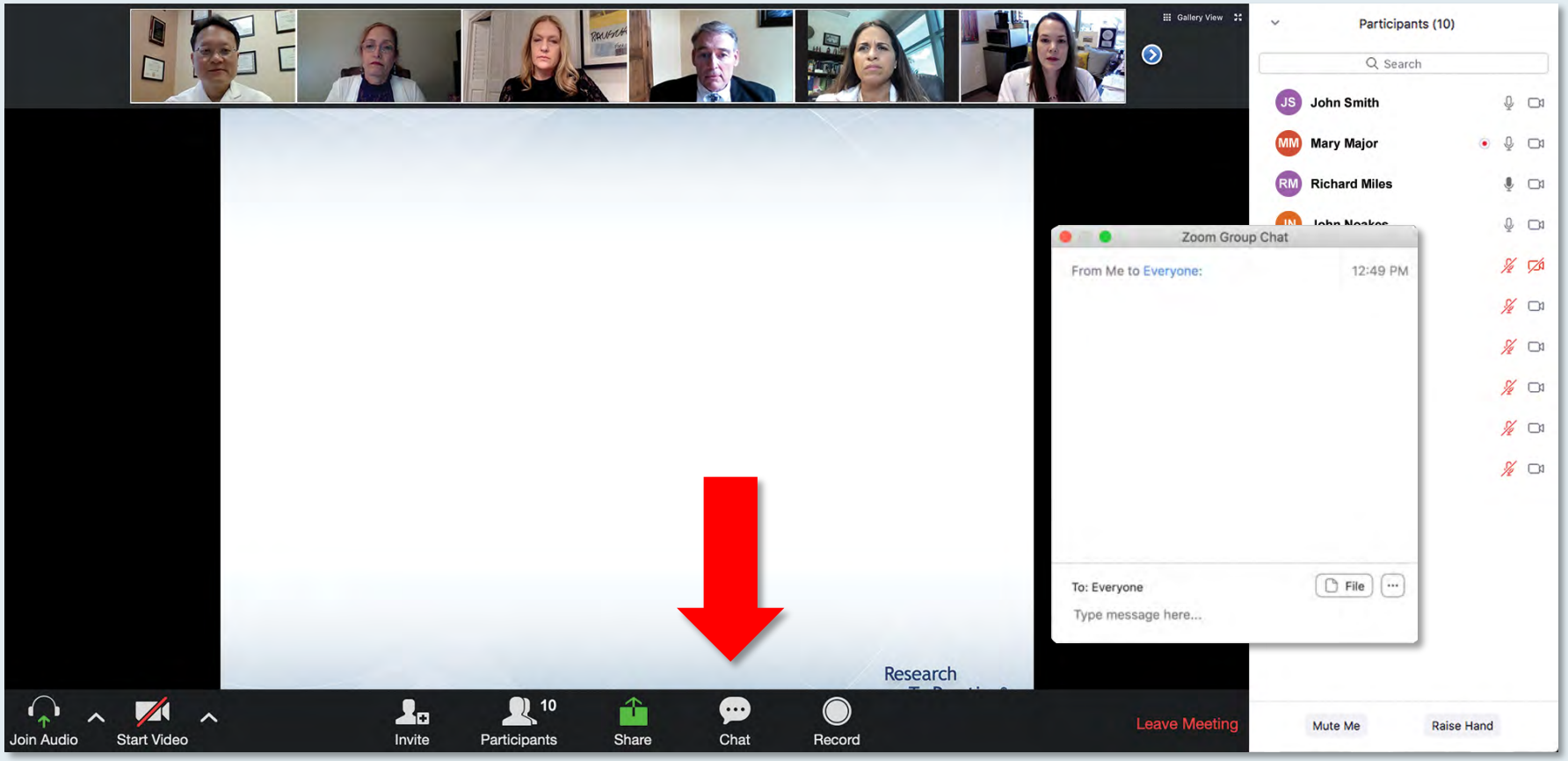
We Encourage Clinicians in Practice to Submit Questions



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

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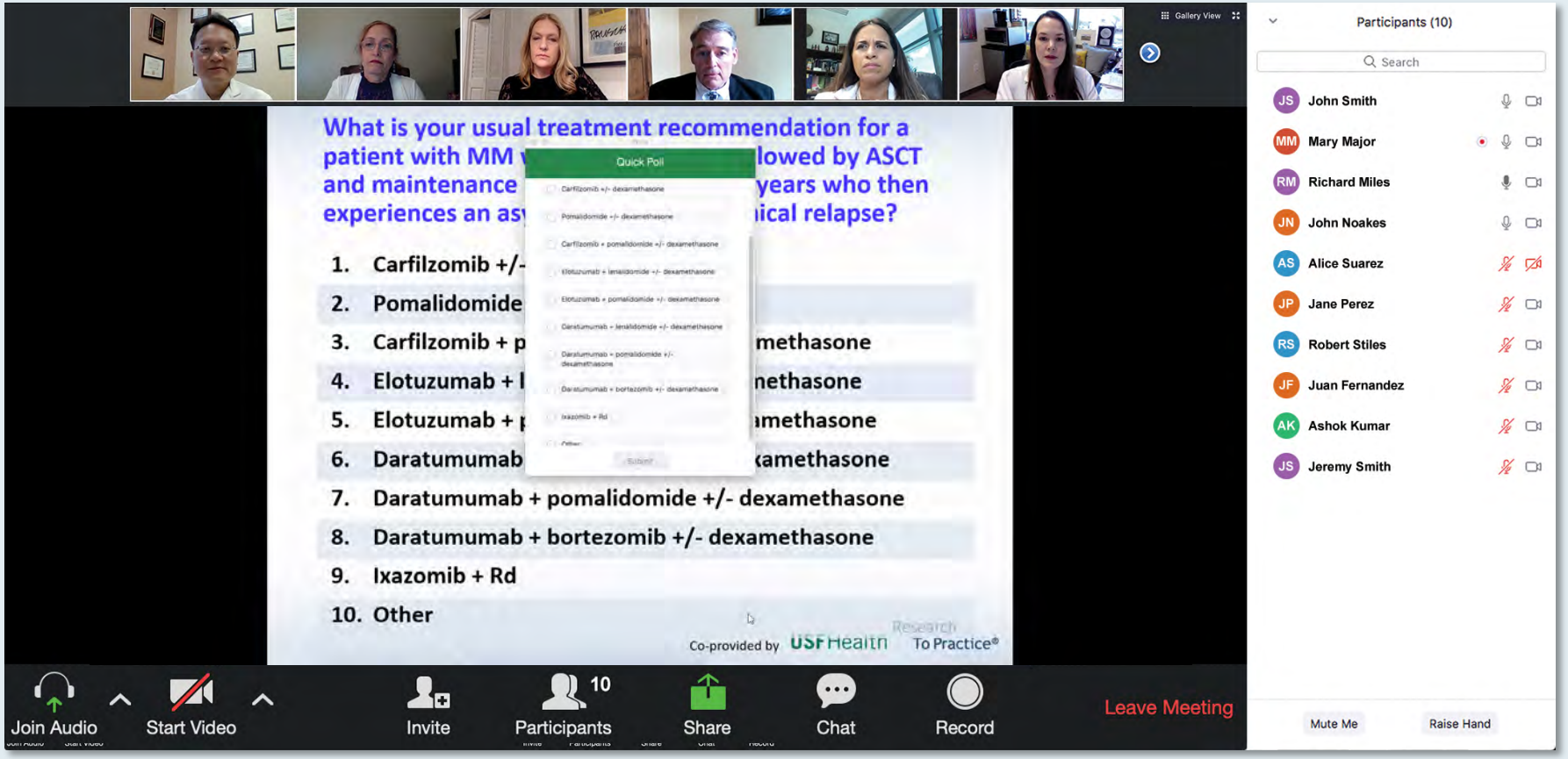
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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ONCOLOGY TODAY

WITH DR NEIL LOVE

Newly Approved Agents in HER2-Positive Metastatic Breast Cancer

DR MARK PEGRAM

STANFORD UNIVERSITY SCHOOL OF MEDICINE

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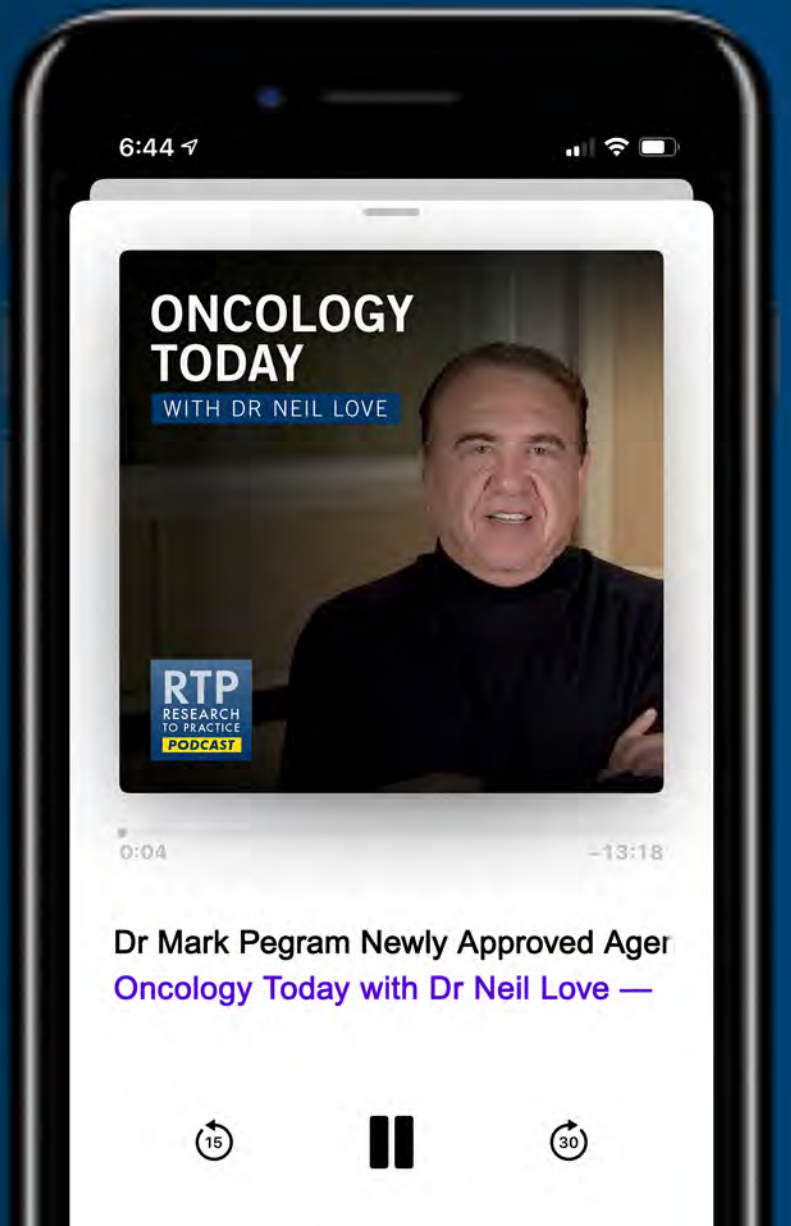

Cases from the Community: Investigators Discuss the Role of PARP Inhibition in the Care of Actual Patients with Ovarian Cancer

Saturday, March 20, 2021
4:00 PM – 5:00 PM ET

Faculty

Susana Banerjee, MBBS, MA, PhD
Richard T Penson, MD, MRCP
Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Thursday, March 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Robert J Motzer, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Monday, March 29, 2021
5:00 PM – 6:00 PM ET

Faculty

Philip A Thompson, MB, BS

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Monday, April 5, 2021
5:00 PM – 6:00 PM ET

Faculty

Bradley J Monk, MD

Moderator

Neil Love, MD

RTP
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TO PRACTICE

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

Tuesday, April 6, 2021
12:00 PM – 1:00 PM ET

Faculty

Sumanta K Pal, MD

Moderator

Neil Love, MD

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TO PRACTICE

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Thursday, April 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Professor Dirk Arnold, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

NCPD credit information will be emailed to each participant within 3 business days.

