Expert Second Opinion: HER2-Positive Breast Cancer

Tuesday, June 22, 2021
5:00 PM – 6:00 PM ET

Faculty

Erika Hamilton, MD
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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Faculty

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Director, Breast and Gynecologic Research Program
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Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
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Associate Professor of Medicine
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Boston, Massachusetts

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Commercial Support

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Dr Love — Disclosures

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Dr O'Shaughnessy — Disclosures

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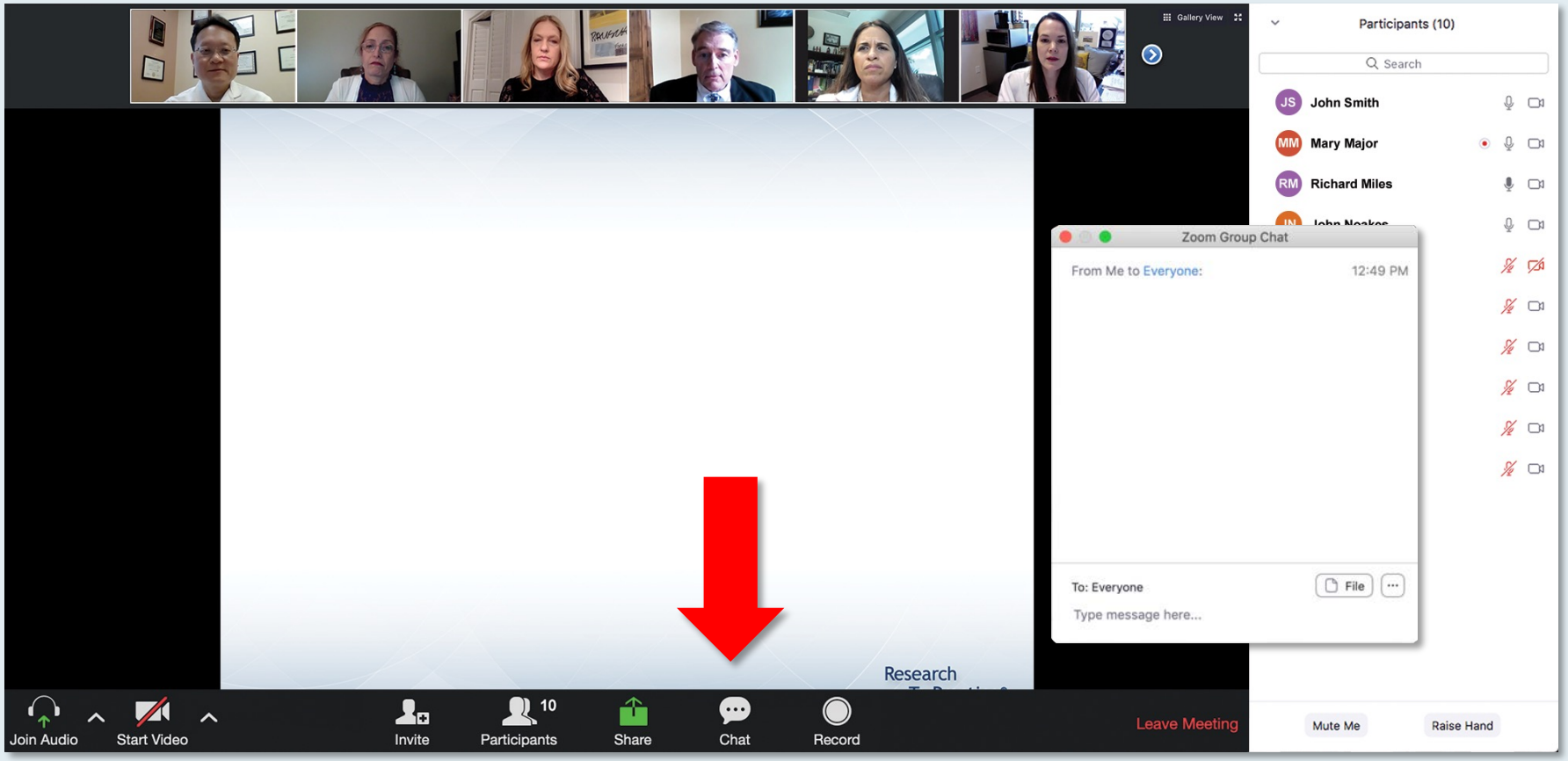
We Encourage Clinicians in Practice to Submit Questions



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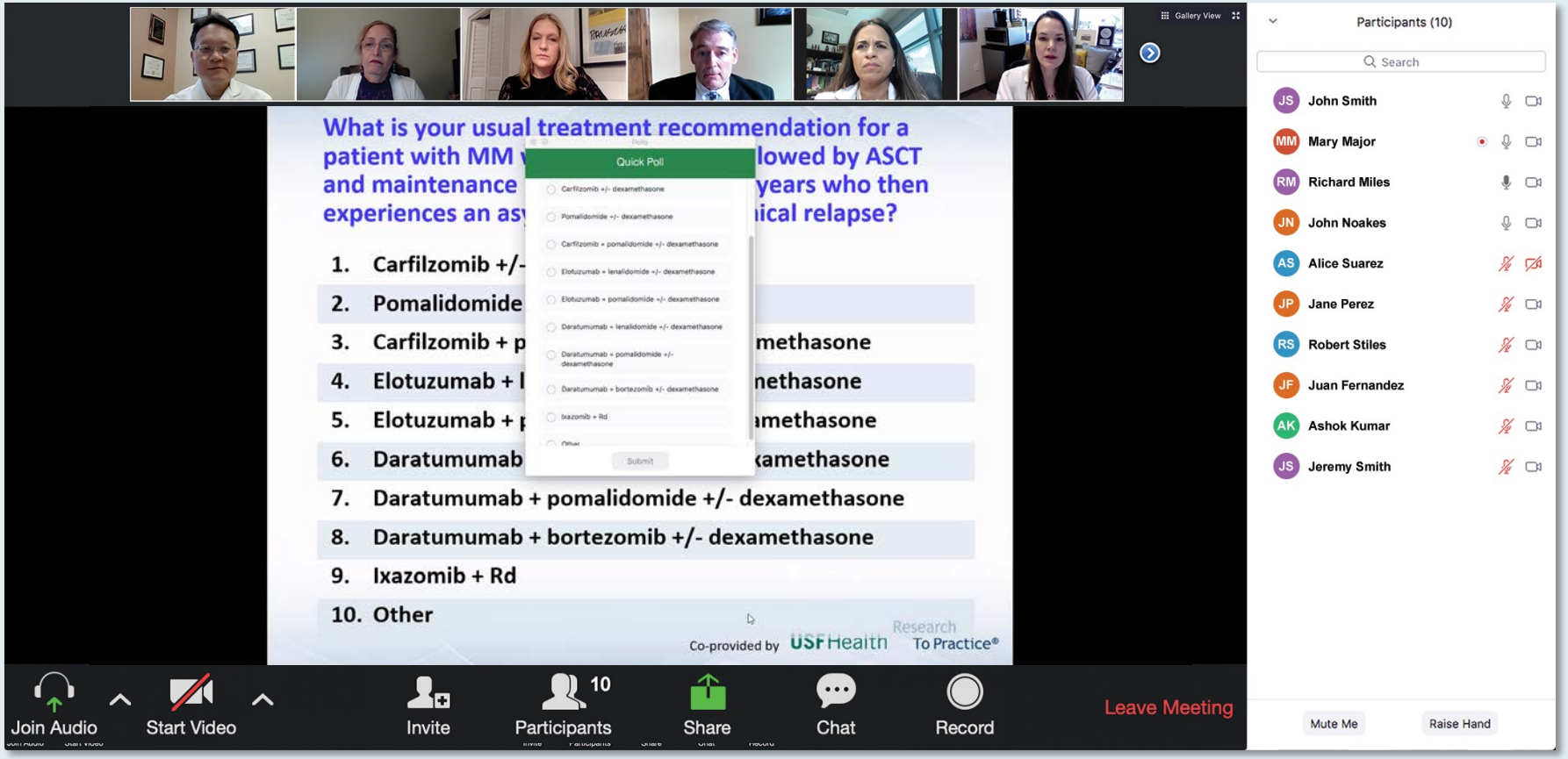

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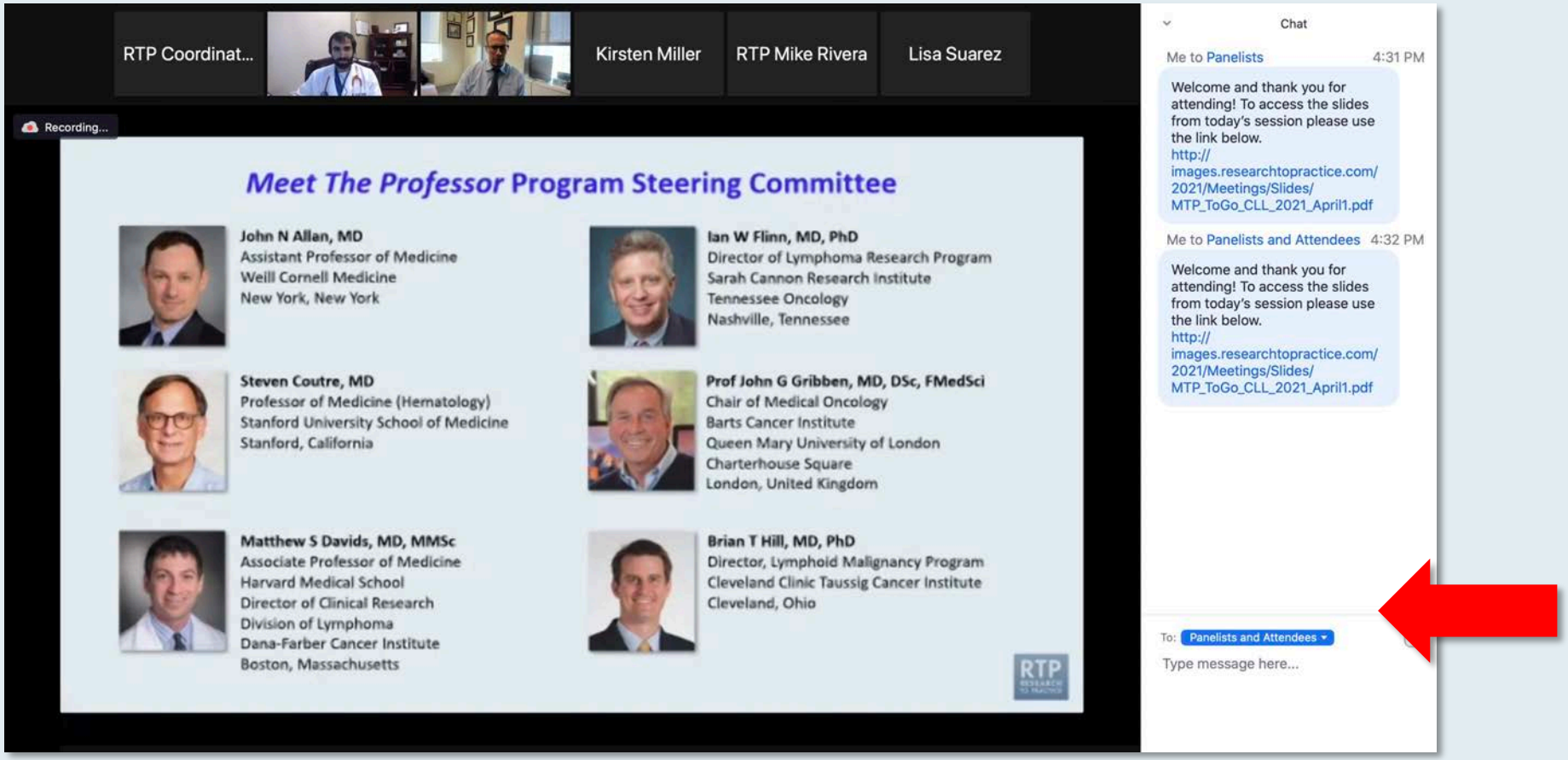