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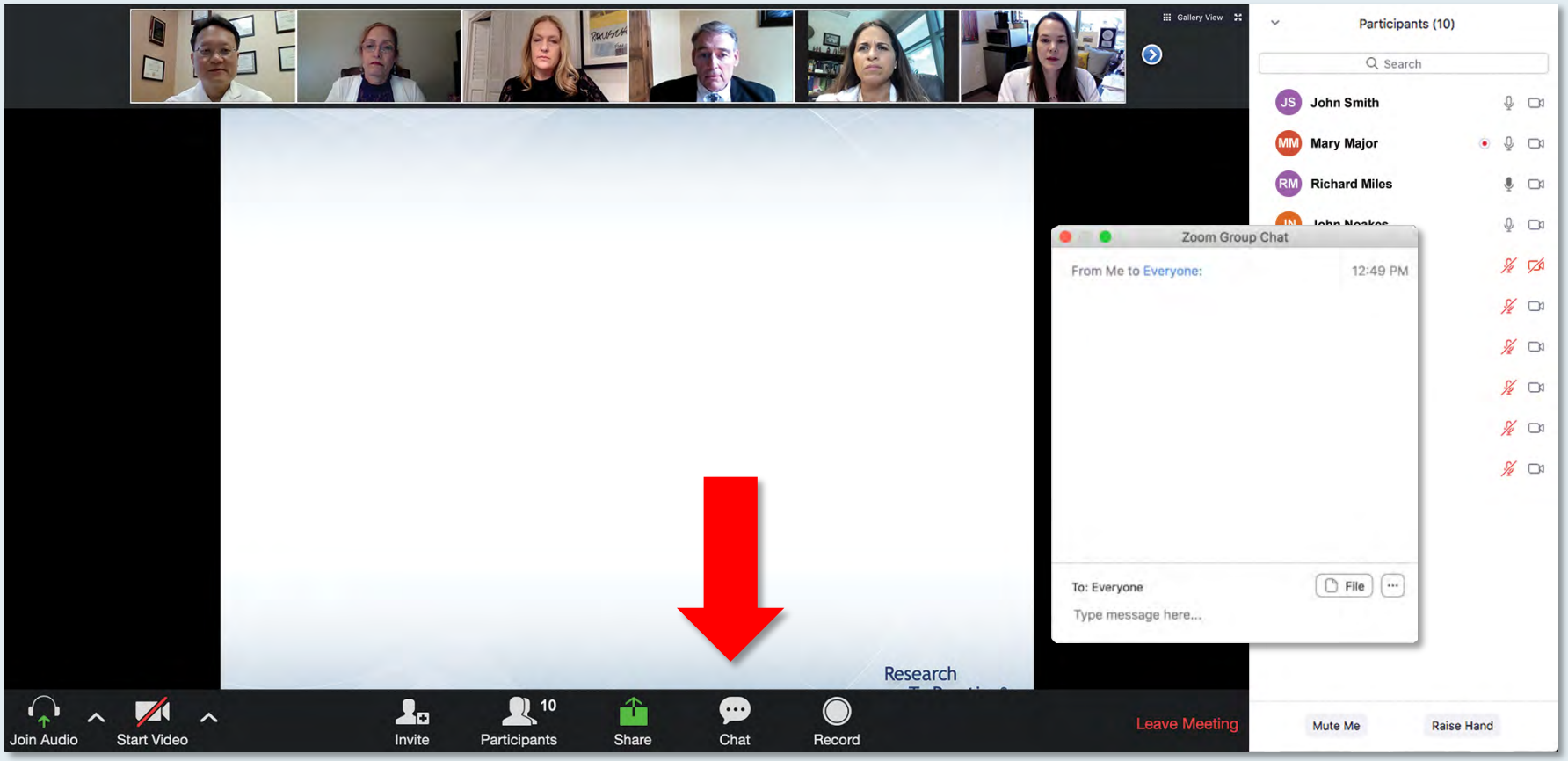

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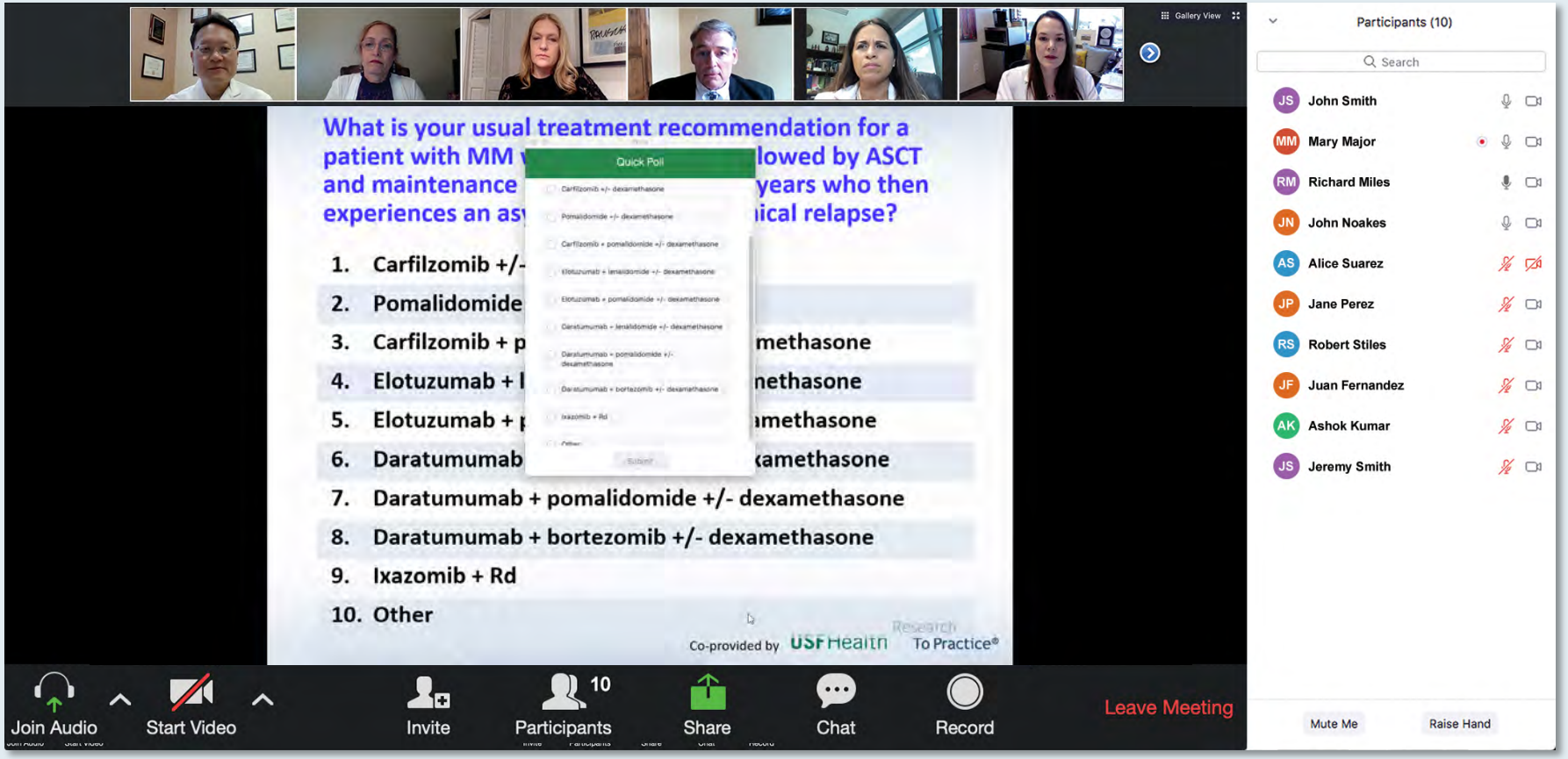

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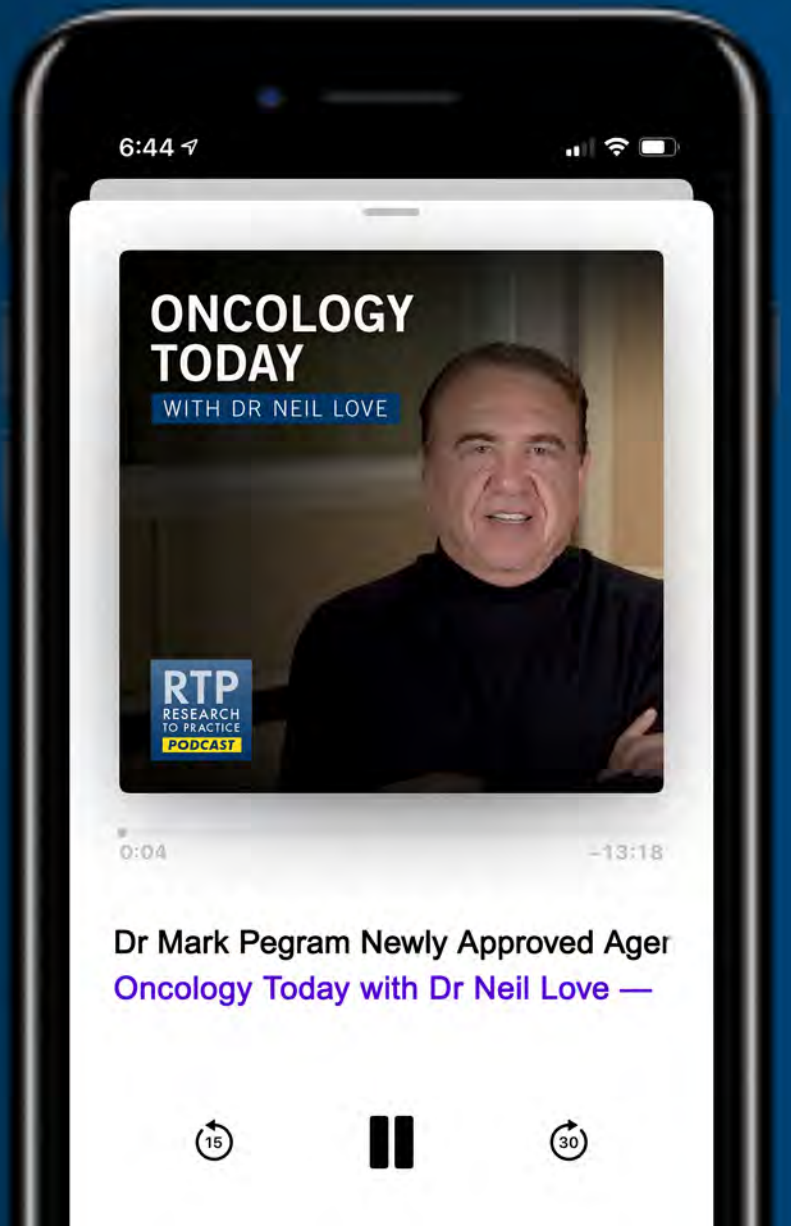

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Alan B Astrow, MD
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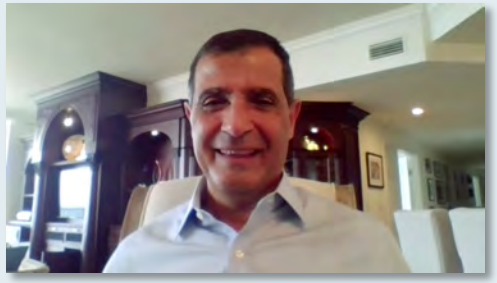
Springfield, Massachusetts

Laurie Matt-Amaral, MD, MPH
Attending Physician
Cleveland Clinic Akron General Medical Center
Akron, Ohio



Atif Hussein, MD, MMM
Program Director
Hematology/Oncology Fellowship
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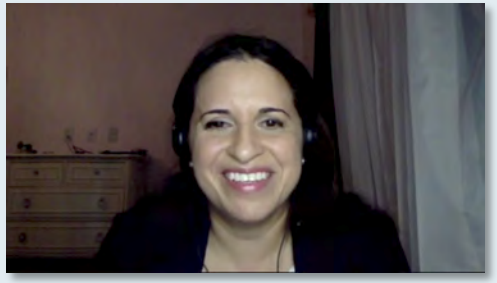
Memorial Healthcare System
Clinical Associate Professor, Florida International University Herbert Wertheim College of Medicine
Hollywood, Florida



Estelamari Rodriguez, MD, MPH
Voluntary Assistant Professor of Clinical Medicine
Associate Director, Community Outreach
Sylvester Comprehensive Cancer Center
University of Miami Miller School of Medicine
Miami, Florida

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Agenda

Module 1: Breast Cancer 2021

- Dr Matt-Amaral: A 42-year-old premenopausal woman with ER-positive, HER2-positive, node-negative breast cancer

Module 2: Management of Localized Disease

- Dr Matt-Amaral: A 73-year-old woman with clinical T4 ER/PR-negative, HER2-positive breast cancer

Module 3: Sequencing of Agents for Metastatic Disease

- Dr Astrow: A 70-year-old woman with a 10-cm Grade III, ER/PR-negative, HER2-positive IDC and pleural metastases
- Dr Rodriguez: A 36-year-old woman with heavily pretreated ER/PR-positive, HER2-positive breast cancer and bone metastases

Module 4: Systemic Treatment of Brain Metastases

- Dr Ma: A 42-year-old Middle Eastern woman with HER2-positive breast cancer and brain metastases
- Dr Hussein: A 43-year-old woman with ER/PR-negative, HER2-positive breast cancer with brain metastasis
- Dr Glynn: A 60-year-old woman with malignant pericardial effusion

DATA + PERSPECTIVES

Clinical Investigators Explore the Current and Future Management of ER-Positive Breast Cancer

Wednesday, December 11, 2019
7:30 PM – 9:00 PM
San Antonio, Texas

Moderator

Neil Love, MD

Faculty

Harold J Burstein, MD, PhD
Matthew Goetz, MD
Stephen RD Johnston, MA, PhD
Joseph A Sparano, MD

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DATA + PERSPECTIVES

Clinical Investigators Explore the Current and Future Management of Triple-Negative Breast Cancer

Thursday, December 12, 2019
7:30 PM – 9:00 PM
San Antonio, Texas

Moderator

Neil Love, MD

Faculty

Erika Hamilton, MD
Professor Sherene Loi, MBBS, PhD
Mark E Robson, MD
Hope S Rugo, MD

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DATA + PERSPECTIVES

Clinical Investigators Explore the Current and Future Management of HER2-Positive Breast Cancer

Friday, December 13, 2019
7:30 PM – 9:00 PM
San Antonio, Texas

Moderator

Neil Love, MD

Faculty

Adam M Brufsky, MD, PhD
Lisa A Carey, MD
Sara Hurvitz, MD
Martine J Piccart-Gebhart, MD, PhD

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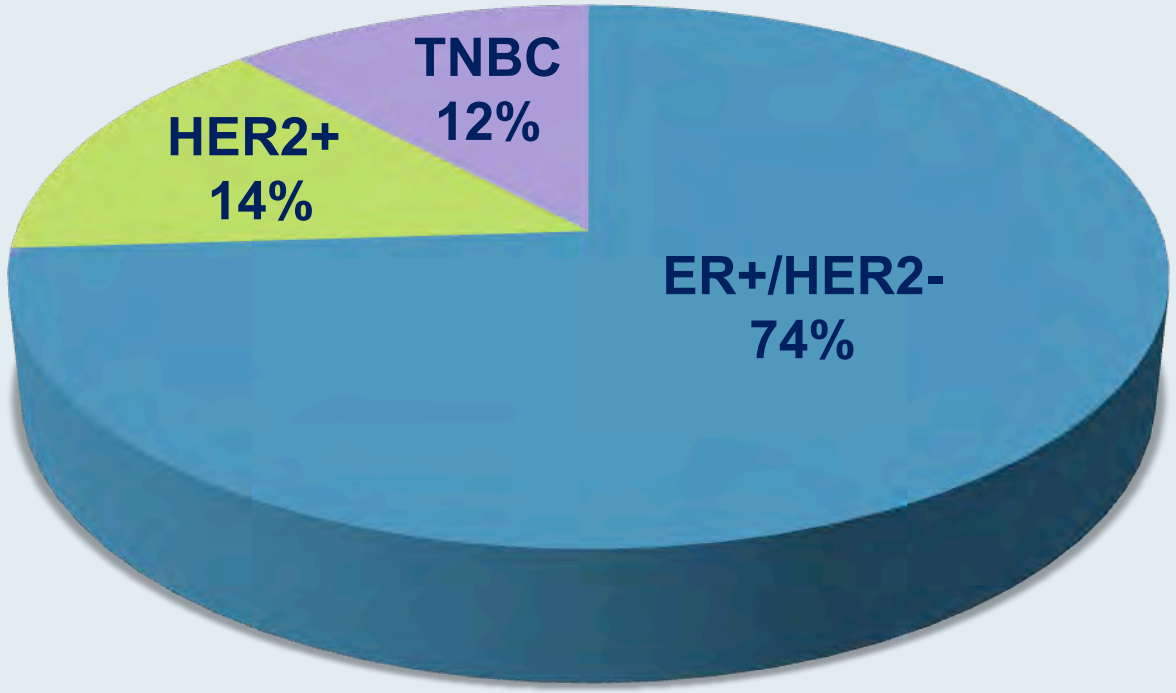
Distribution of Breast Cancer Subtypes



DeSantis CE et al. *CA Cancer J Clin* 2016;66(1):31-42.

Case Presentation: A 42-year-old premenopausal woman with ER-positive, HER2-positive, node-negative breast cancer

Dr Laurie Matt-Amaral

- Mastectomy for ER-positive DCIS revealed a 1.3-cm, ER-positive, PR-negative, HER2-positive, node-negative IDC
- PMH: Depression
- Genetic testing: PMS2 VUS
- Patient is not interested in receiving adjuvant chemotherapy

Questions

- For which patients do you decide to use post-adjuvant neratinib?
- Any tips about how to manage the diarrhea?

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Case Presentation: A 73-year-old woman with clinical T4 ER/PR-negative, HER2-positive breast cancer

Dr Laurie Matt-Amaral

- Presents with clinical T4 breast cancer – whole breast involved with peau d'orange and lymphadenopathy
  - Patient suffered a fall, experienced soreness afterwards, delayed seeking medical attention
- Neoadjuvant taxane/platinum plus dual anti-HER2 therapy

Question

- Which patients should be considered for post-neoadjuvant T-DM1 therapy?

A 60-year-old woman presents with a palpable 2.5-cm breast mass that on biopsy is diagnosed as an ER-negative, HER2-positive infiltrating ductal carcinoma (IDC). Biopsy of a small axillary lymph node is positive. In general, the most common next step in this situation is…

1. Surgery to remove the primary tumor and axillary dissection followed by systemic therapy
2. Neoadjuvant systemic therapy followed by surgery
3. Either a or b
4. Neither a nor b
5. I don't know

A patient with a HER2-positive IDC responds to neoadjuvant chemotherapy and trastuzumab/pertuzumab, but at surgery residual disease is detected. In general, the most common next treatment is…

1. Trastuzumab
2. Trastuzumab/pertuzumab
3. T-DM1
4. Any of the above
5. I don’t know

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Patients who receive post-adjuvant neratinib after chemotherapy/anti-HER2 therapy for HER2-positive localized breast cancer have a significant reduction in the risk of recurrence if the tumor is…

1. ER-positive
2. ER-negative
3. Both a and b
4. Neither a nor b
5. I don’t know

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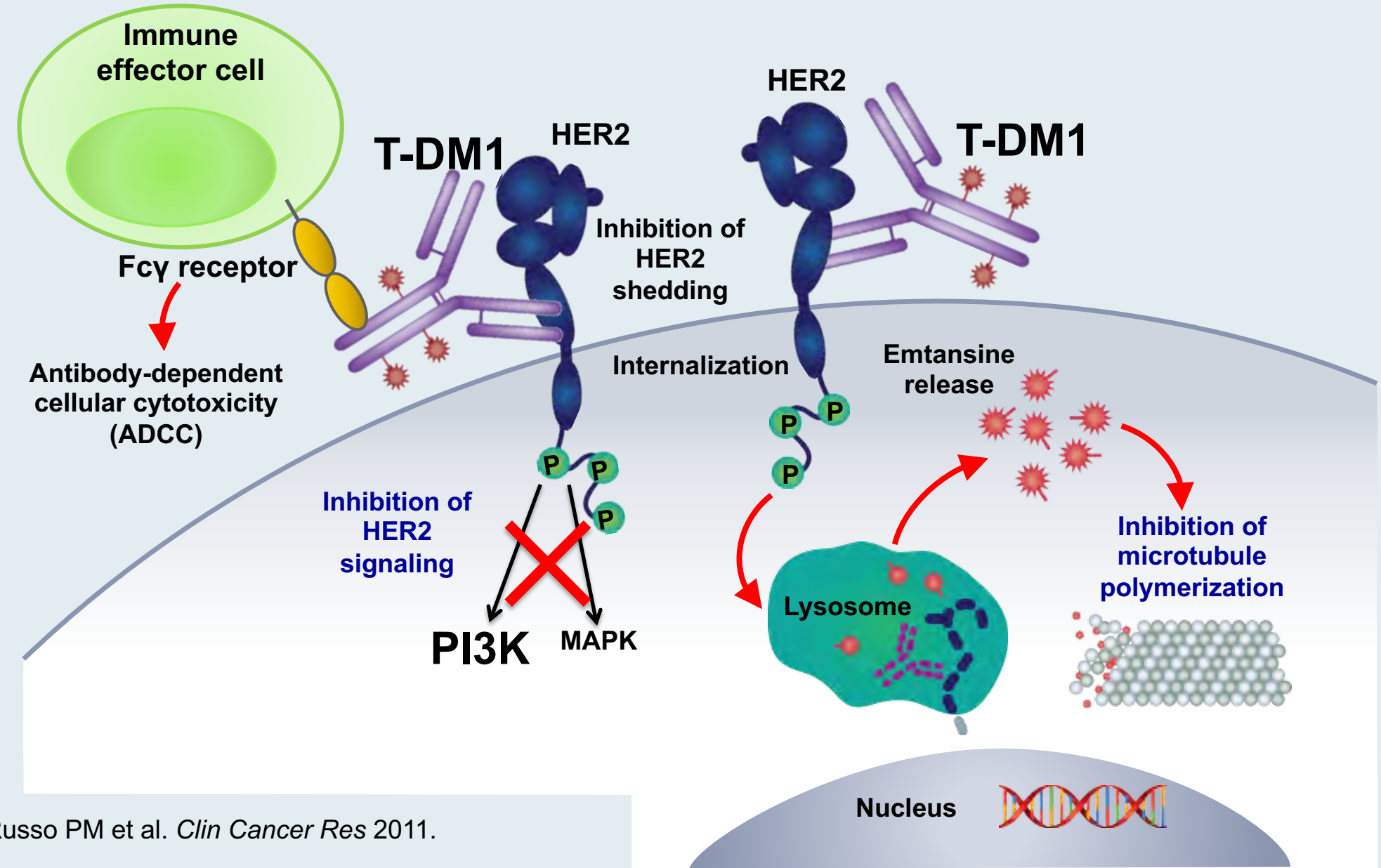
FDA-Approved Agents for Early-Stage HER2-Positive BC

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.

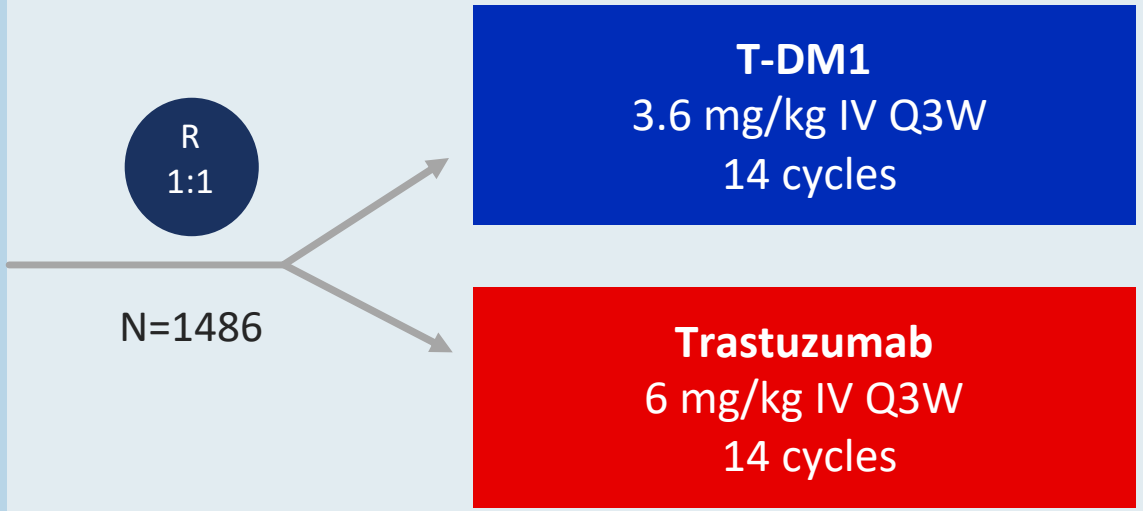
Trastuzumab Emtansine (T-DM1): Mechanisms of Action



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

KATHERINE Study Design

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



Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:

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

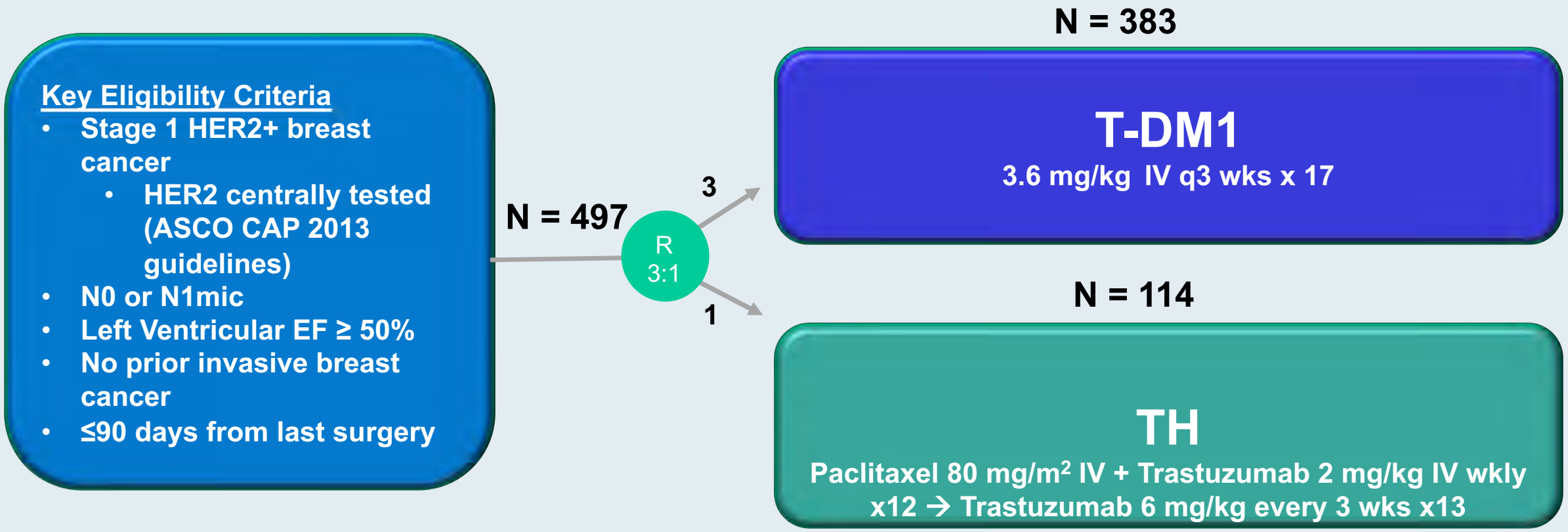
Geyer CE et al. SABCS 2018;Abstract GS1-10.