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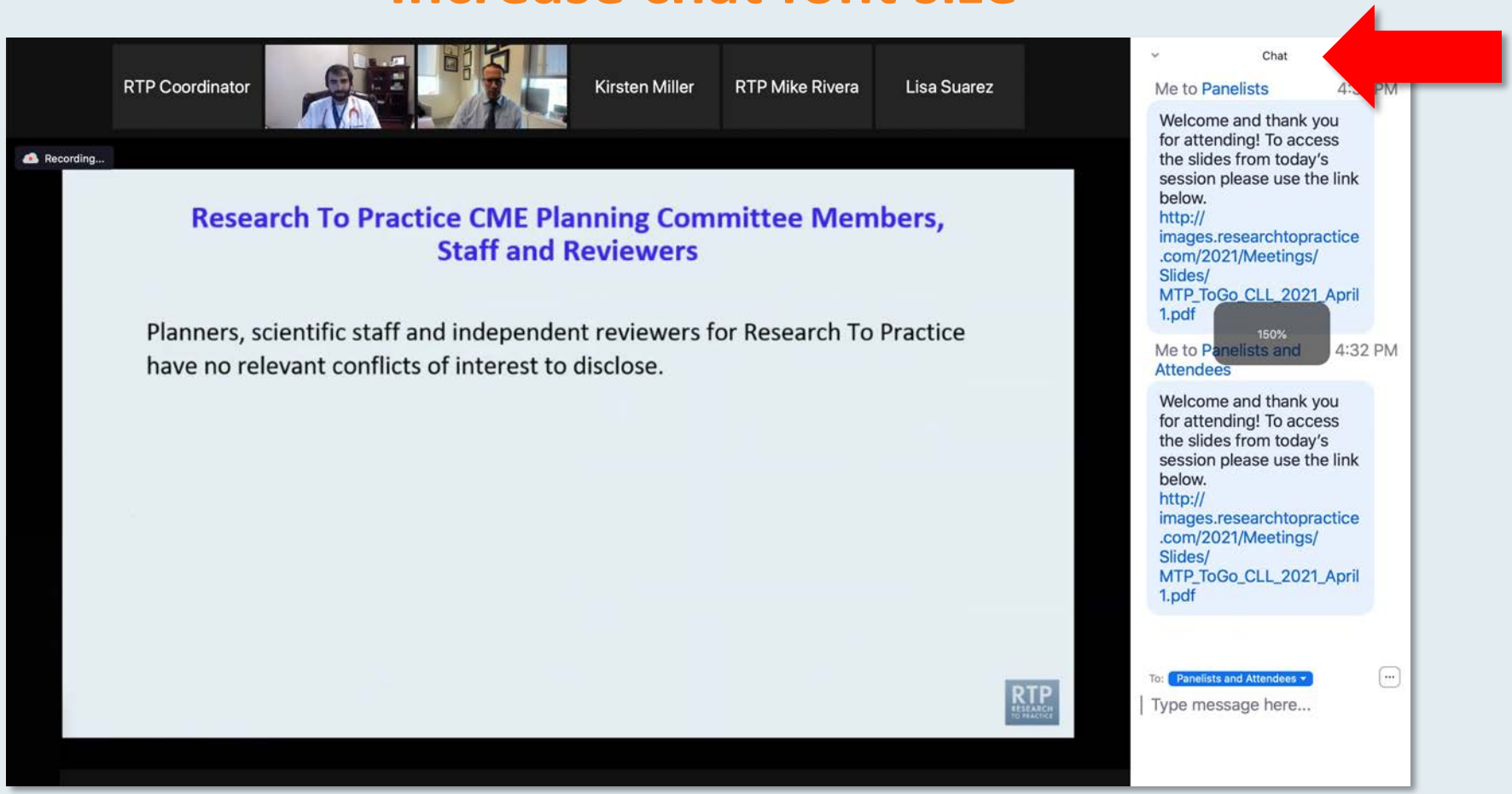

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WITH DR NEIL LOVE

HER2-Positive Localized Breast Cancer

DR ADAM BRUFSKY
UNIVERSITY OF PITTSBURGH

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Multiple Myeloma
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Ovarian Cancer
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Hormonal Therapy for Prostate Cancer
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Bladder Cancer
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Monday, July 26
5:00 PM – 6:00 PM ET

Targeted Therapy for Non-Small Cell Lung Cancer
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ASCO Highlights and More: Investigators Review Recent Data Sets and Provide Perspectives on Current Oncology Care

A Daylong Multitumor Educational Webinar in Partnership with the Texas Society of Clinical Oncology (TxSCO)

Saturday, June 26, 2021
8:00 AM – 3:00 PM Central Time
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RTP RESEARCH TO PRACTICE

Video Consensus or Controversy? Chronic Lymphocytic Leukemia and Follicular Lymphoma

Tuesday, June 29, 2021
5:00 PM – 6:00 PM ET

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Prof John G Gribben, MD, DSc, FMedSci
Brad S Kahl, MD

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Shaji K Kumar, MD
Additional faculty to be announced

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RTP RESEARCH TO PRACTICE

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

In Partnership with Project Echo® and Florida Cancer Specialists

Tuesday, July 6, 2021
5:00 PM – 6:00 PM ET

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David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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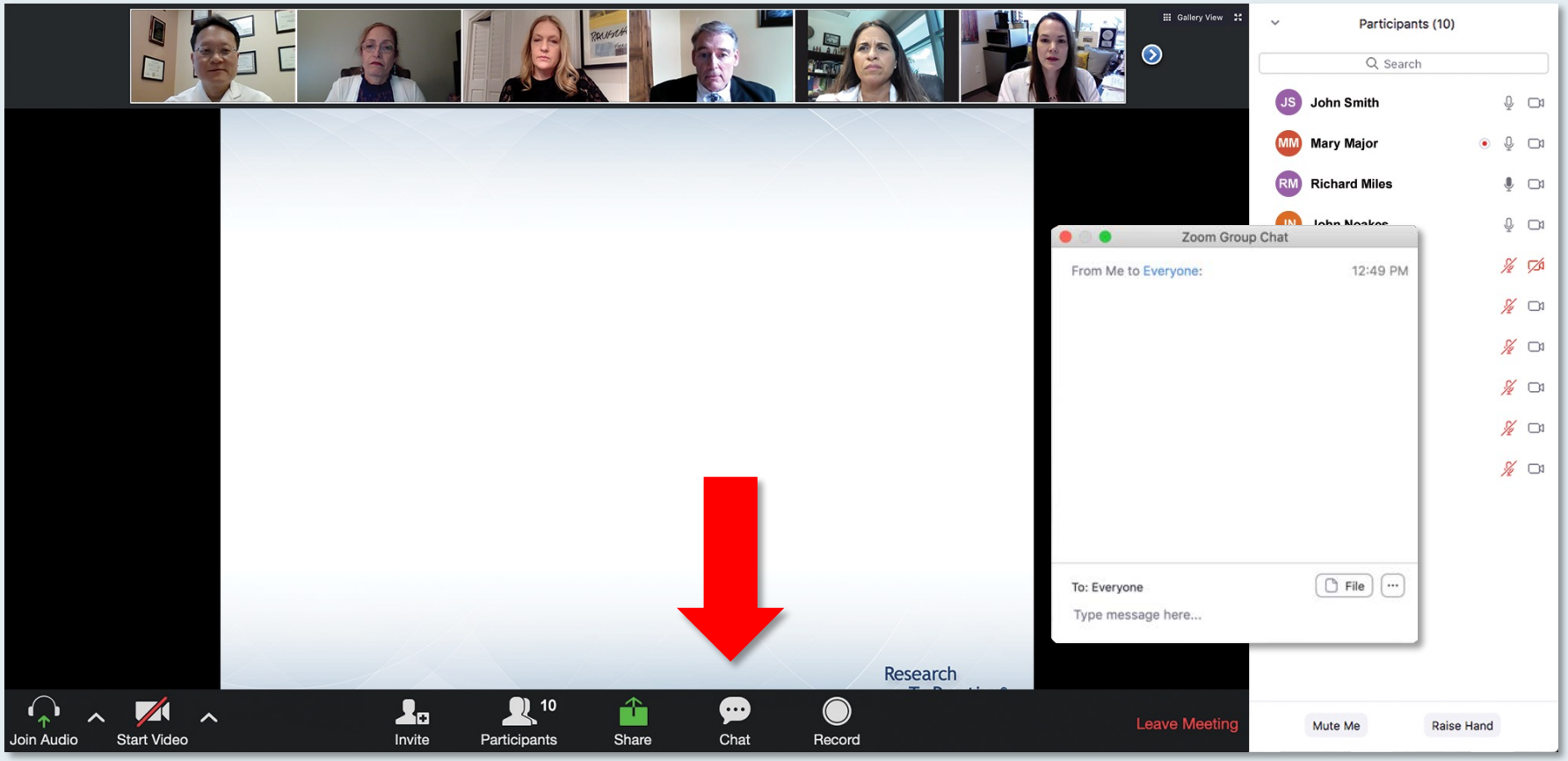

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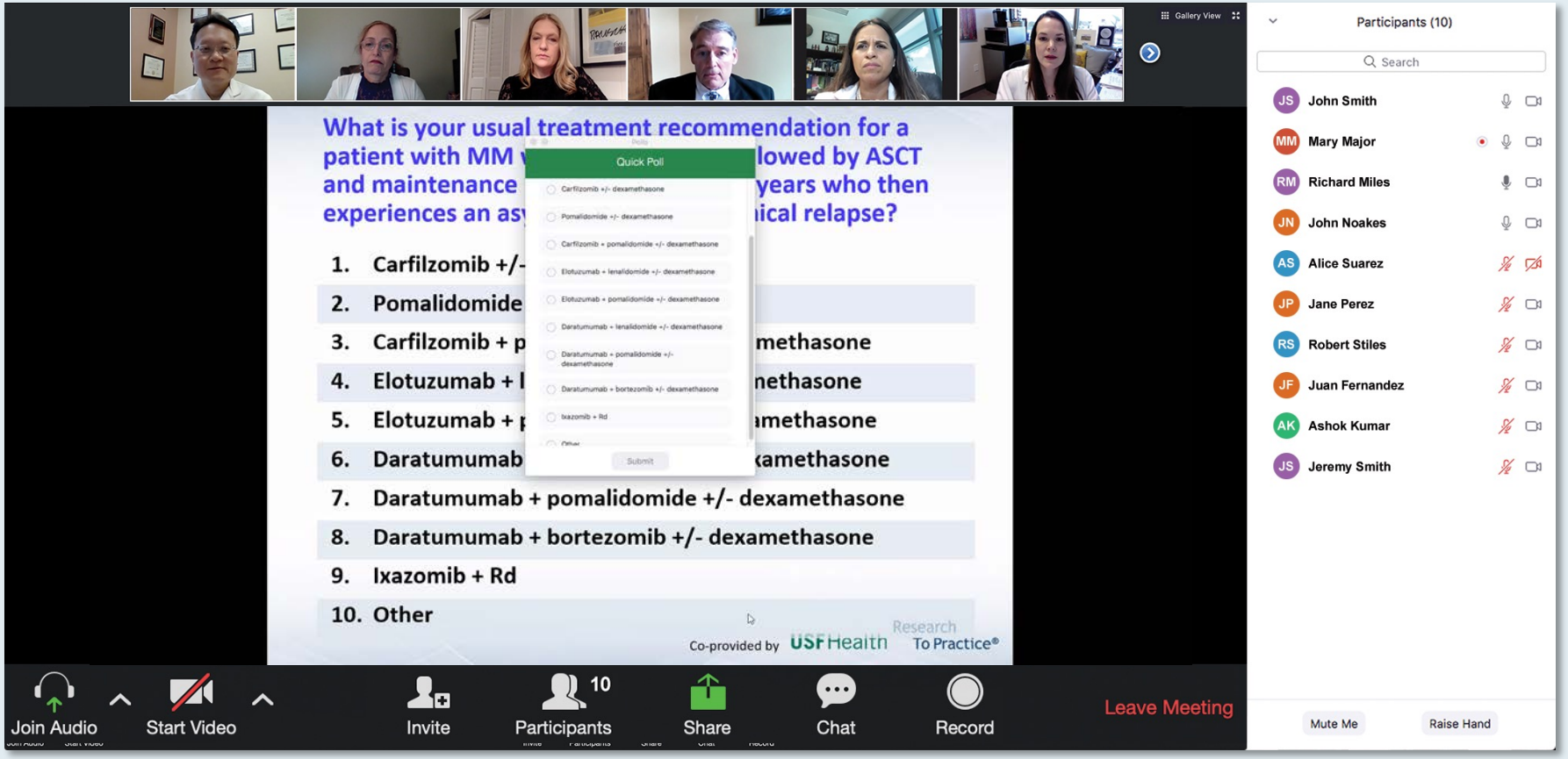

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Contributing Oncologists

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

Ruth O'Regan, MD
Chair, Department of Medicine
Charles A Dewey Professor of Medicine
University of Rochester
Rochester, New York

Ann Partridge, MD, MPH
Vice Chair of Medical Oncology
Director, Program for Young Women with Breast Cancer
Director, Adult Survivorship Program
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Agenda

Module 1: Role of Immunotherapy in HER2-Positive Metastatic Breast Cancer (mBC)?

- Dr Mahtani: A 56-year-old woman with ER-positive, HER2-positive mBC enrolled on a clinical trial of nivolumab/ipilimumab

Module 2: Management of HER2-Positive mBC

- Dr Partridge: A 30-year-old woman with ER-positive, HER2-positive mBC
- Dr Mahtani: A 72-year-old woman with HER2-positive mBC
- Dr O'Regan: A 58-year-old woman with ER-negative, HER2-positive mBC
- Dr Partridge: A 50-year-old woman with ER-positive, HER2-positive mBC

Module 3: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer

- Dr Mahtani: A 44-year-old woman with 5-cm ER-positive, HER2-positive localized breast cancer
- Dr O'Regan: A 53-year-old woman with 4.5-mm ER-positive, HER2-positive breast cancer

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Case Presentation – Dr Mahtani: A 56-year-old woman with ER-positive, HER2-positive metastatic breast cancer enrolled on a clinical trial of nivolumab/ipilimumab

Dr Reshma Mahtani

- 2011: Neoadjuvant TCH for cT2N1 ER+/HER2+ tumor, adjuvant radiation, maintenance trastuzumab x 1 yr, AI completed in 2017
- 2018: Developed left SC adenopathy and imaging revealed retropectoral, axillary and mediastinal nodes, biopsy confirmed ER+/HER2+ recurrence
- Paclitaxel x 14 months → progressive disease extensively involving chest wall
- T-DM1 with neratinib on clinical trial → PD after 3 cycles
- NGS: TMB-high, PD-L1 10%
- Nivolumab with ipilimumab on protocol → dramatic flare of disease in chest wall after first cycle
- Rapid clearing after 2nd dose; all systemic disease now controlled (complete response by RECIST on imaging); response ongoing since 2019 on single agent nivolumab

Questions

- What do you see as the role of immunotherapy in HER2-positive breast cancer?