KATHERINE: Invasive Disease-Free Survival (IDFS) Outcomes

IDFS	T-DM1 (n = 743)	Trastuzumab (n = 743)
IDFS events	12.2%	22.2%
3-year IDFS	88.3%	77.0%
	HR = 0.50; $p < 0.0001$	
Distant recurrence		
3-year event-free rate	89.7%	83.0%
	HR = 0.60	

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

ATEMPT Study Schema



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

Courtesy of Sara M Tolaney, MD, MPH

ATEMPT: Clinically Relevant Toxicity

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

p=0.91

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

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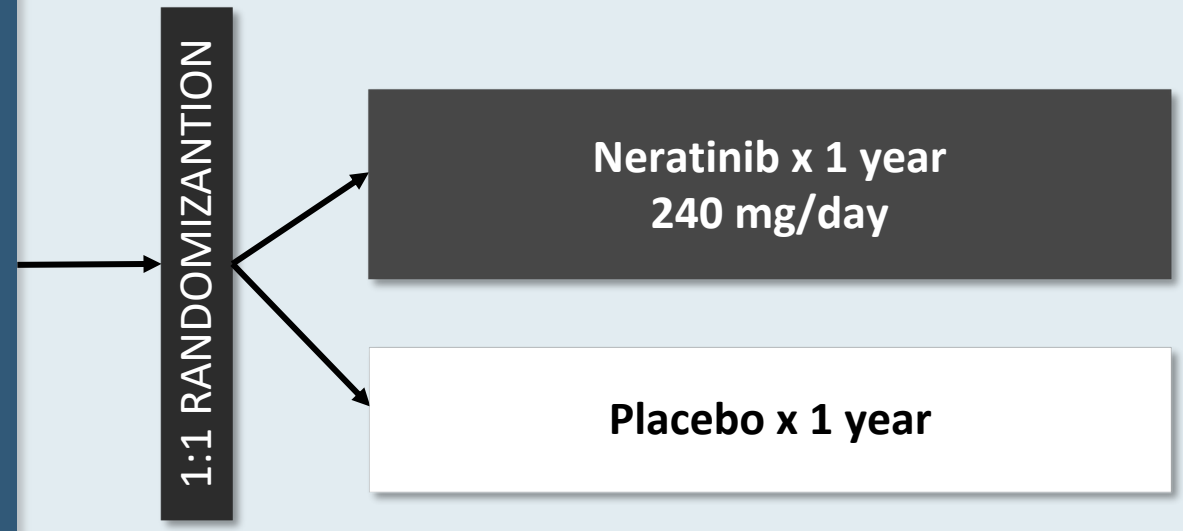
ExteNET Study Design

- HER2+ breast cancer
  - IHC 3+ or ISH amplified (locally determined)
- Prior adjuvant trastuzumab + chemotherapy
- Lymph node +/–, or residual invasive disease after neoadjuvant therapy
- ER/PR +/– (endocrine therapy permitted)



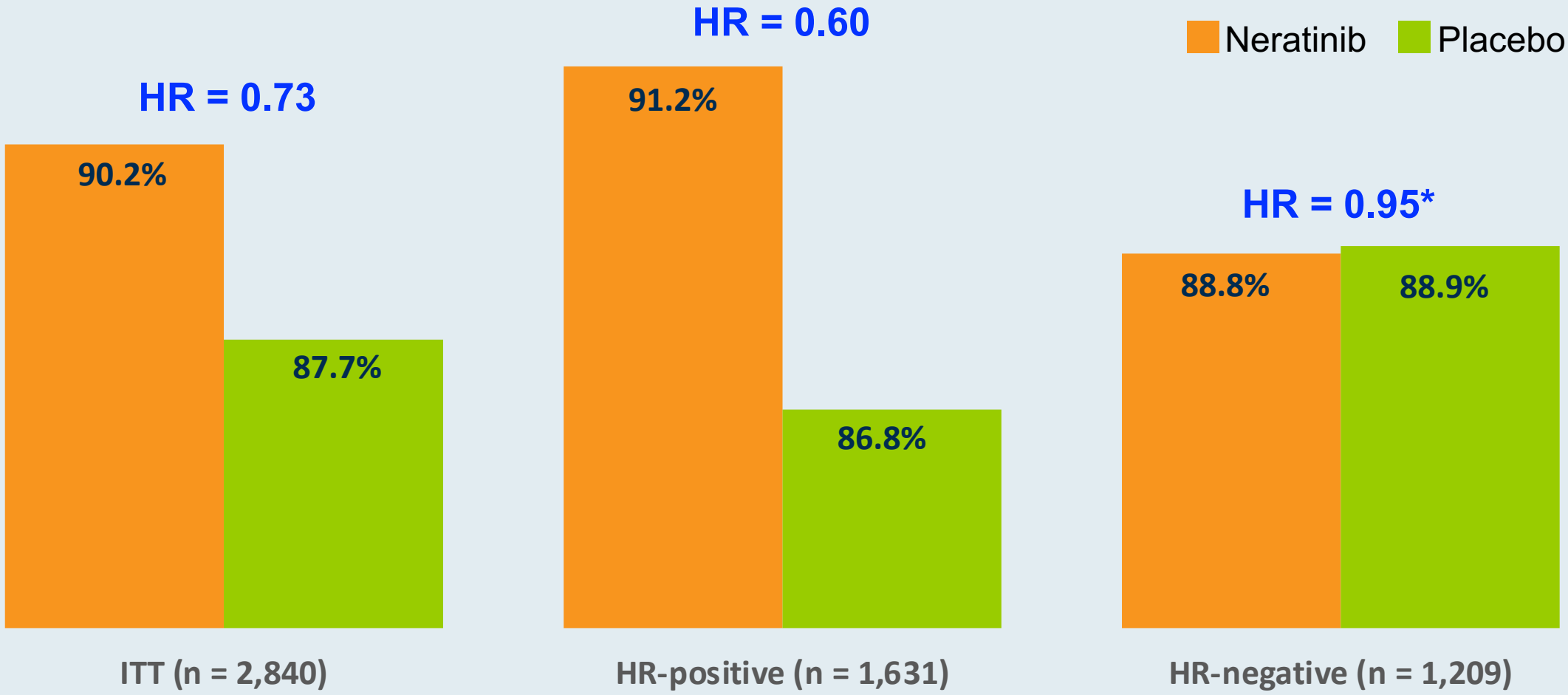
n = 2,840

Primary endpoint: **Invasive disease-free survival (iDFS)**

Secondary endpoints: **DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety**

Martin et al. *Lancet Oncol* 2017;18(12):1688-700.

ExteNET: Five-Year Invasive Disease-Free Survival by Patient Population



* Not statistically significant

Martin M et al. *Lancet Oncol* 2017;18(12):1688-700; Martin M et al. ESMO 2017;Abstract 149O.

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Original Study

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

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

Clin Breast Cancer 2021;21(1):80-91.e.7.

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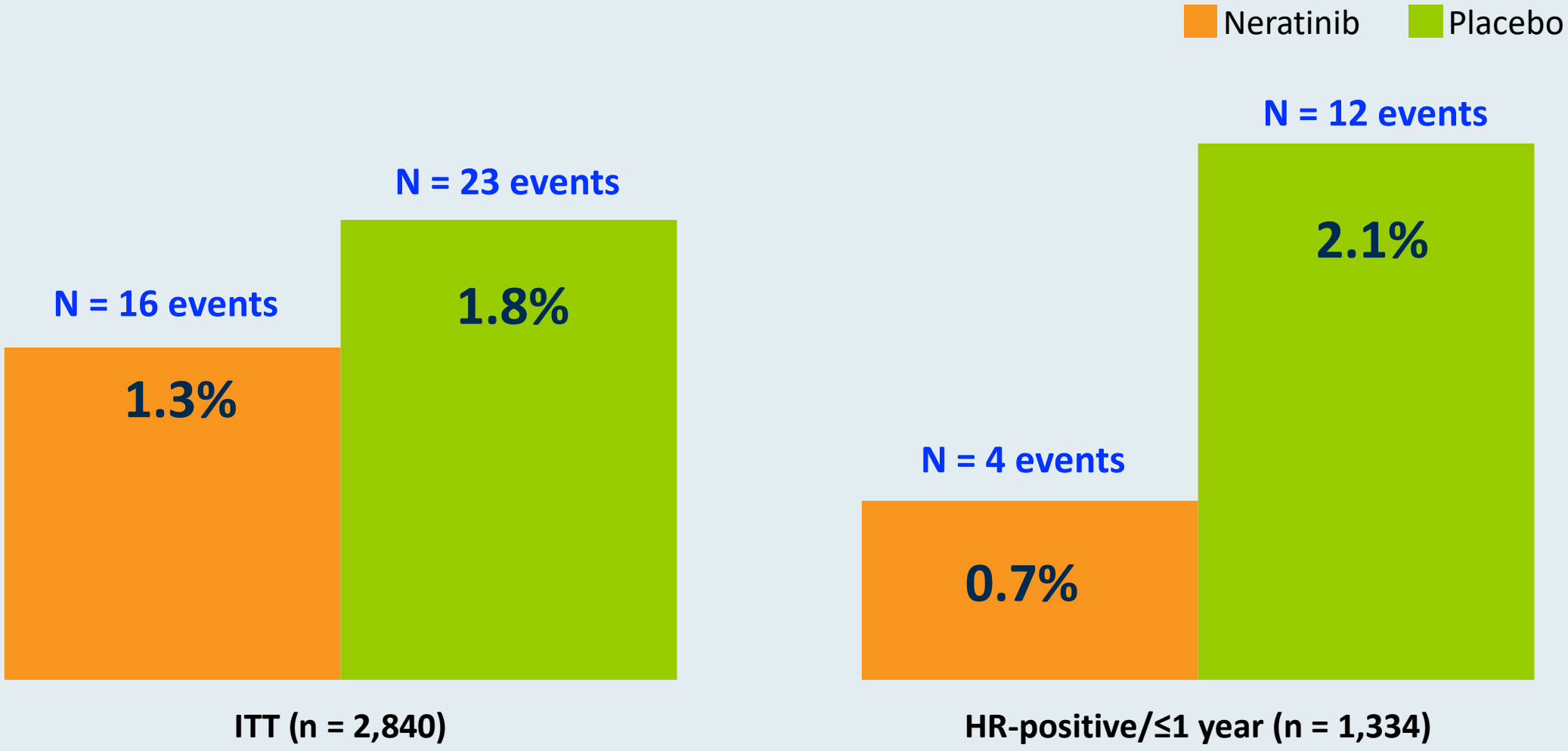
Continued Efficacy of Neratinib in Patients with HER2-Positive Early-Stage Breast Cancer: Final Overall Survival Analysis from the Randomized Phase 3 ExteNET Trial

Holmes FA et al.

SABCS 2020;Abstract PD3-03

ExteNET: Cumulative Incidence of CNS Recurrences



Martin M et al. *Lancet Oncol* 2017;18(12):1688-700; Holmes FA et al. SABCS 2020;Abstract PD3-03.