FDA Grants Accelerated Approval to Pembrolizumab with Trastuzumab and Chemotherapy as First-Line Therapy for HER2-Positive Gastric Cancer

Press Release – May 5, 2021

"On May 5, 2021, the Food and Drug Administration granted accelerated approval to pembrolizumab in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Approval was based on the prespecified interim analysis of the first 264 patients of the ongoing KEYNOTE-811 (NCT03615326) trial, a multicenter, randomized, double-blind, placebo-controlled trial in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients were randomized (1:1) to receive pembrolizumab 200 mg or placebo every 3 weeks, in combination with trastuzumab and either fluorouracil plus cisplatin or capecitabine plus oxaliplatin.

The main efficacy measure for this analysis was overall response rate (ORR) assessed by blinded independent review committee. The ORR was 74% in the pembrolizumab arm and 52% in the placebo arm (one-sided p-value< 0.0001, statistically significant). The median duration of response (DoR) was 10.6 months for patients treated with pembrolizumab and 9.5 months for those in the placebo arm."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-her2-positive-gastric-cancer

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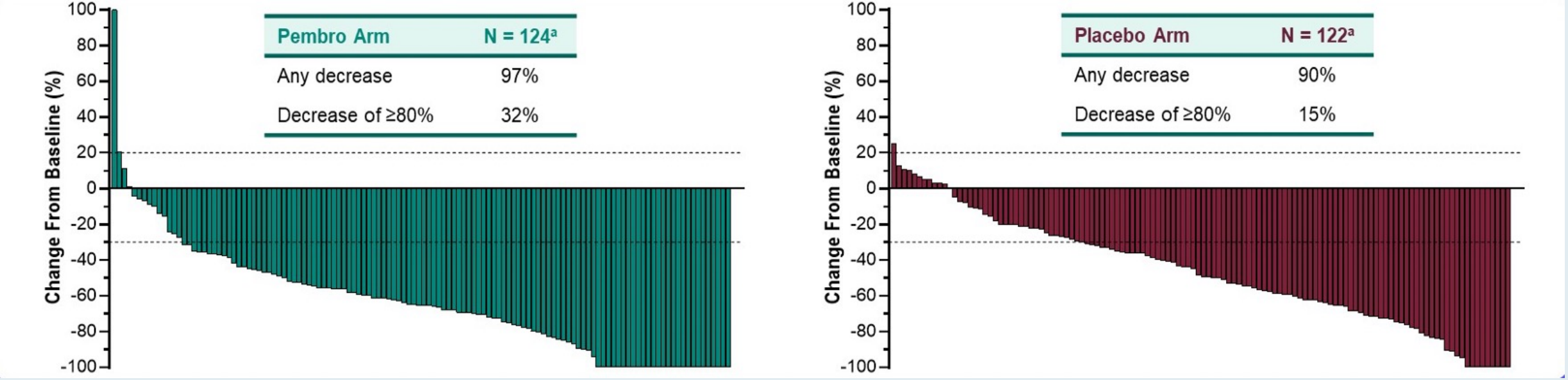
Pembrolizumab plus Trastuzumab and Chemotherapy for HER2+ Metastatic Gastric or Gastroesopahgeal Junction Cancer: Initial Findings of the Global Phase 3 KEYNOTE-811 Study

Janjigian YY et al.
ASCO 2021;Abstract 4013.

KEYNOTE-811: Confirmed Response at First Interim Analysis



[a] Participants with RECIST-measurable disease at baseline and ≥1 post-baseline measurement evaluable for change from baseline in target lesions

Janjigian YY et al. ASCO 2021;Abstract 4013.

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A 65-year-old woman with ER-negative, HER2-positive metastatic breast cancer with bone and soft tissue metastases receives first-line THP and second-line T-DM1 but then experiences symptomatic disease progression. What systemic treatment would you most likely recommend next?

1. Trastuzumab/lapatinib
2. Neratinib/capecitabine
3. Tucatinib/trastuzumab/capecitabine
4. Trastuzumab deruxtecan
5. Margetuximab/chemotherapy
6. Other

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A 65-year-old woman with ER-negative, HER2-positive mBC receives THP followed by T-DM1 on disease progression. She then 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?

1. Continue T-DM1
2. Trastuzumab + chemotherapy
3. Trastuzumab + lapatinib
4. Neratinib + capecitabine
5. Tucatinib + trastuzumab/capecitabine
6. Trastuzumab deruxtecan
7. Margetuximab + chemotherapy
8. Other

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Case Presentation – Dr Partridge: A 30-year-old woman with ER-positive, HER2-positive metastatic breast cancer

Dr Ann Partridge

- 2012: Initial diagnosis of ER-positive, HER2-positive mBC, axillary and vertebral disease
  - She did not want HER2-targeted therapy → tamoxifen with leuprolide
  - Trastuzumab and zoledronic acid added on PD
- 2016 – 2020: Multiple lines of therapy for disease progression: lapatinib with trastuzumab (on leuprolide) → T-DM1 → neratinib with fulvestrant on clinical trial → capecitabine/trastuzumab → vinorelbine/capecitabine
- 7/2020: Trastuzumab deruxtecan with response
- 5/2021: Doxorubicin/trastuzumab

Questions

- In light of recent data such as the WSG-ADAPT HER2+/HR- trial, what do you think about doing early first-line endocrine therapy in ER-positive, HER2-positive breast cancer either alone or in tandem with anti-HER2 therapy such as trastuzumab or pertuzumab, or the combination?

Case Presentation – Dr Mahtani: A 72-year-old woman with HER2-positive metastatic breast cancer

Dr Reshma Mahtani

- 2014: Lumpectomy and ALND for 1.1cm ILC, grade 3, 3/15 positive nodes, ER60%, PR50%, HER2 3+
- 2019: Palpated left breast mass → IDC, grade 2, ER50%, PR50%, HER2 2+, FISH positive
- Docetaxel/HP → docetaxel stopped → letrozole/HP continued → PD in lung after 6 months (pleural effusions requiring PleurX™ drainage) → T-DM1 for 5 months (still required PleurX drainage)
- 1/2021: Assumed care of patient who was symptomatic with weight loss, SOB with minimal exertion (using oxygen), increased drainage from PleurX, ECOG PS 2/bordering on 3.
- Started trastuzumab deruxtecan → rapid improvement in symptoms, but progressed 5 months later
- Tucatinib with trastuzumab/capecitabine and patient is doing well

Questions

- How are you sequencing tucatinib and trastuzumab deruxtecan? Are you reserving tucatinib for when a patient develops brain metastases?

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Case Presentation – Dr O'Regan: A 58-year-old woman with ER-negative, HER2-positive metastatic breast cancer

Dr Ruth O'Regan

- ER-negative, HER2-positive breast cancer metastatic to nodes and lungs
- Docetaxel, trastuzumab, pertuzumab with partial response
- Trastuzumab/pertuzumab alone → PD 6 months later
- T-DM1 with initial response but has progressive disease 9 months later
  - No evidence of brain metastases
- Enrolled on the HER2CLIMB study with tucatinib x 6 months but discontinued due to diarrhea

Questions

- How do you manage diarrhea associated with tucatinib?
- In asymptomatic patients, are you screening for brain metastases to make the decision about whether or not to use tucatinib-based treatment or T-DM1 in the second-line setting?
- Have you use trastuzumab deruxtecan earlier than the third- or fourth-line setting?

RTP RESEARCH TO PRACTICE

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

Dr Ann Partridge

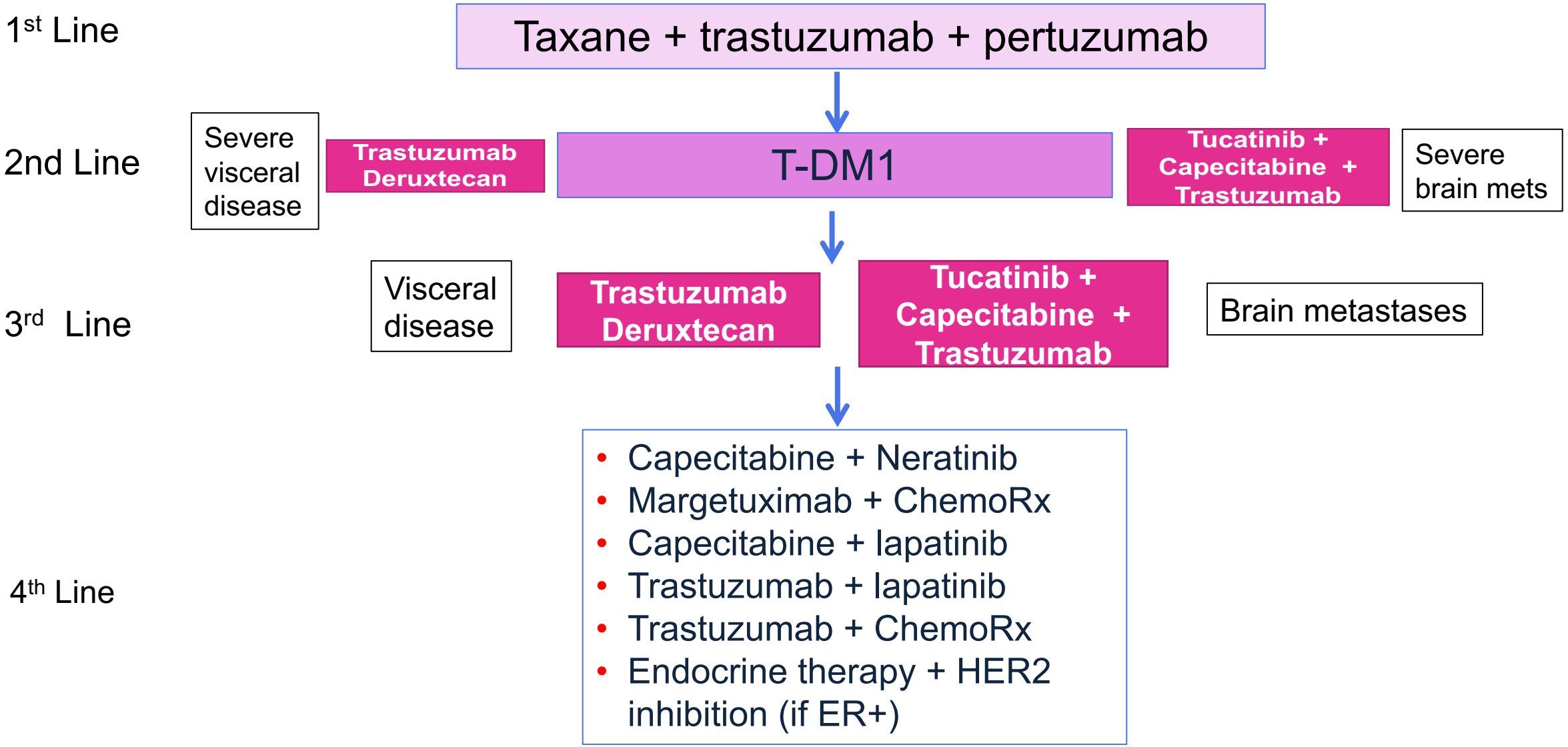
- 2015: Initial diagnosis of ER-positive, HER2-positive BC, metastases to the the liver, lung and peritoneum and bones
- THP x 6 months followed by HP alone → tamoxifen → T-DM1
- AVIATOR clinical trial of trastuzumab with vinorelbine/avelumab
- Tucatinib with trastuzumab/capecitabine
- Considering rebiopsy to confirm HER2 status
- Germline mutation testing: negative for BRCA 1, BRCA 2 and p53

Question

- Would you rebiopsy the tumor at this point?