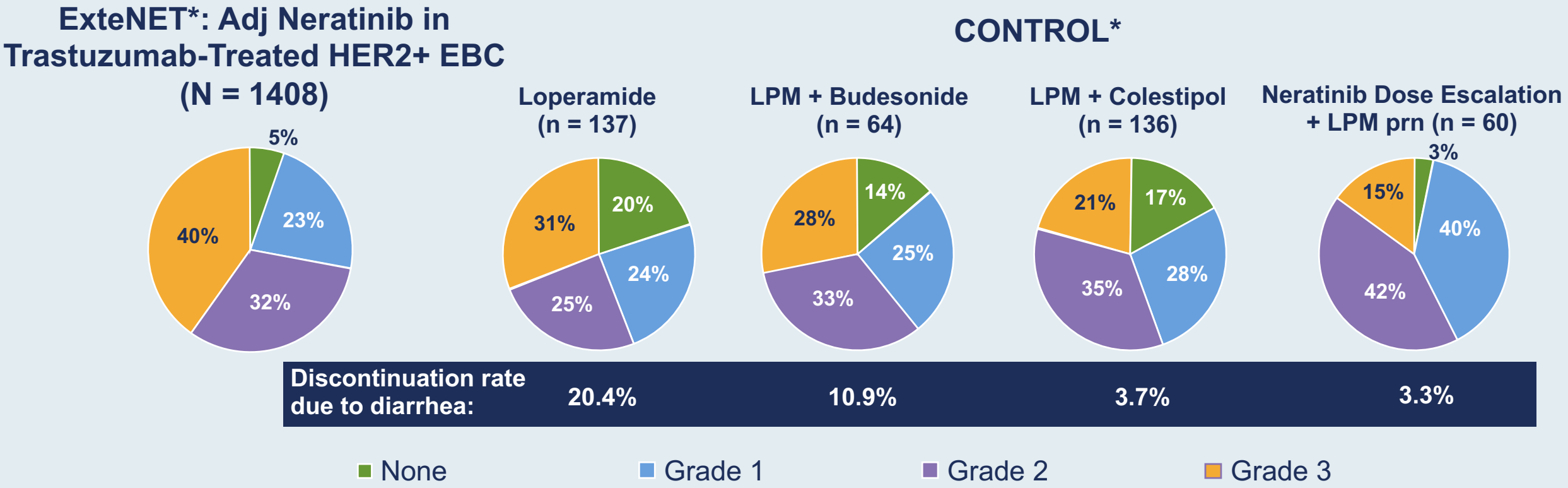
CONTROL Trial: Strategies to Improve Neratinib Tolerability

Methods: Sequential single-arm interventions for patients receiving 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.

Antidiarrheal Prophylaxis Reduces Diarrhea with Neratinib: CONTROL Trial



PREVENTIVE STRATEGIES REDUCED GRADE ≥3 DIARRHEA COMPARED TO EXTENET

Chan et al, SABCS 2019; Chan at al, Lancet Oncol 2016; Hurvitz S, SABCS 2017

Courtesy of Sara M Tolaney, MD, MPH

Agenda

Module 1: Breast Cancer 2021

- Dr Matt-Amaral: A 42-year-old premenopausal woman with ER-positive, HER2-positive, node-negative breast cancer

Module 2: Management of Localized Disease

- Dr Matt-Amaral: A 73-year-old woman with clinical T4 ER/PR-negative, HER2-positive breast cancer

Module 3: Sequencing of Agents for Metastatic Disease

- Dr Astrow: A 70-year-old woman with a 10-cm Grade III, ER/PR-negative, HER2-positive IDC and pleural metastases
- Dr Rodriguez: A 36-year-old woman with heavily pretreated ER/PR-positive, HER2-positive breast cancer and bone metastases

Module 4: Systemic Treatment of Brain Metastases

- Dr Ma: A 42-year-old Middle Eastern woman with HER2-positive breast cancer and brain metastases
- Dr Hussein: A 43-year-old woman with ER/PR-negative, HER2-positive breast cancer with brain metastasis
- Dr Glynn: A 60-year-old woman with malignant pericardial effusion

Case Presentation – Dr Astrow: A 70-year-old woman with history of mild dementia presents with a 10-cm Grade III, ER/PR-negative, HER2-positive IDC and pleural metastases

Dr Alan Astrow

- History of stroke and mild dementia
- Presents with 10 cm left breast mass
- PET-CT: supraclavicular, internal mammary, mediastinal, hilum nodes; hypermetabolic left pleural-based metastases and a single left pulmonary nodule
- Treatment: THP x 12 weeks → trastuzumab/pertuzumab to complete 1 year
- Follow-up PET-CT: complete resolution of lymphadenopathy and the pleural-based metastases
- Difficult for patient to come to clinic
  - Her medical problems contributed to decision to stop the treatment after a year

Question

- How would the faculty approach this situation? Should she still be on trastuzumab/pertuzumab? Should I switch her to T-DM1 or just leave her alone since she's doing well?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Rodriguez: A 36-year-old woman with heavily pretreated ER/PR-positive, HER2-positive breast cancer and bone metastases

Dr Estelamari Rodriguez

- Treated on Phase II PACE trial with fulvestrant plus palbociclib
  - Patient experienced disease progression with bone involvement
- Patient rechallenged with HER2-directed therapy due to concerns of persistent disease not identified in bone biopsy
  - T-DXd plus denosumab/zoledronic acid every 4 weeks
  - Tolerating treatment well

Questions

- What other treatment(s) could be considered at this time, and what are the potential adverse events that we should monitor for?
- When administering T-DXd, how do you evaluate for interstitial lung disease and do you do any routine imaging of the lung?
- Are there any data on the role of T-DXd in the setting of HER2 low metastatic breast cancer?

A Phase III trial evaluating the addition of tucatinib to trastuzumab/capecitabine for metastatic HER2-positive breast cancer resulted in an improvement in overall survival for all patients, including those with brain metastases.

1. Agree
2. Disagree
3. I don’t know

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The recently approved trastuzumab deruxtecan is classified as which type of anti-HER2 agent?

1. Monoclonal antibody
2. Antibody-drug conjugate
3. Small molecule tyrosine kinase inhibitor
4. I don’t know

Trastuzumab deruxtecan carries a black box warning for…

1. QT interval prolongation
2. Interstitial lung disease
3. Cardiovascular events
4. I don’t know

FDA Approves Tucatinib for Patients with HER2-Positive Metastatic Breast Cancer

Press Release – April 17, 2020

"The Food and Drug Administration approved tucatinib in combination with trastuzumab and capecitabine, for adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

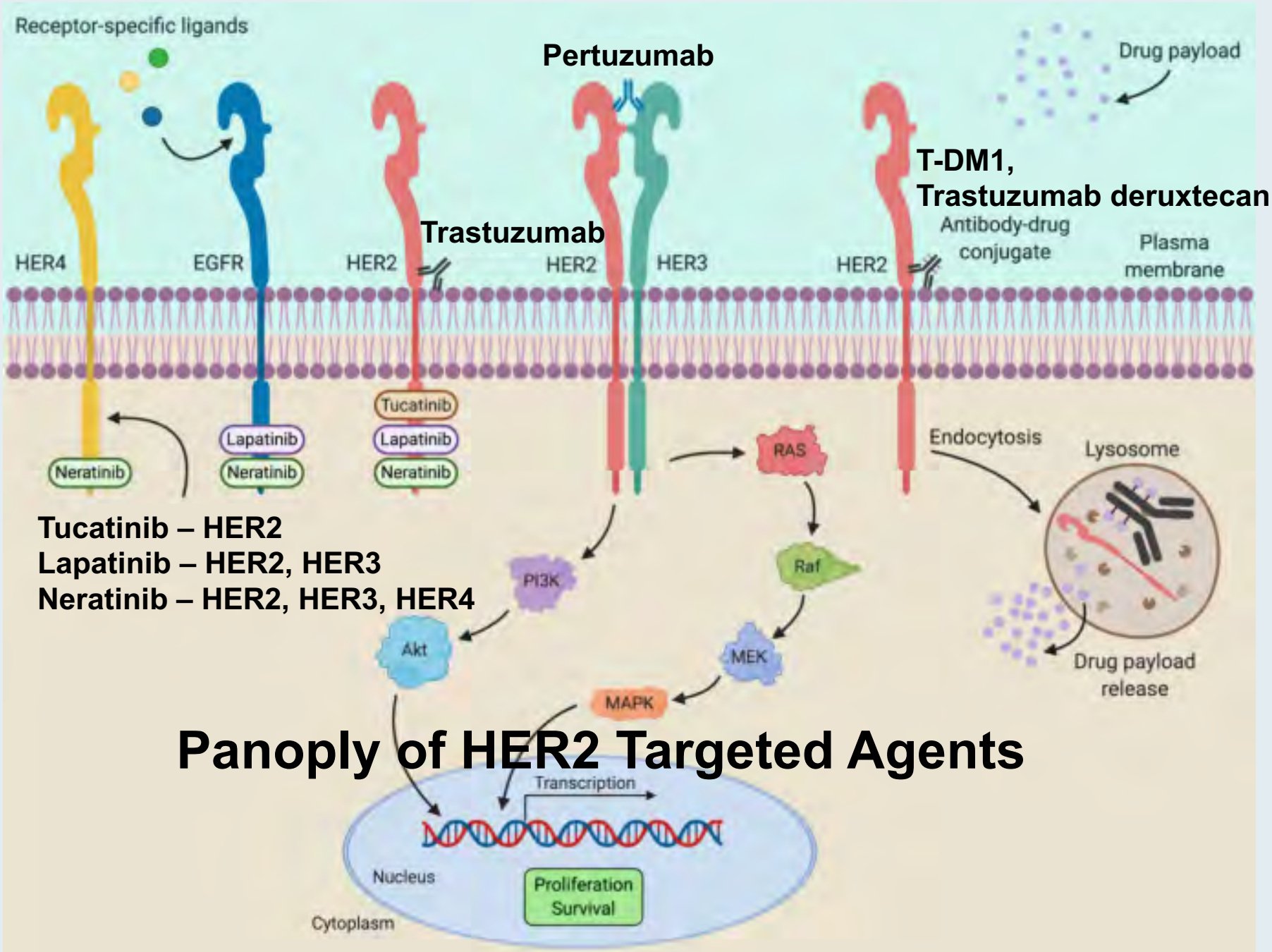
Efficacy was demonstrated in the HER2CLIMB trial (NCT02614794) enrolling 612 patients with HER2-positive metastatic breast cancer who had prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine. Patients received either tucatinib 300 mg twice daily plus trastuzumab and capecitabine (tucatinib arm, n = 410) or placebo plus trastuzumab and capecitabine (control arm, n = 202).

The primary endpoint was progression-free survival (PFS), assessed by a blinded independent central review, evaluated in the initial 480 randomized patients. The median PFS in patients receiving tucatinib was 7.8 months compared to 5.6 months for patients enrolled on the control arm (HR 0.54; $p < 0.00001$)."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tucatinib-patients-her2-positive-metastatic-breast-cancer