RTP RESEARCH TO PRACTICE

Clinical Pathway for HER2+ Metastatic Breast Cancer
2021

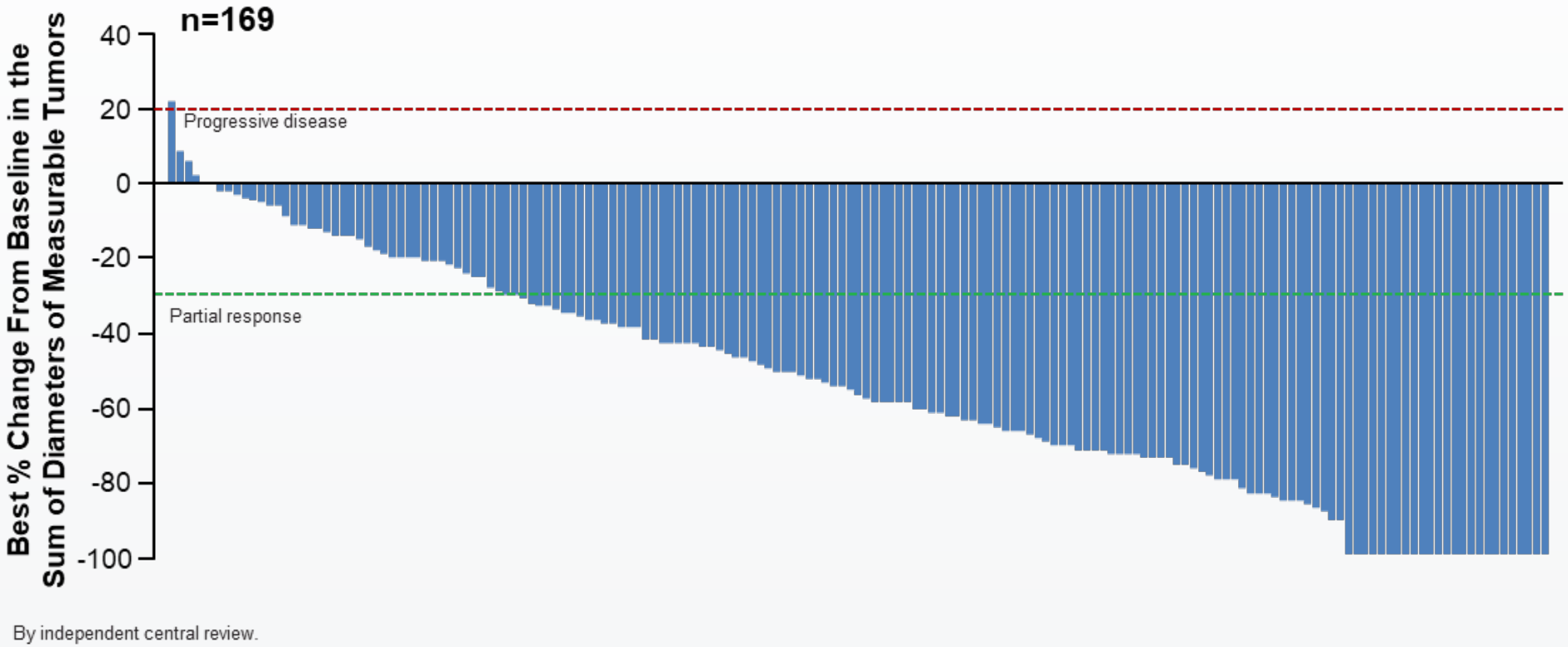


NCCN 2021

Courtesy of Joyce O'Shaughnessy, MD

DESTINY-Breast01: Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in MBC (Updated Results)

Best percentage change from baseline in tumor size



- With increased maturity of the data, the **median DOR was 20.8 months** (95% CI, 15.0-NE)

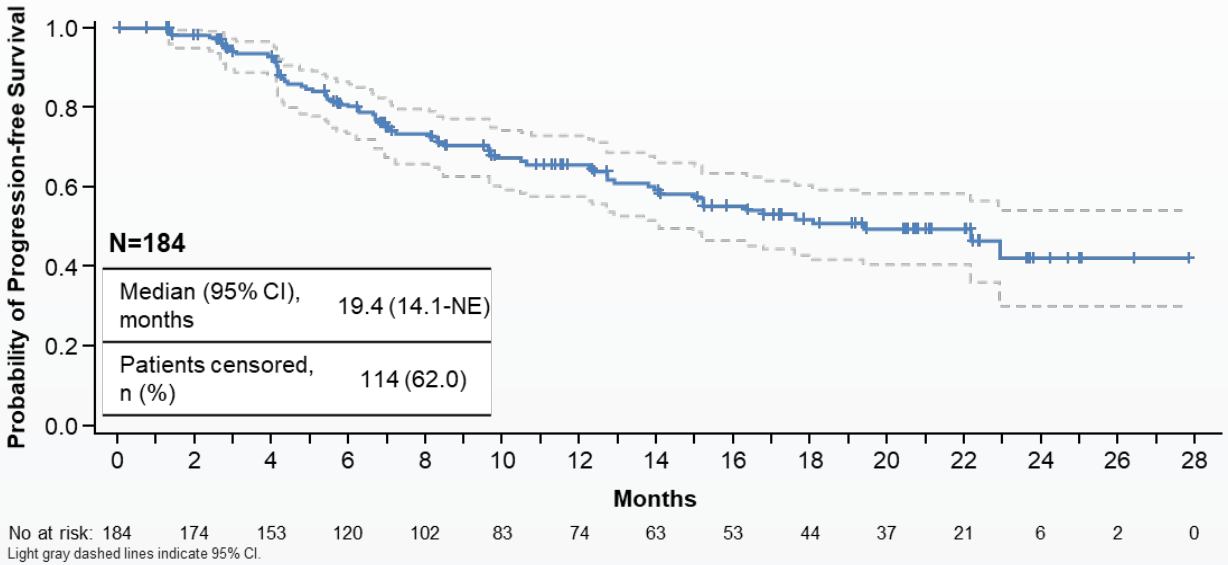
DOR, duration of response; NE, not estimable; MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

1. Modi S et al. *NEJM* 2020;382:610-21; 2. Modi S et al. *SABCS*, Dec 8-11, 2020. Abstr PD3-06.

Courtesy of Joyce O'Shaughnessy, MD

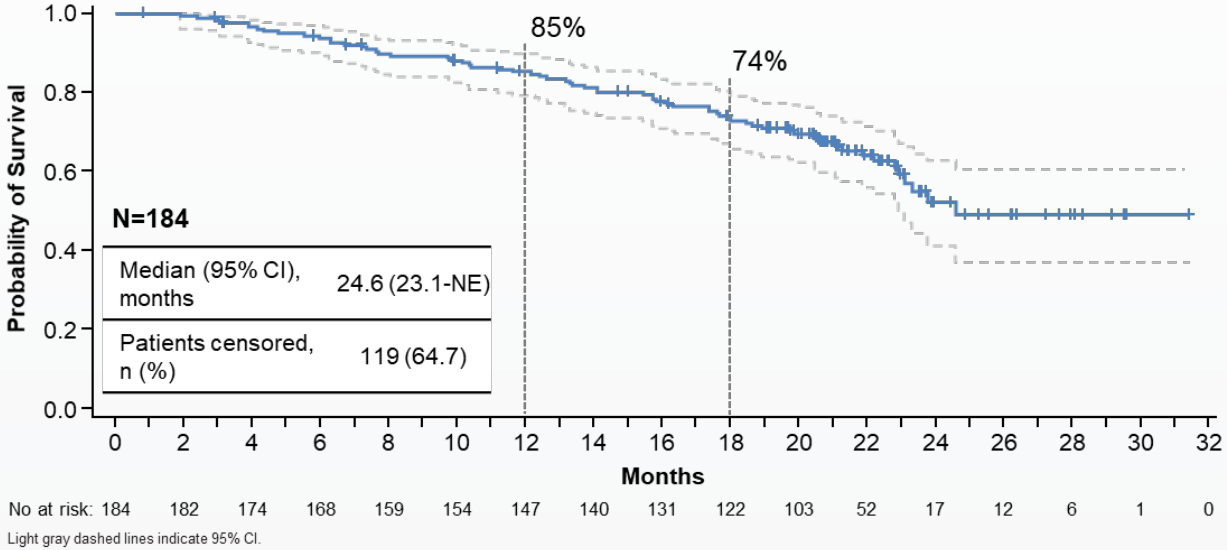
DESTINY-Breast01: Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in MBC (Updated Results)

PFS



- **Median follow-up:** 20.5 mos (range, 0.7-31.4 mos)
- **Median PFS**: 19.4 mos (95% CI, 14.1-NE)

OS



- **Estimated OS:** median 24.6 mos (95% CI, 14.1-NE)
  - 12 mos: 85% (95% CI, 79-90)
  - 18 mos: 74% (95% CI, 67-80)

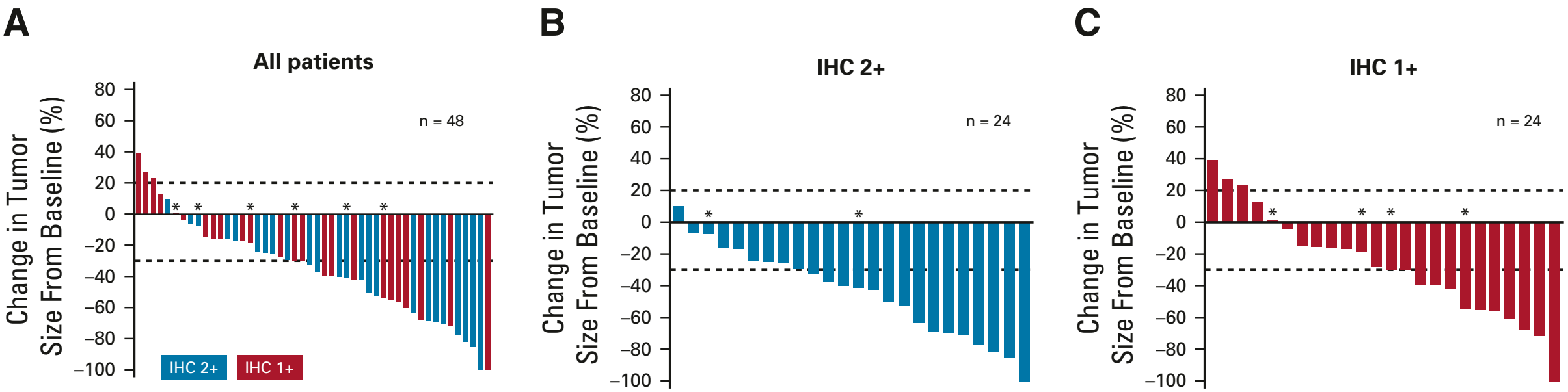
MBC, metastatic breast cancer; NE, not estimable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

1. Modi S et al. *NEJM* 2020;382:610-21; 2. Modi S et al. *SABCS*, Dec 8-11, 2020. Abstr PD3-06.

Courtesy of Joyce O'Shaughnessy, MD

Trastuzumab Deruxtecan for HER2 Low Breast Cancer

Similar Benefit for HER2 2+ and 1+



ORR=37%

mPFS = 11.1 mo

ORR=35.7%

ORR=38.5%

Modi S et al, JCO 2020

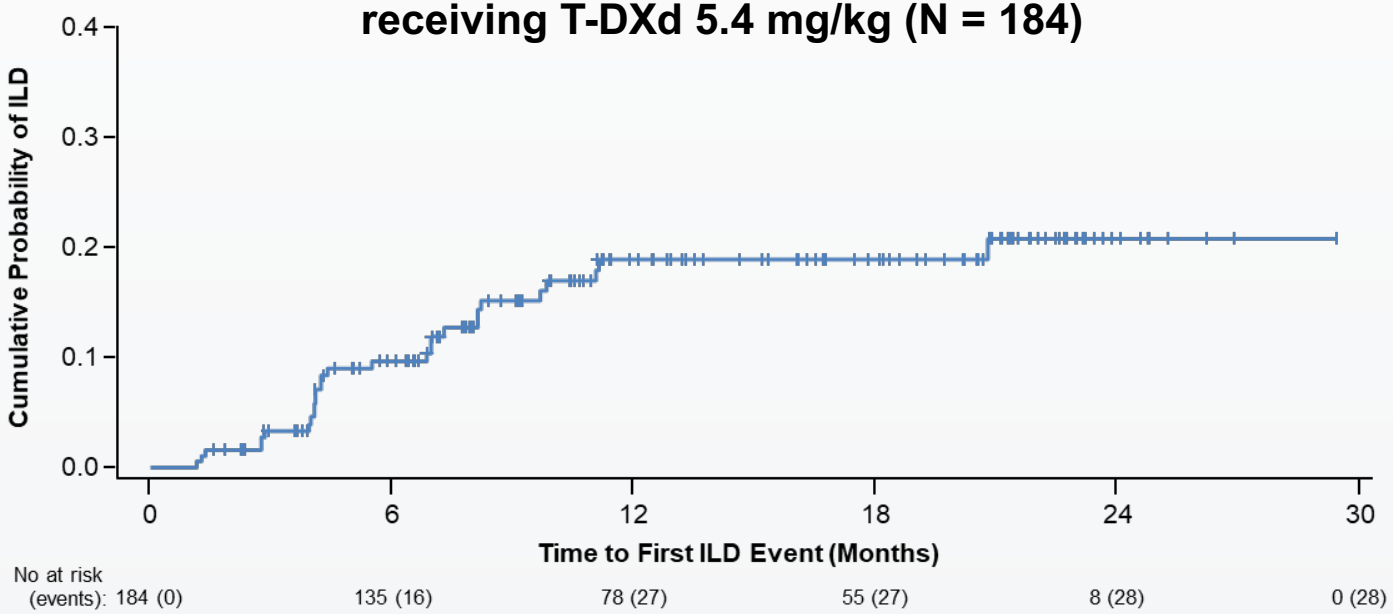
Courtesy of Joyce O'Shaughnessy, MD

DESTINY-Breast01: Interstitial Lung Disease Associated with Trastuzumab Deruxtecan

Incidence of interstitial lung disease among patients receiving T-DXd 5.4 mg/kg (N = 184)*

Data cutoff	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aug 2019	25 (13.6%)	5 (2.7%)	15 (8.2%)	1 (0.5%)	0	4 (2.2%)
Jun 2020	28 (15.2%)	6 (3.3%)	16 (8.7%)	1 (0.5%)	0	5 (2.7%)

Cumulative probability of adjudicated drug-related any-grade ILD among patients receiving T-DXd 5.4 mg/kg (N = 184)



*As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan. 1. Modi S et al. *NEJM* 2020;382:610-21; 2. Modi S et al. *SABCS*, Dec 8-11, 2020. Abstr PD3-06.