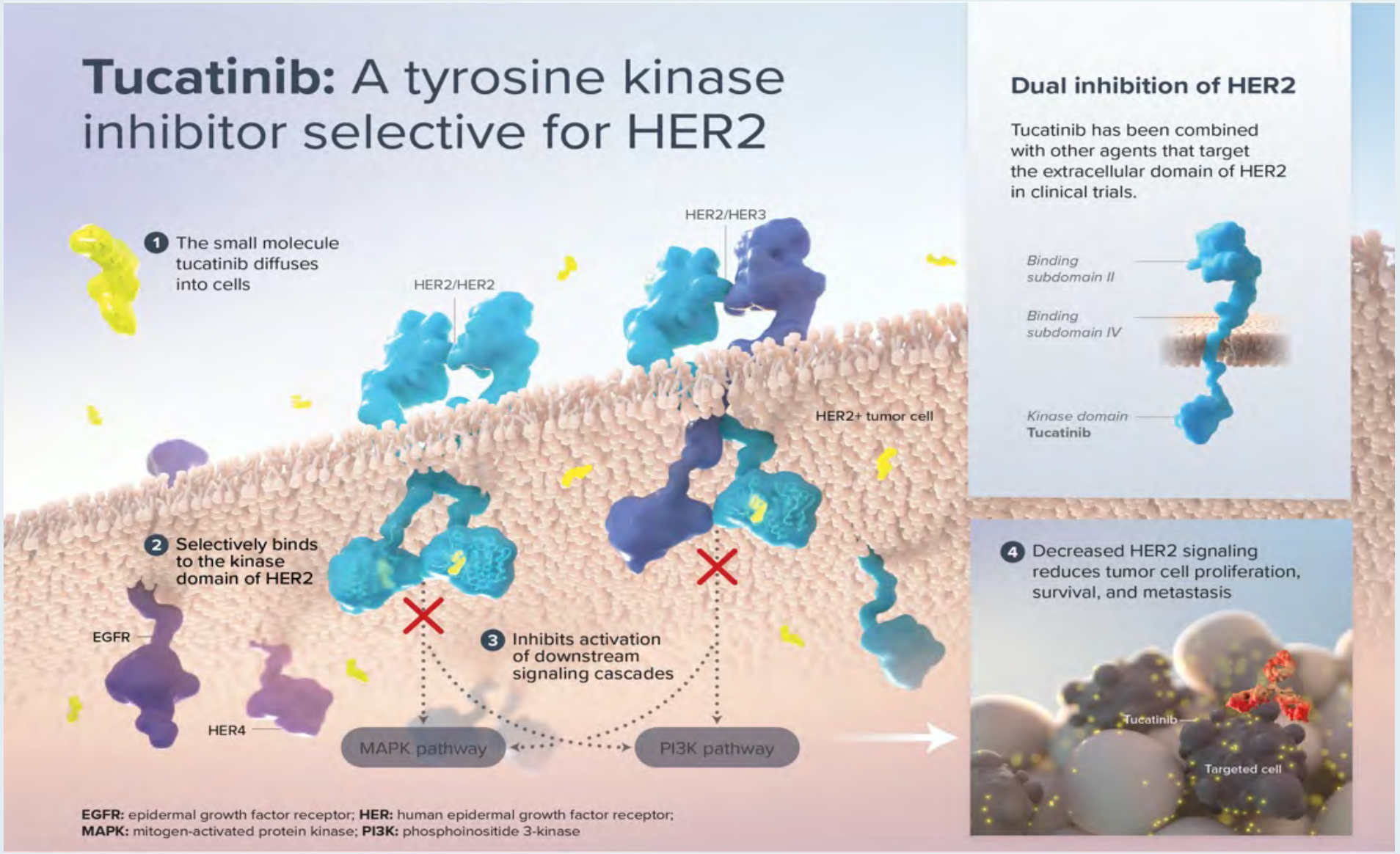
RTP RESEARCH TO PRACTICE

Panoply of HER2 Targeted Agents



Tesch ME, Gelmon KA. Drugs 2020;80:1811-30.

Tucatinib Mechanism of Action



www.seagen.com/science/pipeline/tucatinib

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

FDA Approval of Trastuzumab Deruxtecan for Unresectable or Metastatic HER2-Positive Breast Cancer

Press Release – December 20, 2019

"The Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

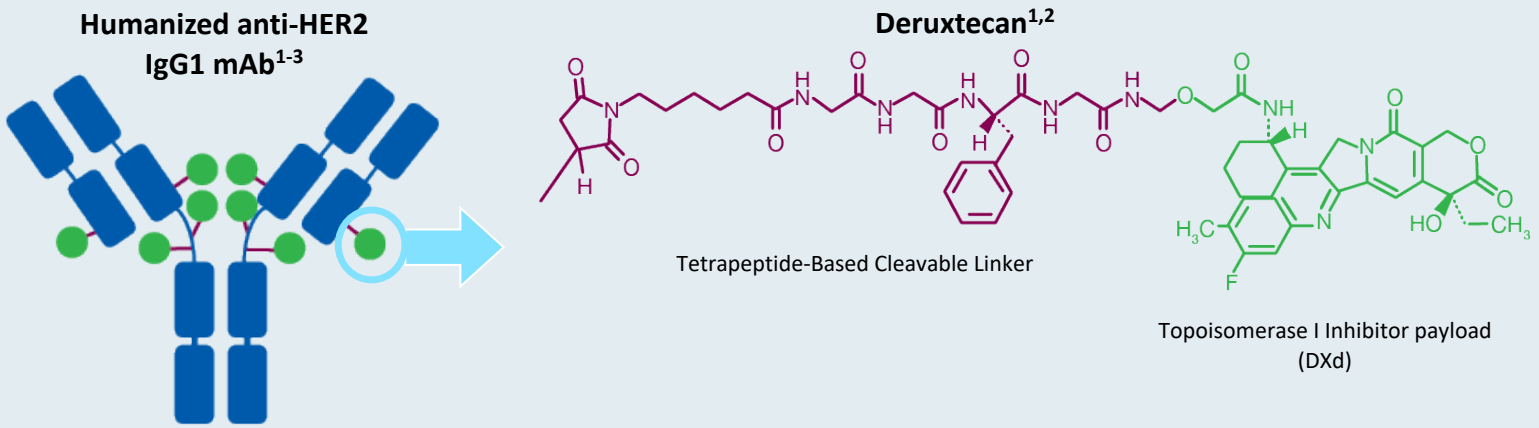
Efficacy was investigated in DESTINY-Breast01 (NCT03248492), a multicenter, single-arm trial enrolling 184 female patients with HER2-positive, unresectable and/or metastatic breast cancer who had received two or more prior anti-HER2 therapies. Patients received fam-trastuzumab deruxtecan-nxki 5.4 mg/kg by intravenous infusion every 3 weeks until unacceptable toxicity or disease progression."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2-positive-breast-cancer

Trastuzumab Deruxtecan (DS-8201) Is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

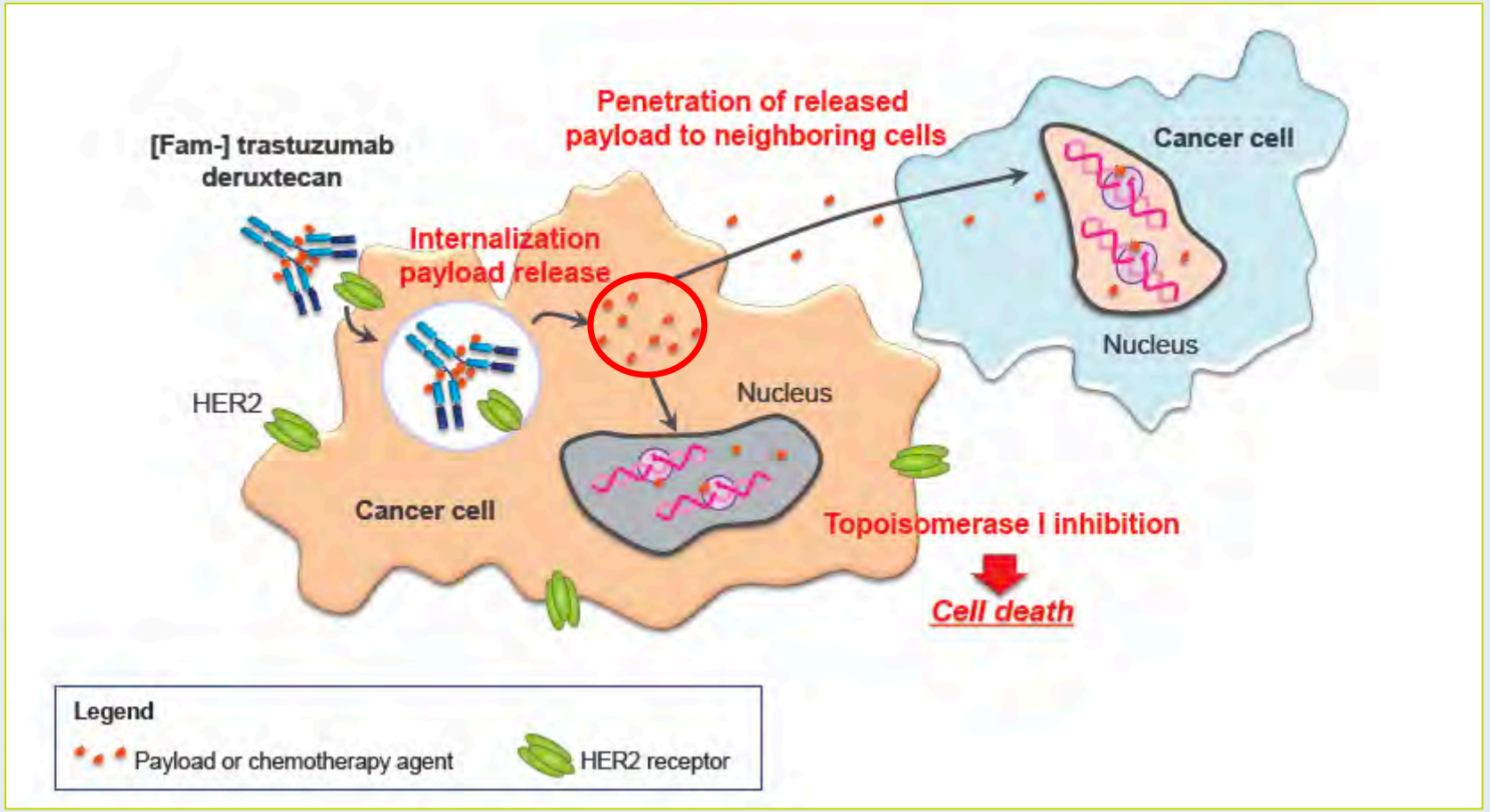


Payload MOA: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

Krop IE et al. SABCS 2019;Abstract GS1-03.

RTP RESEARCH TO PRACTICE

Trastuzumab Deruxtecan's Membrane-Permeable Payload Can Attack Neighboring Cancer Cells (a Bystander Effect)



ADCC = antibody-dependent cellular cytotoxicity; HER2 = human epidermal growth factor receptor 2; Topo-1 = topoisomerase I.

1. Ogitani Y et al. *Cancer Sci*. 2016;107:1039–1046 . 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097–5108.

The NEW ENGLAND JOURNAL of MEDICINE

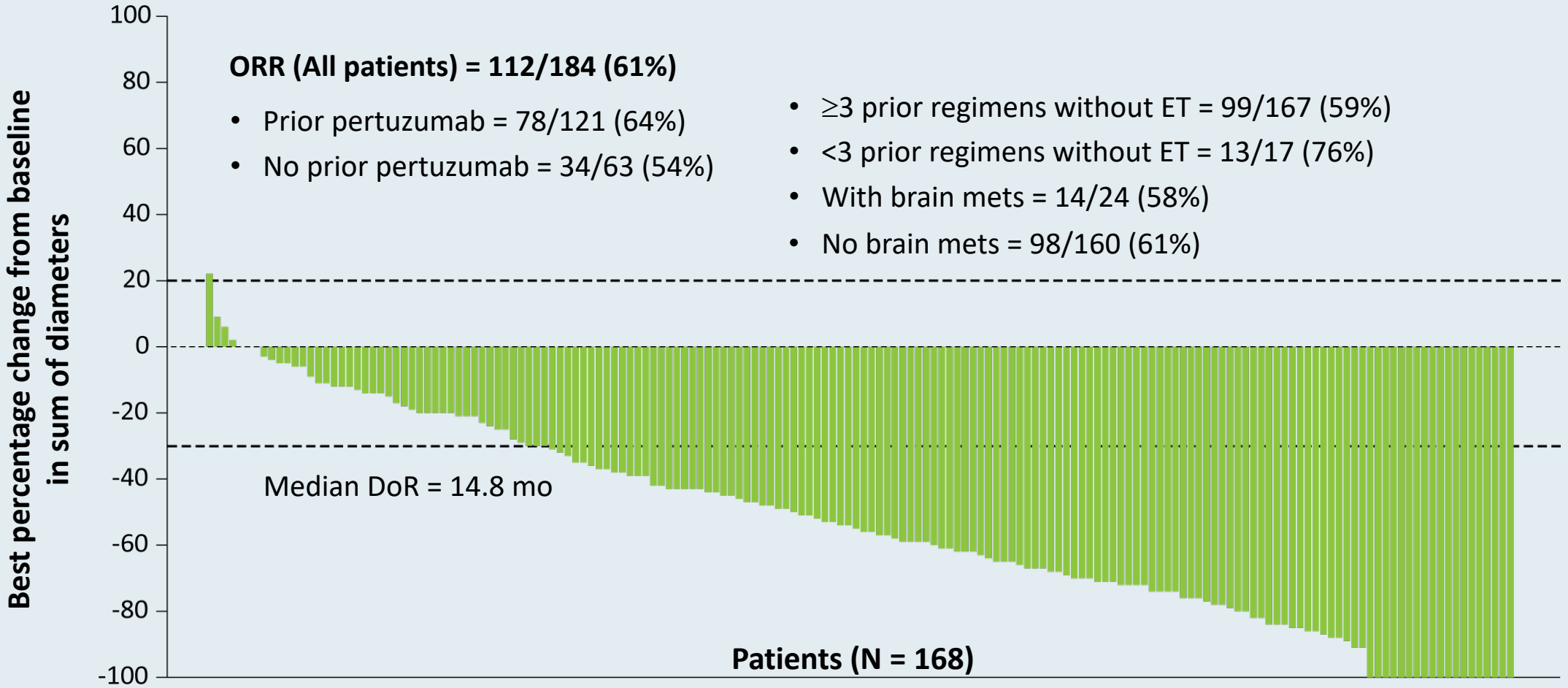
ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

N Engl J Med 2020;382(7):610-21.

DESTINY-Breast01: Response According to Tumor Size and Subgroup Analyses

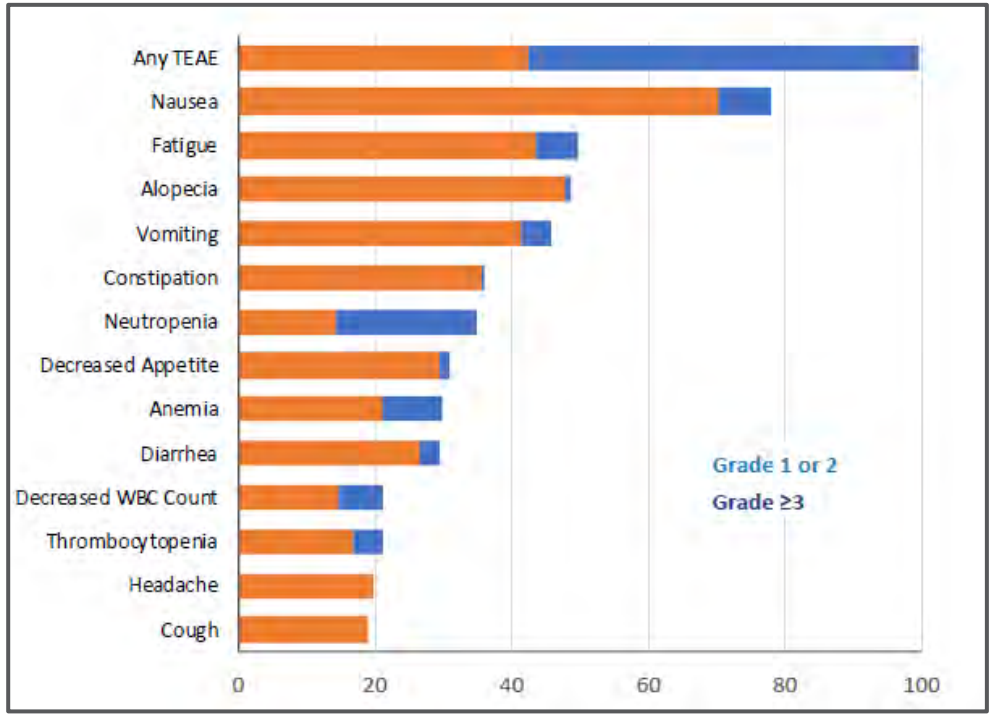


Modi S et al. *N Engl J Med* 2020;382(7):610-21.

RTP RESEARCH TO PRACTICE

DESTINY-Breast01 Trial: Adverse events with T-Dxd

Treatment-emergent Adverse Events in >15% of Patients[a]



a Patients who received T-DXd 5.4 mg/kg.

Interstitial Lung Disease

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6-76 weeks)

Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

- Serious TEAEs, 22.8% (drug related, 12.5%)
- TEAEs associated with discontinuation, 15.2% (drug related, 14.7%); **the majority were due to pneumonitis/ILD (8.7%)**

@ErikaHamilton9

Courtesy of Erika Hamilton, MD

Krop I et al SABCS 2019

Pneumonitis associated with T-Dxd

ILD in Phase 1/2 studies[1]

	All-grade	Grade 5
All subjects N=665	9.9%	0.8%
Breast cancer, any dose N=510	10.6%	0.8%
Breast cancer, 5.4 mg/kg N=269	5.6%	0.4%

Conclusions

- **Higher likelihood of developing ILD associated with[1]:**
  - **Higher dose (≥6.4 mg/kg)**
  - **Japanese origin:** *Japanese patients 49% of N=665 sample*
  - **Number of prior therapies:** *Many patients in Phase1/2 have multiple prior lines of therapy*
- **Median 149 days (~6 months) to onset[1] allows for monitoring & intervention**
- **Education and guidelines implementation underway**

Source: [1]Powell et al, SABCS 2018; Poster #P6-17-06, Abstract #979

Courtesy of Sara Hurvitz, MD

Symptom identification for diagnosis of ILD

Talk to your patients about their symptoms….

- ✓ Have you been coughing recently? Is it a dry cough?
- ✓ Have you had any shortness of breath, especially during or after physical activity?
- ✓ Have you experienced any new breathing or respiratory problems?
- ✓ If you already have respiratory problems, have they gotten worse?
- ✓ Have you had a fever?
- ✓ Have you been feeling tired?
- ✓ Have you lost weight?

Symptom identification is vital to identification of ILD/pneumonitis!

Courtesy of Erika Hamilton, MD

Management of Interstitial Lung Disease in Clinical Studies of Trastuzumab Deruxtecan

Monitor

Suspected ILD

Interrupt drug

Rule out ILD if the patient exhibits:

- Radiographic changes suggesting ILD
- Acute onset of new/worsening pulmonary or related symptoms (eg, cough, dyspnea, fever)

Confirm

Assessments should include:

- High-resolution CT
- Pulmonologist consultation and, if indicated, ID consultation
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and BAL if indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gasses, if indicated
- As soon as ILD suspected, collect 1 blood sample for PK assessment, if feasible

All ILD events should be followed until resolution and after drug discontinuation.

Manage

Hold drug for any ILD events independent of grade

- **Grade 1:** Hold until fully resolved, then:
  - *If resolved ≤ 28 d from onset:* maintain dose
  - *If resolved > 28 d after onset:* reduce dose by 1 level
  - *If grade 1 ILD occurs beyond cycle Day 22 and has not resolved within 49 d from last infusion:* discontinue drug
- **Grades 2-4:** permanently discontinue treatment and follow toxicity management guidelines for trastuzumab deruxtecan

Fam-trastuzumab deruxtecan-nxki PI.

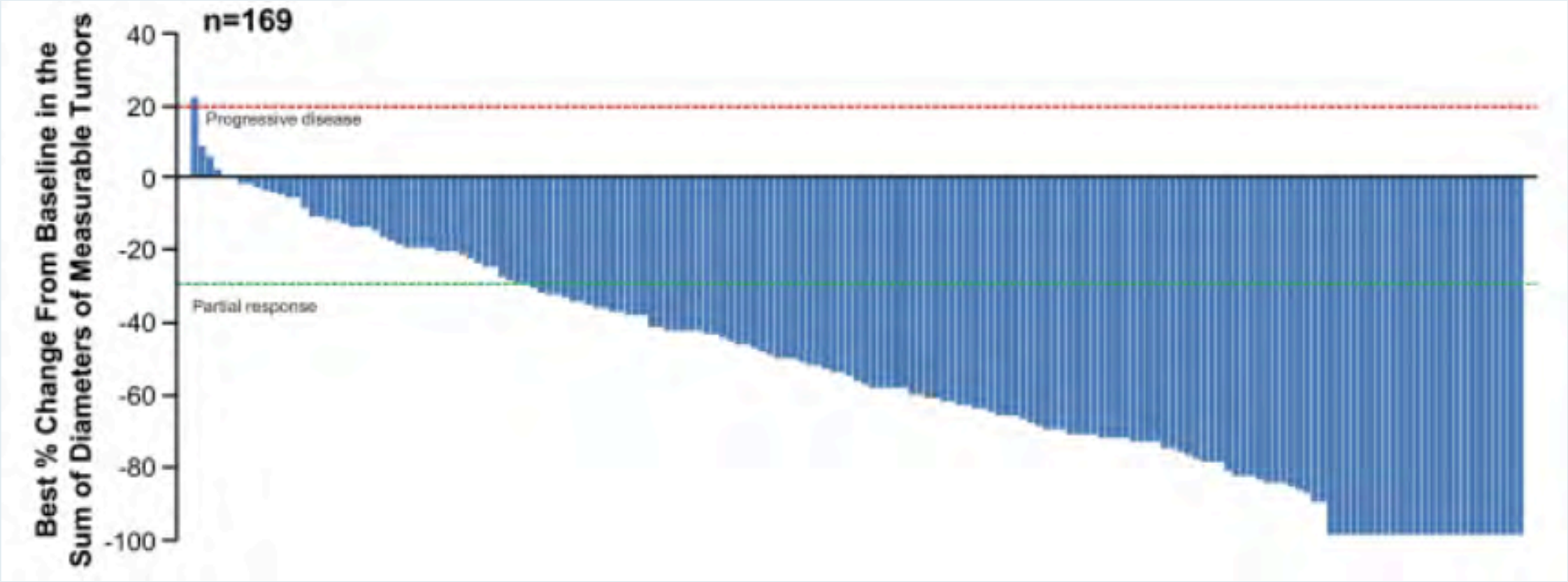
Courtesy of Sara Hurvitz, MD

Continued 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 Percentage Change from Baseline in Tumor Size



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

RTP RESEARCH TO PRACTICE

FDA Approves Margetuximab for HER2-Positive mBC

Press Release – December 16, 2020

"On December 16, 2020, the Food and Drug Administration approved margetuximab-cmkb in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Efficacy was evaluated in SOPHIA (NCT02492711), a randomized, multicenter, open-label trial of 536 patients with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized (1:1) to margetuximab plus chemotherapy or trastuzumab plus chemotherapy. Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting (≤ 2, > 2), and number of metastatic sites (≤ 2, > 2)."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-margetuximab-metastatic-her2-positive-breast-cancer

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].**

Agenda

Module 1: Breast Cancer 2021

- Dr Matt-Amaral: A 42-year-old premenopausal woman with ER-positive, HER2-positive, node-negative breast cancer

Module 2: Management of Localized Disease

- Dr Matt-Amaral: A 73-year-old woman with clinical T4 ER/PR-negative, HER2-positive breast cancer

Module 3: Sequencing of Agents for Metastatic Disease

- Dr Astrow: A 70-year-old woman with a 10-cm Grade III, ER/PR-negative, HER2-positive IDC and pleural metastases
- Dr Rodriguez: A 36-year-old woman with heavily pretreated ER/PR-positive, HER2-positive breast cancer and bone metastases

Module 4: Systemic Treatment of Brain Metastases

- Dr Ma: A 42-year-old Middle Eastern woman with HER2-positive breast cancer and brain metastases
- Dr Hussein: A 43-year-old woman with ER/PR-negative, HER2-positive breast cancer with brain metastasis
- Dr Glynn: A 60-year-old woman with malignant pericardial effusion

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Case Presentation – Dr Ma: A 42-year-old Middle Eastern woman with HER2-positive breast cancer and brain metastases

Dr Yanjun Ma

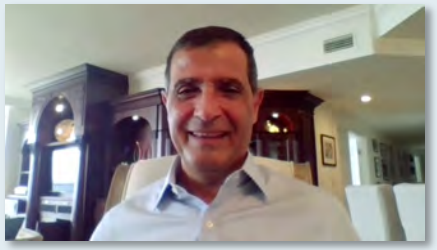
- 10/2018: Neoadjuvant TCHP → right mastectomy with axillary nodal dissection
- 5/2019: XRT planned but noted right axillary discomfort and palpable node
  - Tumor size doubled extending to chest wall with significant increase in pain in 2 weeks
- PET: Diffuse right chest wall, axillary, internal mammary, and supraclavicular nodal metastases with direct muscle invasion
- MRI: 2 occipital lobe metastases
- Treated with AC → SBRT to brain lesions → T-DM1 x 1 cycle (D/Ced due to liver toxicity)
- 2/2020: Single-agent neratinib and faring well

Questions

- What are the faculty's thoughts on administering tucatinib if this patient becomes neratinib-refractory?
- Does T-DXd penetrate the CNS? If so, how well?

RTP RESEARCH TO PRACTICE

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



Dr Atif Hussein

- 1/2016: Stage IIIC Grade 3 left, ER/PR-negative, HER2-positive IDC
  - S/p neoadjuvant TCH-P x 6 → left MRM and ALND, adjuvant RT and trastuzumab (completed 2/2017)
  - 3/2018: Completed adjuvant neratinib study (ExteNET)
- 3/2019: Resection of 4-cm ER/PR-negative, HER2-positive left parietal mass → SBRT
  - CT chest/abdomen/pelvis and bone scan: Negative
- 4/2019: Capecitabine/lapatinib
- 7/2019 brain MRI: New left parietal lesion at previous site → second subtotal resection
- 10/2019: T-DM1
- 1/2020 brain MRI: Complete resolution of left parietal mass
- 12/2020: T-DM1 cycle 22. Brain MRIs, CT and bone scans – No evidence of disease

Question

- If this patient presented today post-neratinib, lapatinib and capecitabine, what treatment would you recommend – T-DM1, tucatinib, capecitabine/trastuzumab, other?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Glynn: A 60-year-old woman with malignant pericardial effusion

Dr Philip Glynn

- 11/2008: Initial diagnosis – ER/PR-positive, HER2-negative IDC
  - Received multiple treatments, including hormonal therapy, carboplatin/gemcitabine, capecitabine, *nab*-paclitaxel
- 7/2020: Patient developed liver metastases, recurrence of pericardial effusion
  - Biopsy: HER2-positive disease
- Treated with T-DM1
  - Performance status improved, tolerating treatment well
- 2/2021: Patient inquires about treatment break

Question

- Given that this patient did not exhibit any impairments in her quality of life, I advised her we should continue therapy, but what are the faculty's thoughts on this case?