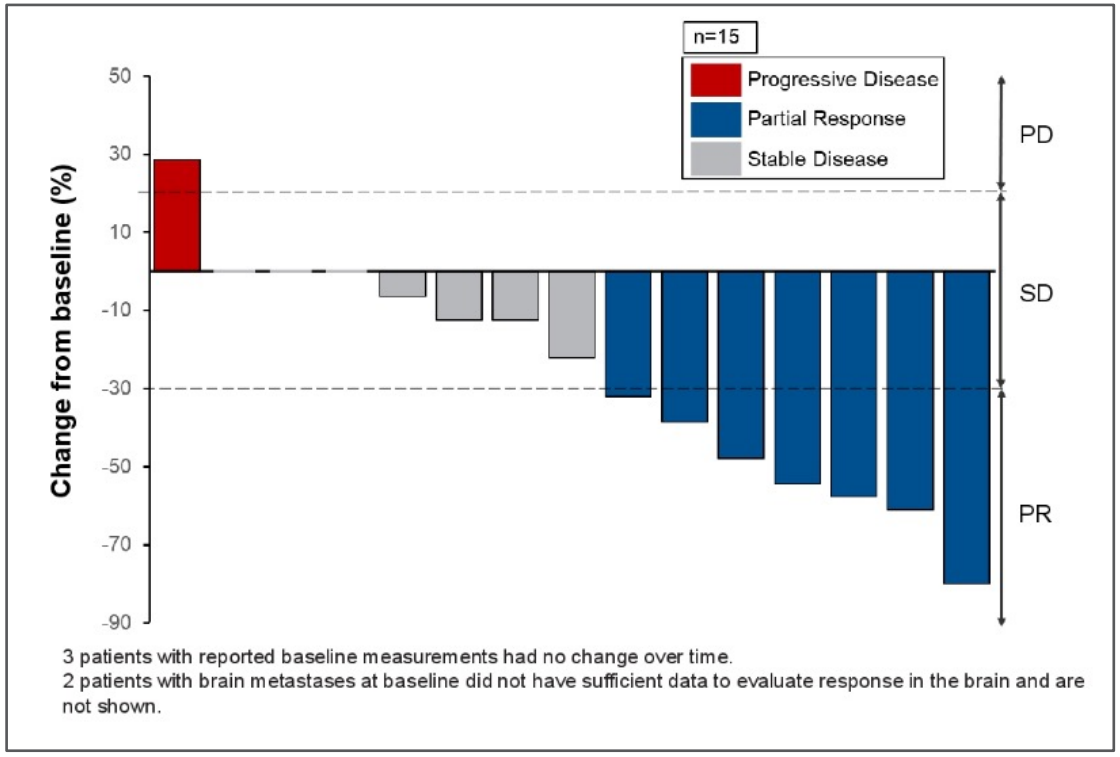
Courtesy of Joyce O'Shaughnessy, MD

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

Jerusalem GH et al.
ASCO 2021;Abstract 526.

DESTINY Breast-01: Efficacy with T-DXd – CNS Subgroup

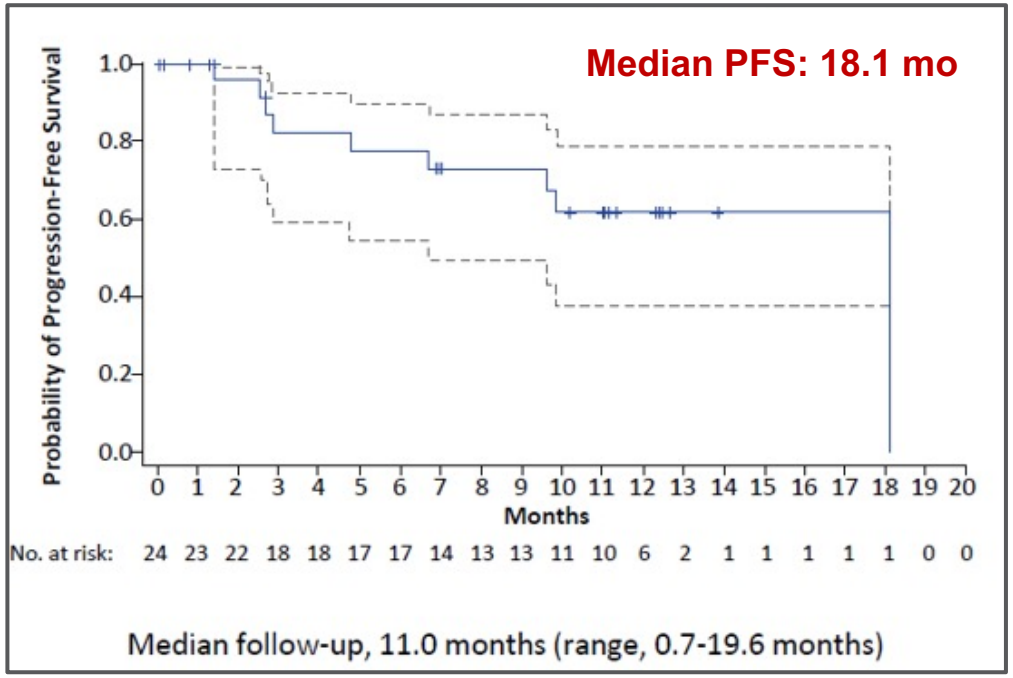
Best response in brain lesions in CNS subgroup[1]



CNS subgroup N=24
Brain lesions at BL n=17
Evaluable for response in brain n=15

❖ 7/17 pts with brain lesions at BL had a PR in CNS lesions (41.2%)

PFS in CNS subgroup[2] (n=24)



- Confirmed ORR in CNS subgroup: 58.3%
- Median DoR in CNS subgroup: 16.9 months

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Courtesy of Erika Hamilton, MD

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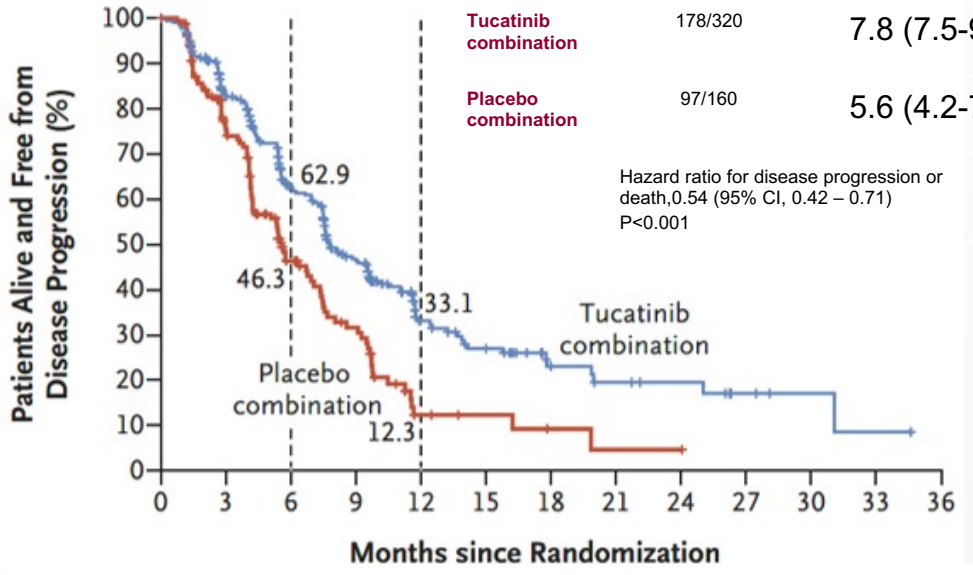
1. Jerusalem G et al ASCO 2021; Abstract 526
2. Jerusalem G et al ESMO Breast 2020

HER2CLIMB:
PFS and OS with Tucatinib in Patients with HER2+ MBC

PFS (primary end-point analysis population*)

	No. of Events / No. of Patients	Mediation Duration (95% CI)
Tucatinib combination	178/320	7.8 (7.5-9.6)
Placebo combination	97/160	5.6 (4.2-7.1)

Hazard ratio for disease progression or death,0.54 (95% CI, 0.42 – 0.71)
P<0.001



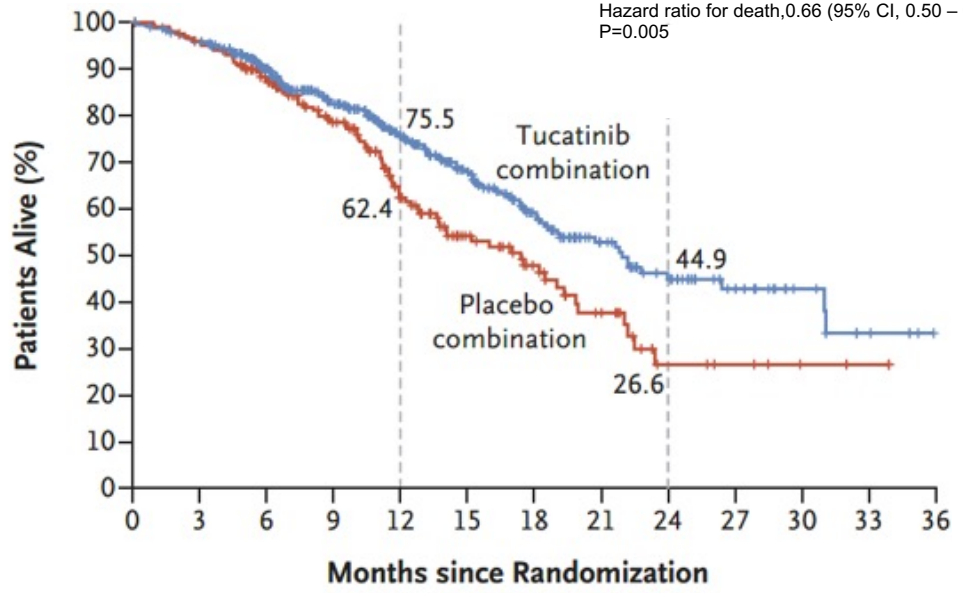
No. at Risk

Tucatinib combination	320	235	152	98	40	29	15	10	8	4	2	1	0
Placebo combination	160	94	45	27	6	4	2	1	1	0	0	0	0

OS (total population†)

	No. of Deaths/No. of Patients	Mediation Duration (95% CI)
Tucatinib combination	130/140	21.9 (18.3 - 31.0)
Placebo combination	85/202	17.4 (13.6 - 19.9)

Hazard ratio for death,0.66 (95% CI, 0.50 – 0.88)
P=0.005



No. at Risk

Tucatinib combination	410	388	322	245	178	123	80	51	34	20	10	4	0
Placebo combination	202	191	160	119	77	48	32	19	7	5	2	1	0

- 47.5% (n=291) patients had brain metastases at baseline
- Patients with both active and stable brain metastases were included

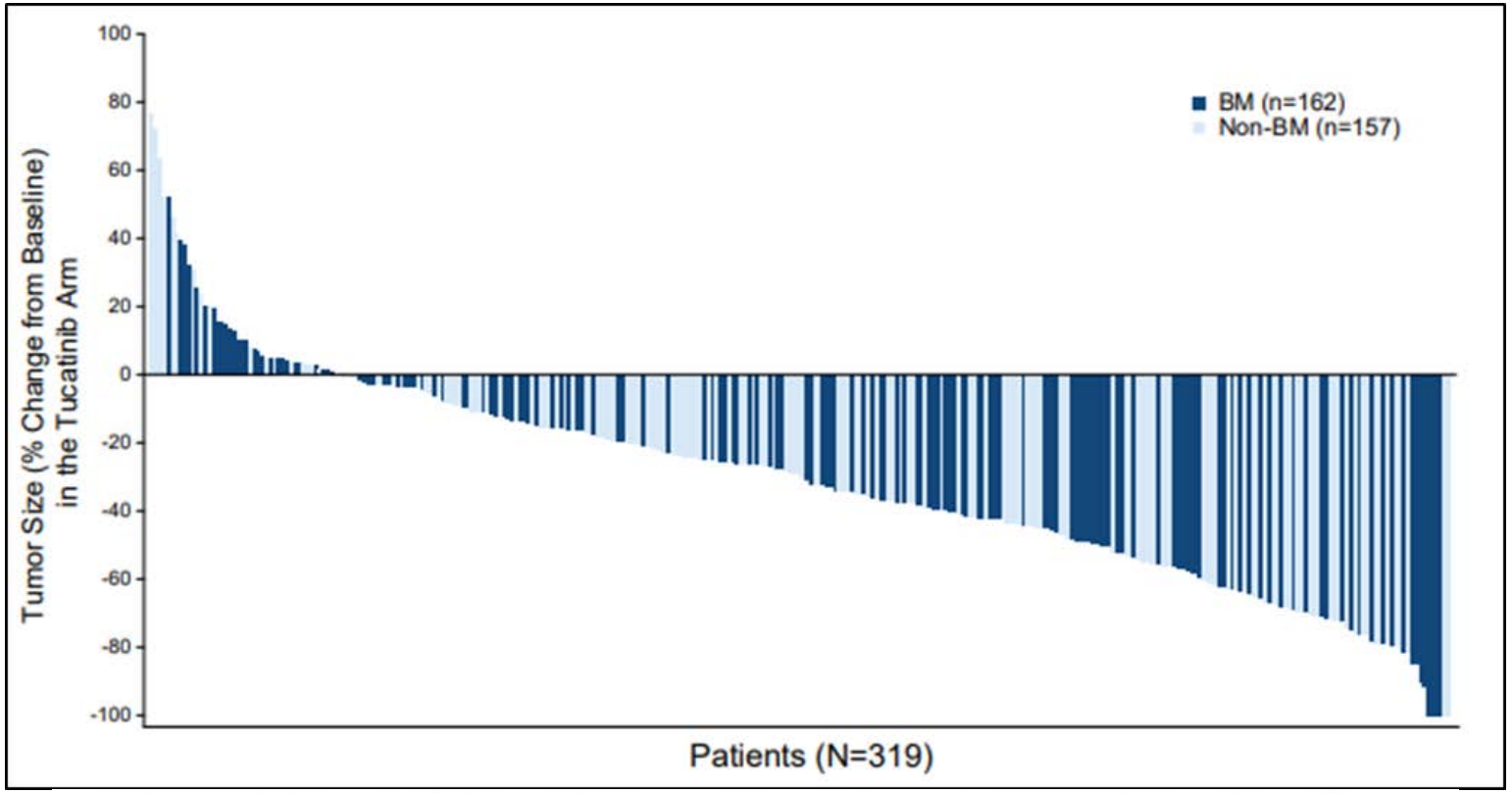
*Estimated PFS at 1 year among first 480 patients randomized; †Estimated OS at 2 years among total population of 612 patients randomized; HR: hazard ratio; ICR: independent central review; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; T-DM1: trastuzumab emtansine

Murthy RK et al. *NEJM* 2019;382:597-609

Courtesy of Joyce O'Shaughnessy, MD

HER2CLIMB: Change in tumor size in the tucatinib arm

Change in tumor size based on RECIST v1.1 on Tucatinib arm (regardless of presence/absence of brain mets)



BM: Brain mets

- The DCR was 92% in the tucatinib arm and 85% in the placebo arm.