RTP RESEARCH TO PRACTICE

Brain Metastases Are Common in Advanced Cancers

Primary site	Incidence rate
Lung cancer – overall	16%-20%
SCLC NSCLC	~30% ~13%
Breast cancer – overall	10%-15%
HER2-positive Triple-negative	25%-50% 20%

Glitza Oliva IC et al. *Ann Oncol* 2018;29:1509-20
Schouten LJ et al. *Cancer* 2002;94(10):2698-705
Barnholtz-Sloan JS et al. *J Clin Oncol* 2004;22(14):2865-72
Chamberlain MC et al. *Neuro-Oncology* 2017;19(1):i1-24

TBCRC 022: Phase II Study Design

Eligibility

- **HER2-positive mBC**
- **Measurable CNS metastases**
- **ECOG PS 0-2**

Neratinib (240 mg orally once daily) and capecitabine 750 mg/m^2 BID

(for 14 days followed by 7 days rest)

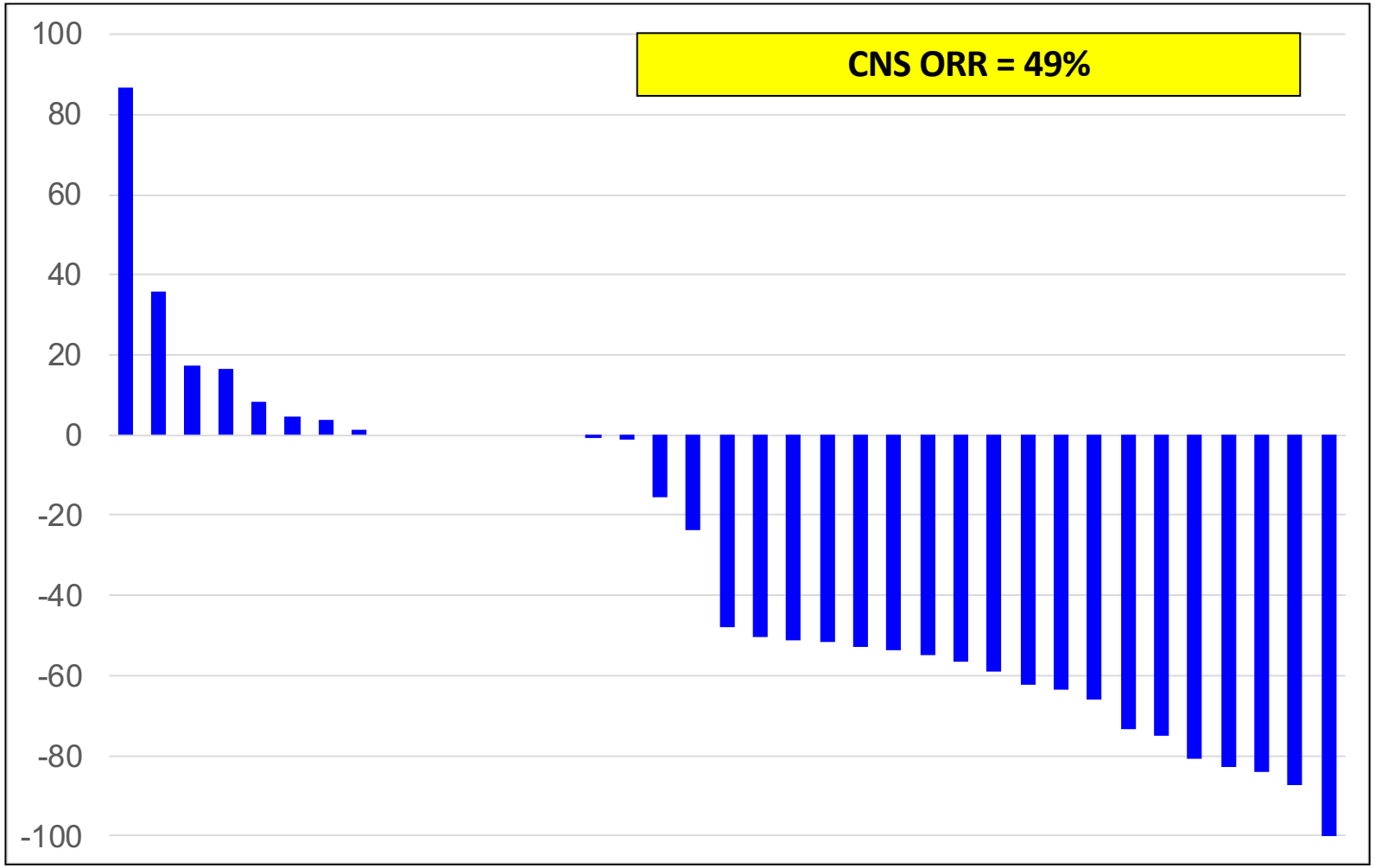
Follow-up every 3 weeks

PD (CTCs, cfDNA)

- **If CNS PD – Off study**
- **If non-CNS PD – Extension with trastuzumab offered**

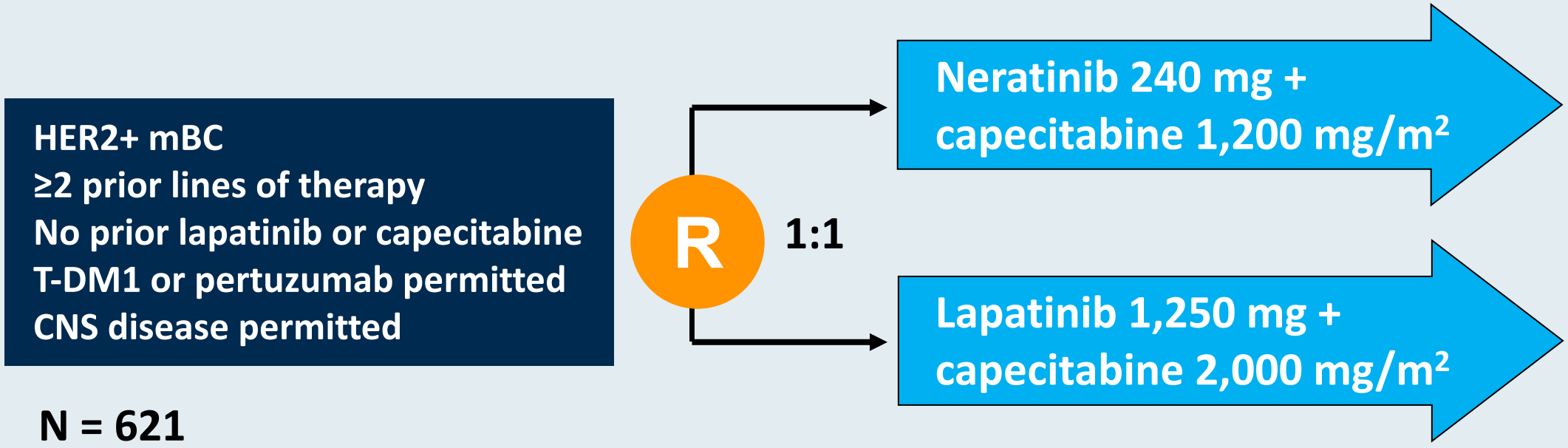
Freedman R et al. JCO 2019 and Clin Br Cancer 2020

TBCRC 022: CNS Volumetric Response



Freedman R, et al. JCO 2019 and Clin Br Cancer 2020

NALA: Phase III Trial Design



N = 621

Coprimary endpoints: PFS (central) and OS

Saura C et al. *J Clin Oncol* 2020;38(27):3138-49.

NALA: Neratinib for HER2-Positive mBC in Patients with Baseline CNS Disease

	CNS metastases at baseline (n = 101)		No CNS metastases at baseline (n = 520)	
	Neratinib + cape (n = 51)	Lapatinib + cape (n = 50)	Neratinib + cape (n = 256)	Lapatinib + cape (n = 264)
Median PFS	7.8 mo	5.5 mo	9.0 mo	6.9 mo
	HR = 0.66		HR = 0.76	
Median OS	16.4 mo	15.4 mo	25.6 mo	23.6 mo
	HR = 0.90		HR = 0.85	

Saura C et al. SABCS 2020;Abstract PD13-09.

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

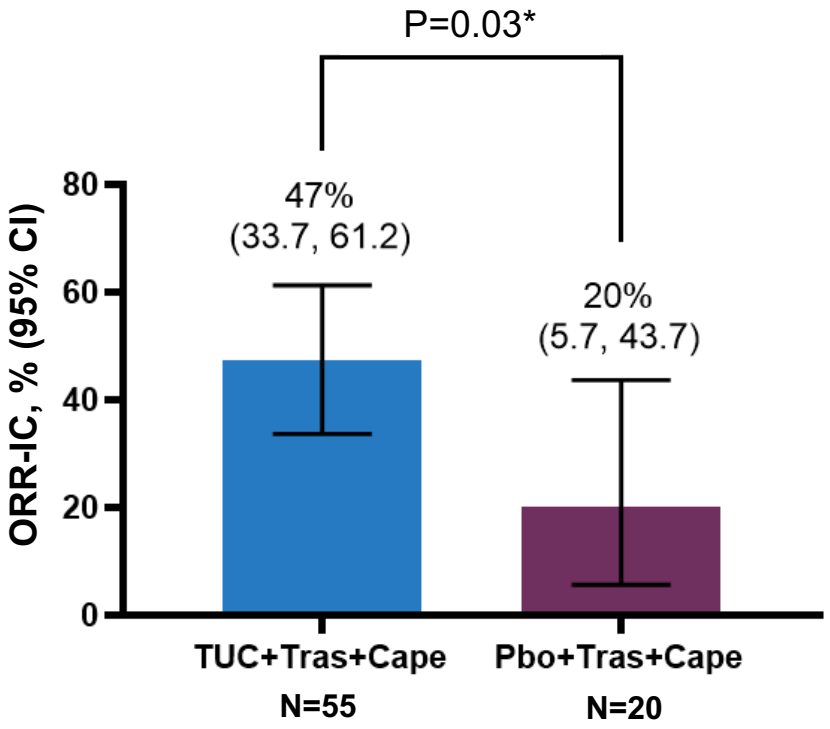
Nancy U. Lin, MD[1]; Virginia Borges, MMSc, MD[2]; Carey Anders, MD[3]; Rashmi K. Murthy, MD, MBE[4]; Elisavet Paplomata, MD[5]; Erika Hamilton, MD[6]; Sara Hurvitz, MD[7]; Sherene Loi, MD, PhD[8]; Alicia Okines, MBChB, MD[9]; Vandana Abramson, MD[10]; Philippe L. Bedard, MD[11]; Mafalda Oliveira, MD, 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.

RTP RESEARCH TO PRACTICE

HER2CLIMB: Intracranial Response Rate (ORR-IC) in Patients with Active Brain Metastases and Measurable Intracranial Lesions at Baseline

Confirmed Objective Response Rate (RECIST 1.1)



*Stratified Cochran-Mantel-Haenszel P value

	TUC+Tras+Cape (N=55)	Pbo+Tras+Cape (N=20)
Best Overall Intracranial Response[a], n (%)		
Complete Response (CR)	3 (5.5)	1 (5.0)
Partial Response (PR)	23 (41.8)	3 (15.0)
Stable Disease (SD)	24 (43.6)	16 (80.0)
Progressive Disease (PD)	2 (3.6)	0
Not Available[b]	3 (5.5)	0
Subjects with Objective Response of Confirmed CR or PR, n	26	4
Duration of Intracranial Response (DOR-IC)[e] (95% CI)[f], months	6.8 (5.5, 16.4)	3.0 (3.0, 10.3)

(a) Confirmed Best overall response assessed per RECIST 1.1. (b) Subjects with no post-baseline response assessments. (c) Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934). (d Cochran-Mantel-Haenszel test controlling for stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. (e) As estimated using Kaplan-Meier methods. (f) Calculated using the complementary log-log transformation method (Collett, 1994).

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Courtesy of Carey K Anders, MD

Cases from the Community: Investigators Discuss the Role of PARP Inhibition in the Care of Actual Patients with Ovarian Cancer

Saturday, March 20, 2021
4:00 PM – 5:00 PM ET

Faculty

Susana Banerjee, MBBS, MA, PhD
Richard T Penson, MD, MRCP
Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

NCPD credit information will be emailed to each participant within 3 business days.