Courtesy of Erika Hamilton, MD

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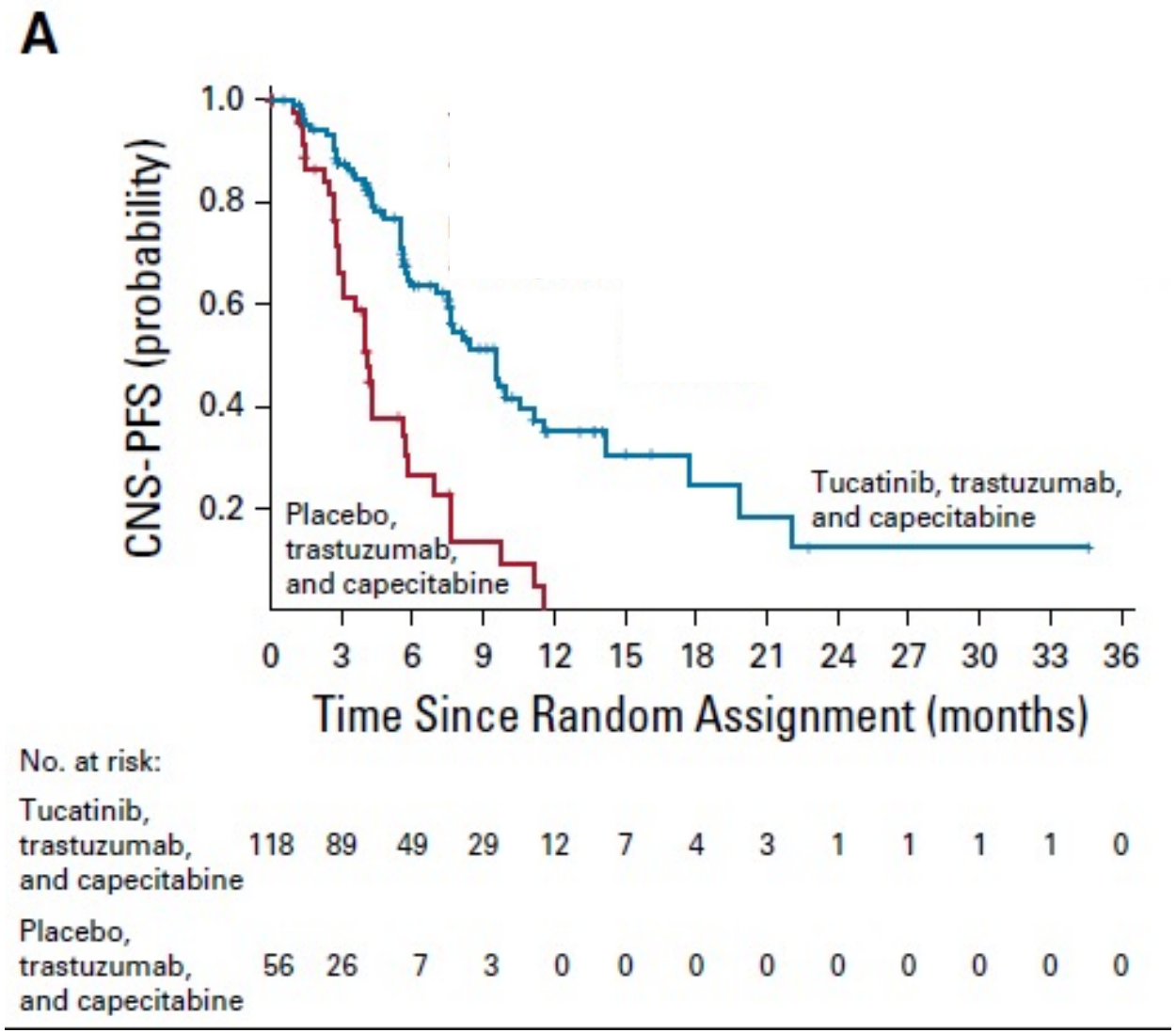
Bachelot T et al. ESMO 2020

HER2CLIMB: CNS-PFS benefit in patients with brain metastases



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	Median PFS (months)
Tucatinib arm	9.5
Placebo arm	4.1
	HR 0.36 p <0.00001

Risk of progression or death in patients with active brain mets was reduced by 64%

Courtesy of Erika Hamilton, MD

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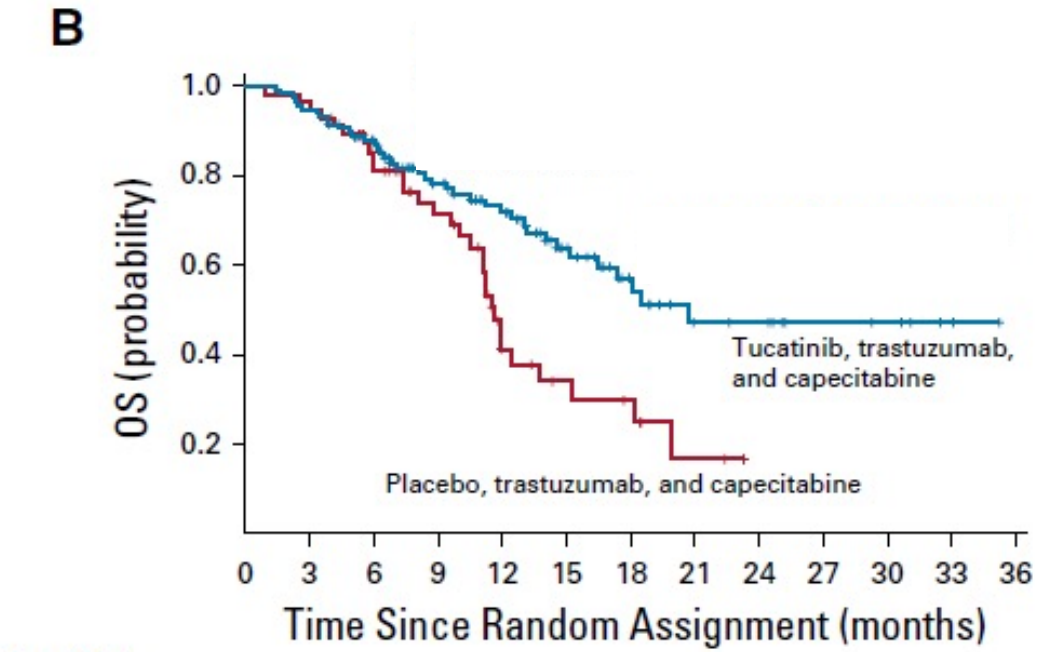
Lin NU et al. JCO 2020

HER2CLIMB: Overall survival in patients with brain metastases



	Median OS (months)
Tucatinib arm	20.7
Placebo arm	11.6
	HR 0.49 p 0.004

Risk of death in patients with active brain mets was reduced by 51%

Health related QoL assessed in pts with brain mets (n=164):

- Addition of Tucatinib to cape/trastuzumab significantly prolonged time to worsening of HRQoL EQ-5D-5L Health Score
- Compared to the placebo arm, pts on tucatinib arm has 49% reduction in the risk of deterioration

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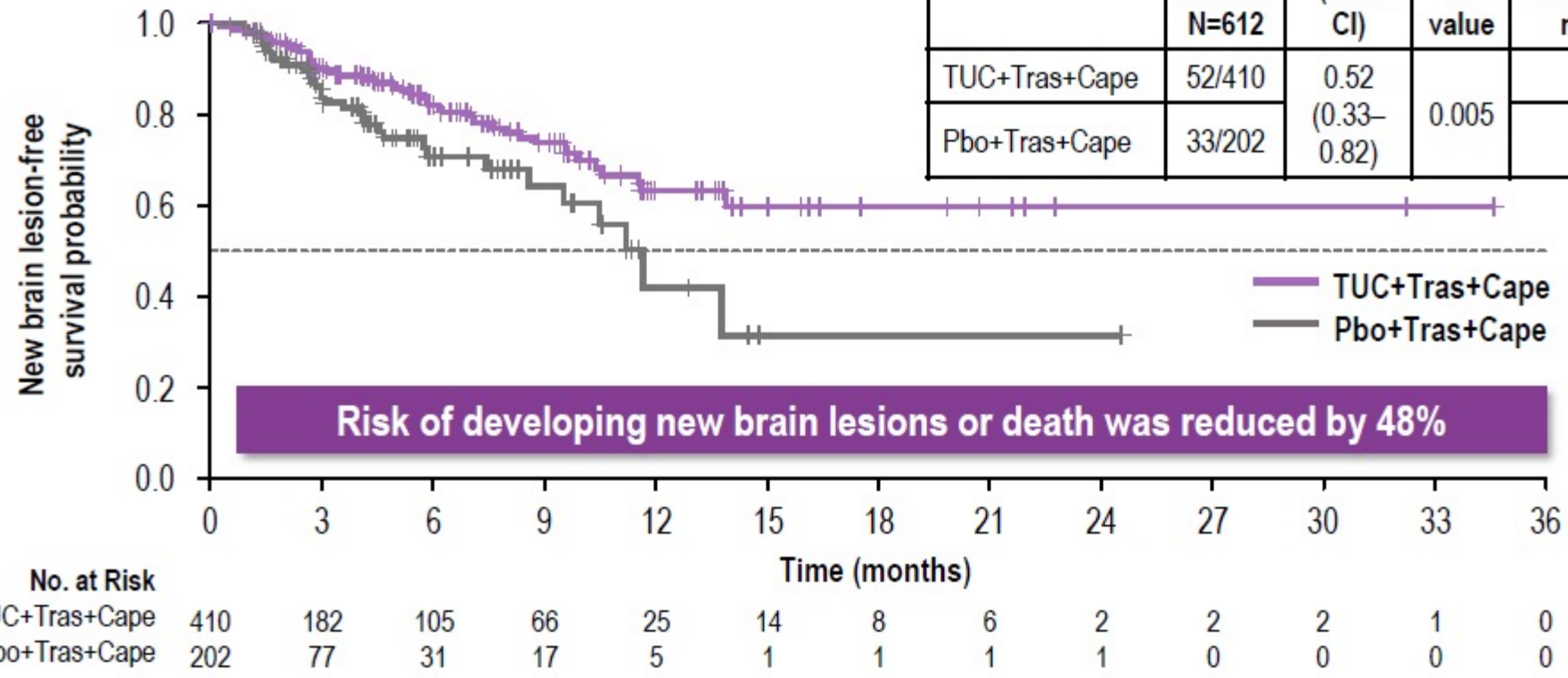
Courtesy of Erika Hamilton, MD

Lin NU et al. JCO 2020

HER2CLIMB: Time to new brain lesions or death (all patients)

	Events N=612	HR (95% CI)	P value	Median new brain lesion-free survival, months (95% CI)
TUC+Tras+Cape	52/410	0.52 (0.33–0.82)	0.005	NR (13.9–NR)
Pbo+Tras+Cape	33/202			11.7 (9.5–NR)



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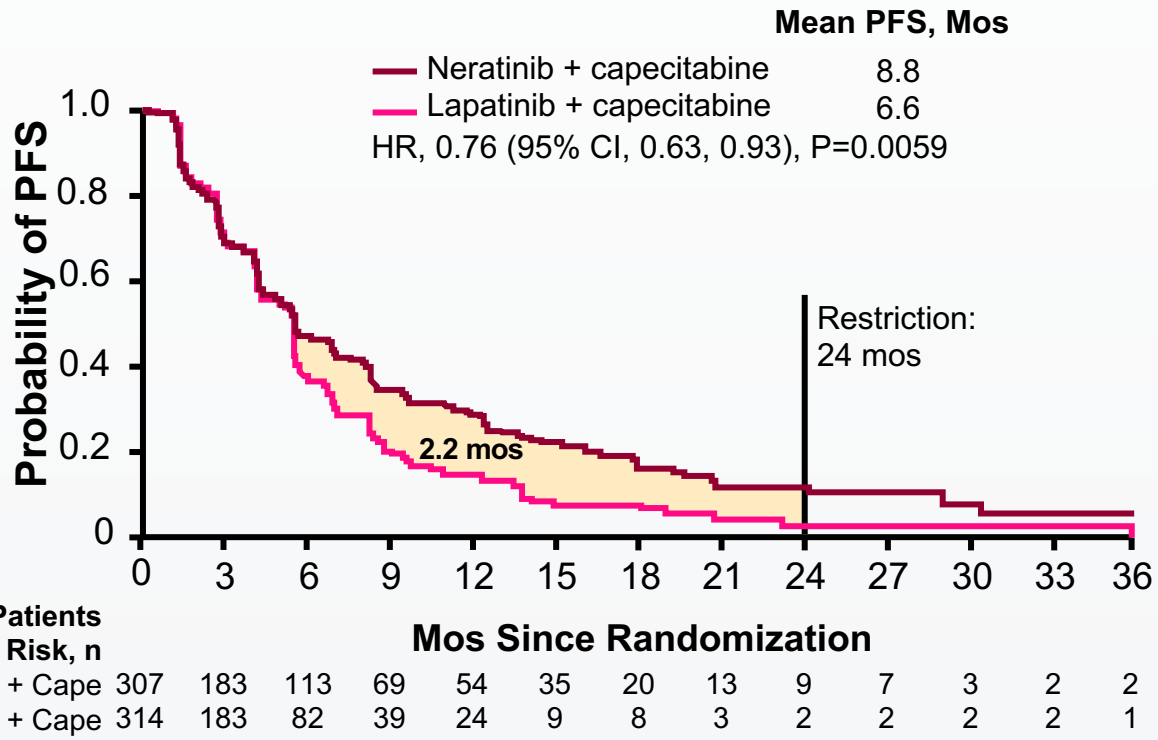
Courtesy of Erika Hamilton, MD

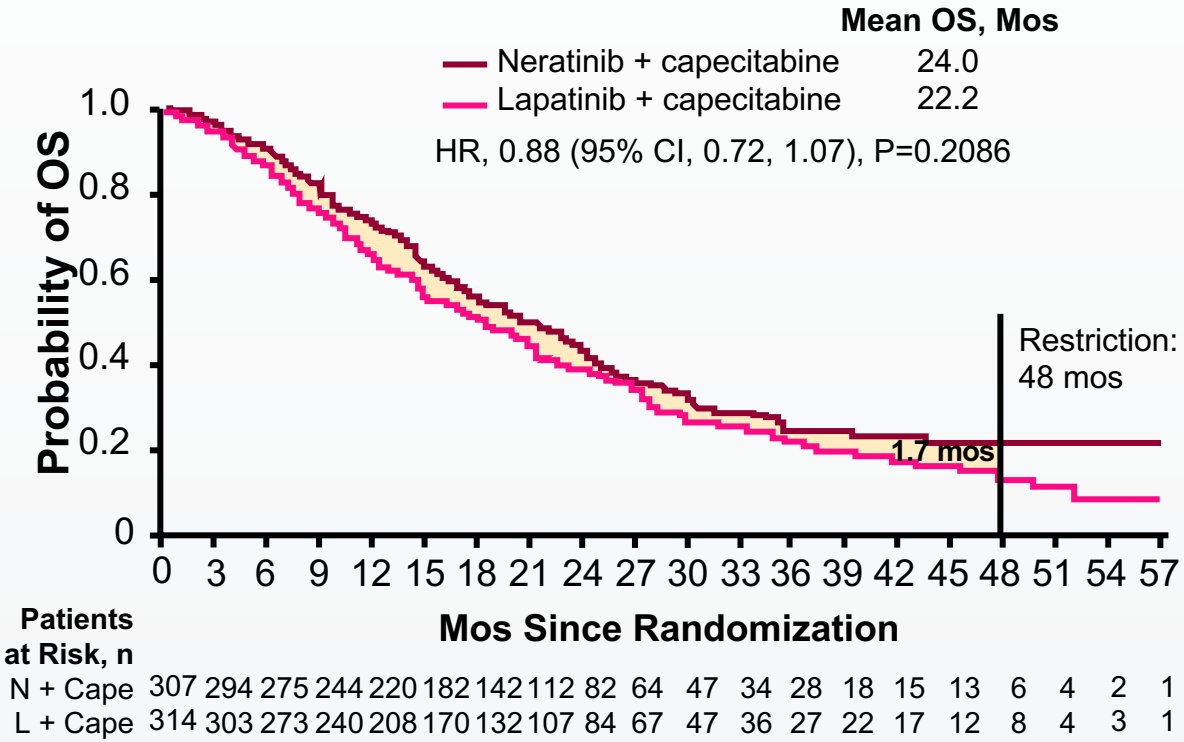
Bachelot T et al ESMO 2020

NALA:
PFS and OS with Neratinib in Patients with HER2+ MBC

PFS (centrally assessed)



OS (coprimary endpoint)



PFS, progression-free survival; OS, overall survival

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

Courtesy of Joyce O'Shaughnessy, MD

NALA: Outcomes in patients with CNS disease

NALA: Phase III study of Neratinib+capecitabine vs Lapatinib+capecitabine in HER2+ MBC

Table 1. Efficacy outcomes in patients with CNS disease at baseline

	CNS metastases at baseline (n=101)		
	N+C (n=51)		L+C (n=50)
Progression-free survival[a]			
Hazard ratio (95% CI)		0.66 (0.41–1.05)	
P-value		0.0741	
Restricted mean PFS[b], months	7.8		5.5
Difference, months		2.3	
Overall survival			
Hazard ratio (95% CI)		0.90 (0.59–1.38)	
P-value		0.6352	
Restricted mean OS[b], months	16.4		15.4
Difference, months		1.0	

CNS-specific outcomes	N+C (n=51)		L+C (n=50)
CNS progression-free survival			
Median, months	12.4		8.3
Hazard ratio (95% CI)		0.62 (0.32–1.18)	
P-value		0.143	

81 patients (80.2%) had received prior CNS-directed radiotherapy and/ or surgery

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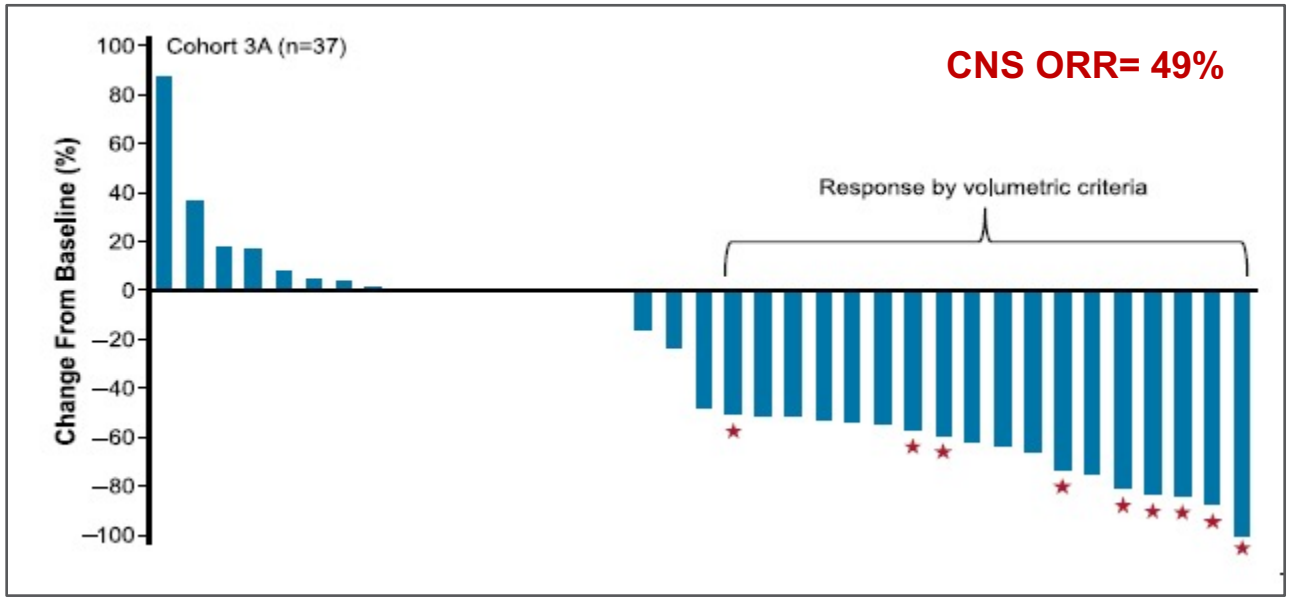
Courtesy of Erika Hamilton, MD

Saura C et al. SABCS 2020 Abstract PD13-09

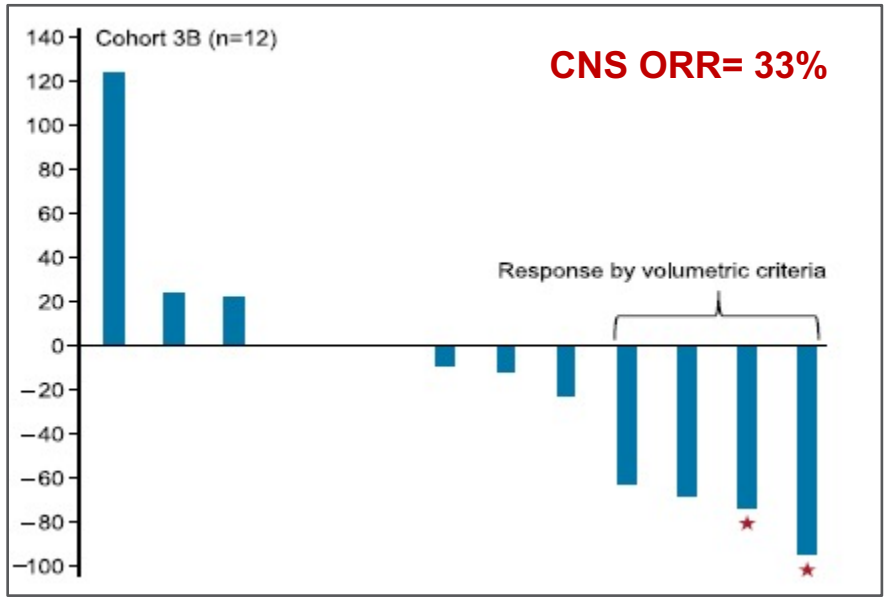
Neratinib+capecitabine for HER2+ BC pts with brain mets

TBCRC 022: Phase II study of Neratinib+capecitabine in HER2+ MBC pts with brain mets

No prior treatment with Lapatinib



Prior treatment with Lapatinib



★ Patients who also had a CNS response by RANO-brain mets criteria

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Courtesy of Erika Hamilton, MD

Freedman RA *et al*. JCO. 2019;37:1081

Ongoing Phase 3 Clinical Trials of Investigational Regimens for Advanced HER2+ BC

	DESTINY02[1]	TULIP[2]	DESTINY03[3]	HER2CLIMB-02[4]
Line of therapy	3rd-line	3rd-line	2nd-line	2nd-line
Trial design	Phase 3 randomized, open-label, active-controlled	Phase 3 randomized, open-label, active-controlled	Phase 3 randomized, open-label, active-controlled	Phase 3 randomized, double-blind, placebo-controlled
Treatment arms	TDXd Physician's choice (capecitabine + lapatinib or trastuzumab)	Trastuzumab duocarmazine Physician's choice	TDXd T-DM1	Tucatinib + T-DM1 Placebo + T-DM1
Planned patient numbers	~600	345 (planned), 436 (actual)	~500	~460
Prior treatment	HER2 therapies, including T-DM1	≥2 HER2-targeted regimens or T-DM1	Trastuzumab + taxane; no prior HER2-targeted ADC	Trastuzumab + taxane
Primary endpoint	Median ICR PFS	Median ICR PFS	Median ICR PFS	Median INV PFS
Est. completion	Sep 2024	Jul 2021	Apr 2023	Apr 2024

ADC: antibody-drug conjugate; ; ICR, independent review committee; INV, investigator-assessed; PFS, progression-free survival; T-DM1: trastuzumab emtansine; TDXd: trastuzumab deruxtecan

1. www.clinicaltrials.gov NCT03523585; 2. www.clinicaltrials.gov NCT03262935; 3. www.clinicaltrials.gov NCT03529110; 4. Hurvitz SA et al. *Ann Oncol* 2020;31:S390.

Courtesy of Joyce O'Shaughnessy, MD

Positive Topline Results of Pivotal Phase III TULIP® Study in HER2-Positive Unresectable Locally Advanced or Metastatic BC

The Phase III TULIP study of the antibody-drug conjugate (ADC) trastuzumab duocarmazine (SYD985) versus Physician's Choice in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer met its primary endpoint of progression-free survival (PFS), demonstrating a statistically significant improvement over physician's choice. PFS is defined as the time from the date of randomization to the date of first documented disease progression or death due to any cause, whichever occurred earlier. The study also demonstrated preliminary supportive overall survival (OS) results.

https://www.prnewswire.com/news-releases/byondis-announces-positive-topline-results-of-pivotal-phase-iii-tulip-study-in-patients-with-her2-positive-unresectable-locally-advanced-or-metastatic-breast-cancer-301306890.html

Courtesy of Joyce O'Shaughnessy, MD

Phase III DESTINY-Breast09 trial for HER2-positive metastatic BC initiated

The first patient was dosed on the DESTINY-Breast09, a head-to-head phase III trial evaluating the safety and efficacy of trastuzumab deruxtecan (T-DXd) with or without pertuzumab compared to standard of care (THP: taxane, trastuzumab and pertuzumab) as a potential first-line treatment in patients with HER2 positive metastatic breast cancer on June 14, 2021. This is the first trial to evaluate T-DXd in the first-line metastatic setting in patients with HER2 positive breast cancer.

https://www.businesswire.com/news/home/20210614005114/en/DESTINY-Breast09-Head-to-Head-First-Line-Phase-3-Trial-of-ENHERTU%C2%AE-Initiated-in-Patients-with-HER2-Positive-Metastatic-Breast-Cancer

Courtesy of Joyce O'Shaughnessy, MD

Agenda

Module 1: Role of Immunotherapy in HER2-Positive Metastatic Breast Cancer (mBC)?

- Dr Mahtani: A 56-year-old woman with ER-positive, HER2-positive mBC enrolled on a clinical trial of nivolumab/ipilimumab

Module 2: Management of HER2-Positive mBC

- Dr Partridge: A 30-year-old woman with ER-positive, HER2-positive mBC
- Dr Mahtani: A 72-year-old woman with HER2-positive mBC
- Dr O'Regan: A 58-year-old woman with ER-negative, HER2-positive mBC
- Dr Partridge: A 50-year-old woman with ER-positive, HER2-positive mBC

Module 3: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer

- Dr Mahtani: A 44-year-old woman with 5-cm ER-positive, HER2-positive localized breast cancer
- Dr O'Regan: A 53-year-old woman with 4.5-mm ER-positive, HER2-positive breast cancer

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

1. None
2. Paclitaxel/trastuzumab
3. Paclitaxel/trastuzumab/pertuzumab
4. ACTH (doxorubicin/cyclophosphamide/paclitaxel/trastuzumab)
5. ACTHP (ACTH/pertuzumab)
6. TCH (docetaxel/carboplatin/trastuzumab)
7. TCHP (TCH/pertuzumab)
8. Other

A 65-year-old woman presents with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven positive axillary nodes and receives neoadjuvant TCHP. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend if at surgery the patient were found to have a pathologic complete response?

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

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Mahtani: A 44-year-old woman with 5-cm ER-positive, HER2-positive localized breast cancer

Dr Reshma Mahtani

- 1/2020: Presents with palpable right breast mass and bloody nipple discharge from the left nipple she had noted back in July 2019 but attributed to having stopped breast feeding
  - Imaging: multi focal disease in the right breast with largest mass 5-cm extending to subareolar region, prominent right axillary nodes.
  - Biopsy: right breast mass and node IDC, grade 3, ER98%, PR25%, HER2 3+
  - Biopsy: Left breast with multi-focal disease, no abnormal nodes. Biopsy of largest LEFT breast mass (2cm), IDC, grade 1, ER95%, PR 50%, HER2 1+
- Genetic testing: negative (multi-gene panel)
- Neoadjuvant TCHP → surgery → complete response on right side, residual low grade IDC, 2cm on left, 0/2 SLN
- Completed adjuvant radiation and HP; given OFS and AI

Question

- Would you offer this patient extended adjuvant therapy with neratinib?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr O'Regan: A 53-year-old woman with 4.5-mm ER-positive, HER2-positive breast cancer

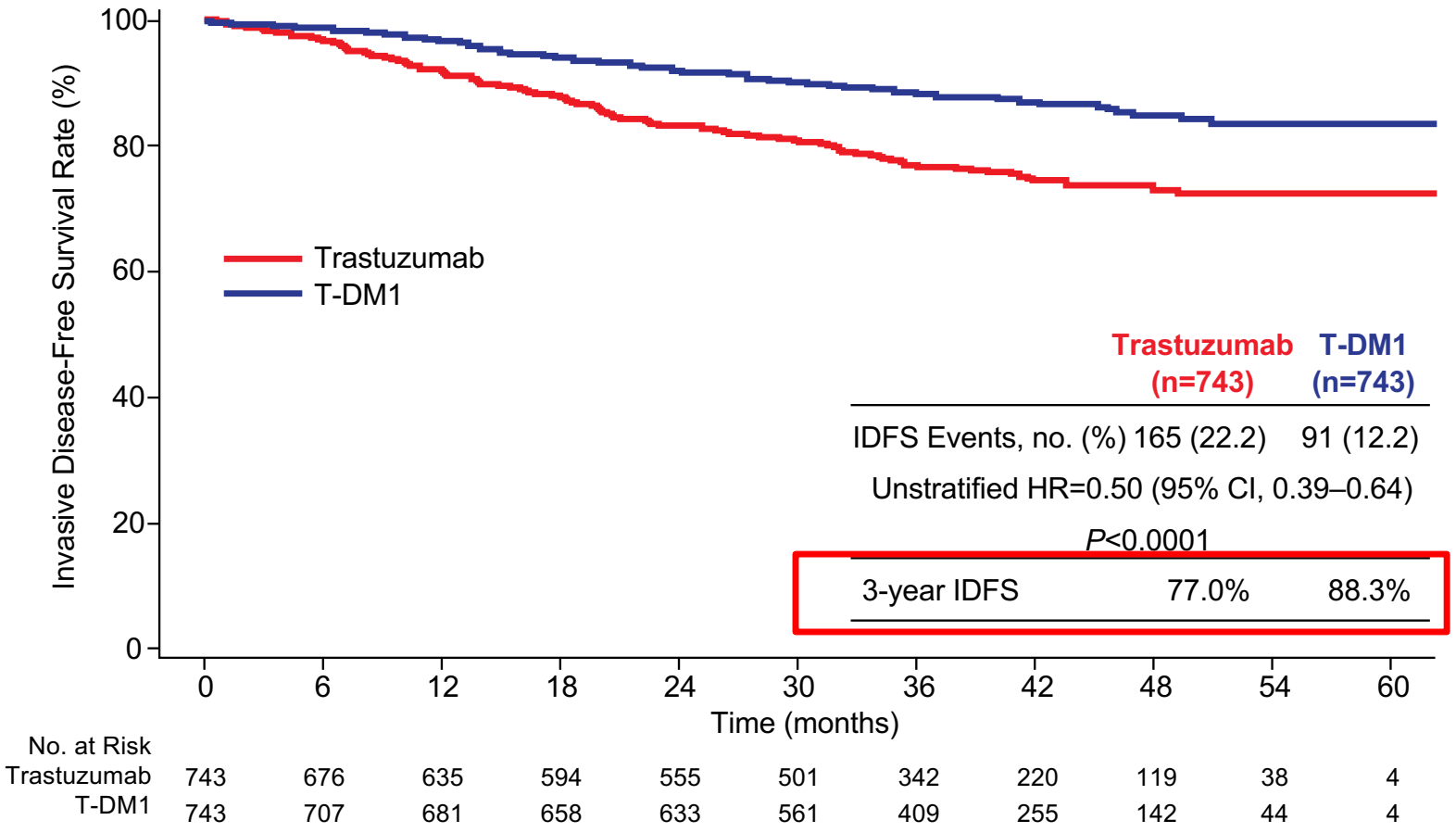
Dr Ruth O'Regan

- Presents with abnormal mammogram for both breasts
  - Biopsy: DCIS
- Bilateral mastectomies with SLNB (node-negative)
- Biopsy: 4.5 mm ER-positive, PR-negative, HER2-positive (IHC3+) breast cancer in right breast
- Repeat FISH on tumor sample

Questions

- How would you manage her? Would you feel strongly about treating her with paclitaxel/trastuzumab?
- Would you give a patient like this T-DM1?

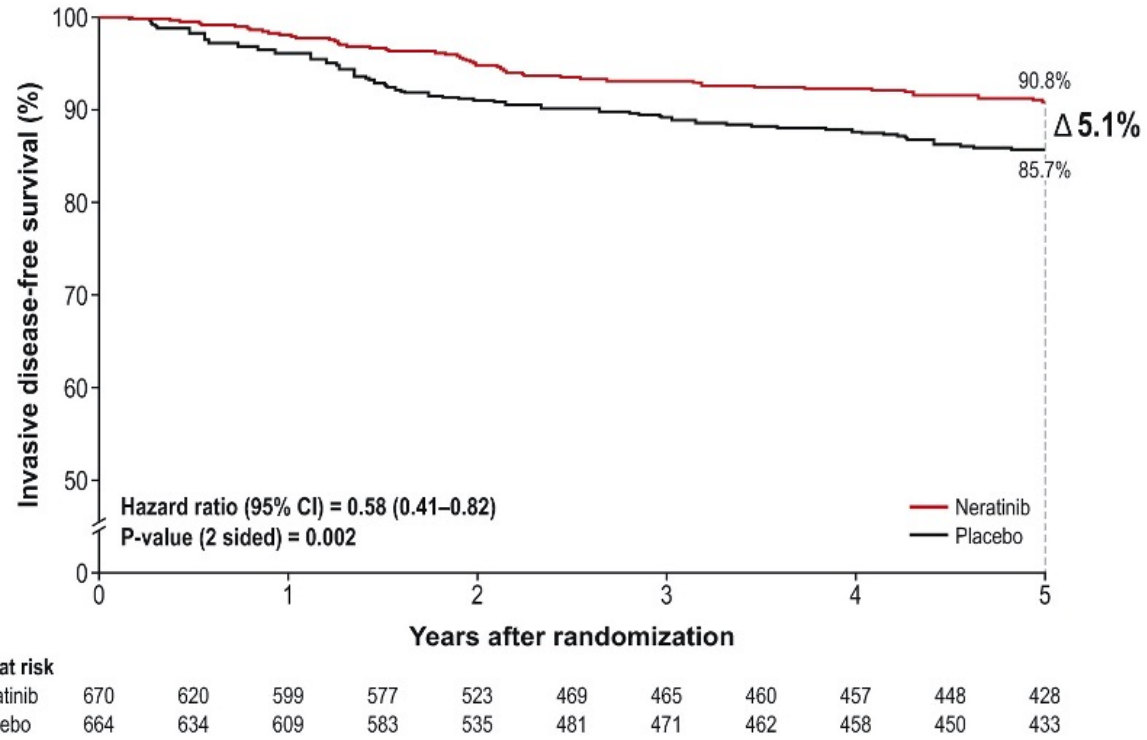
KATHERINE: Invasive Disease-Free Survival



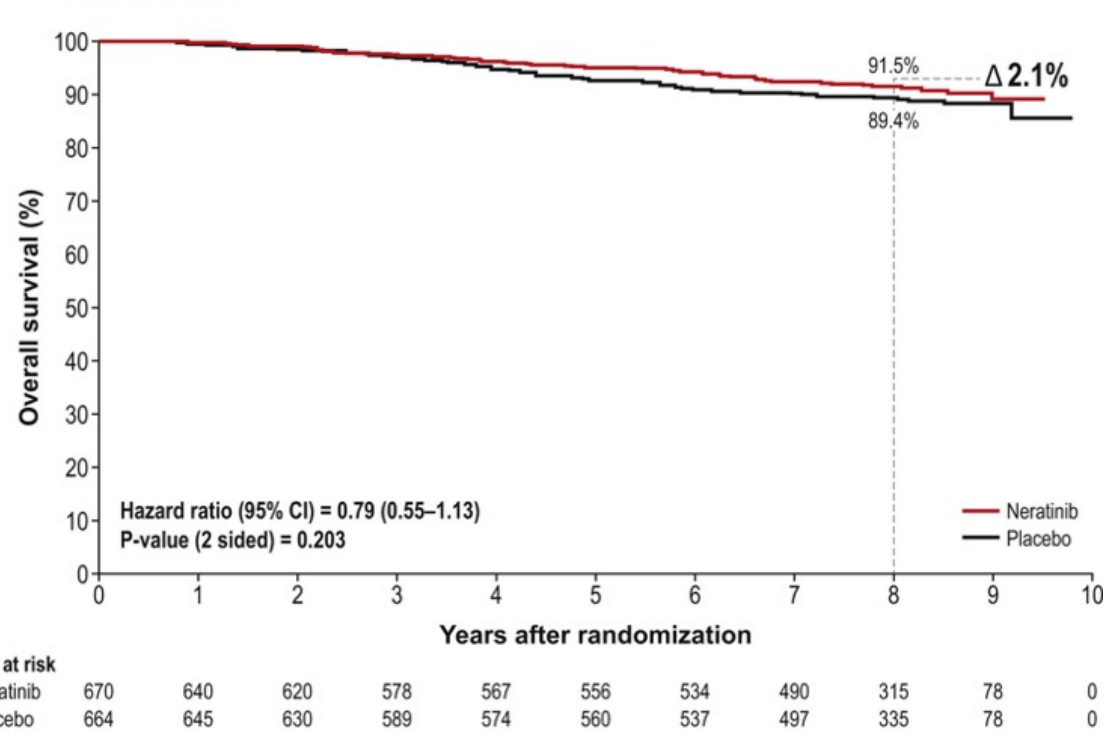
Courtesy of Ian E Krop, MD, PhD

ExteNET: Updated analysis of patients HR+ and ≤1 year from trastuzumab

iDFS at 5yrs



Overall Survival

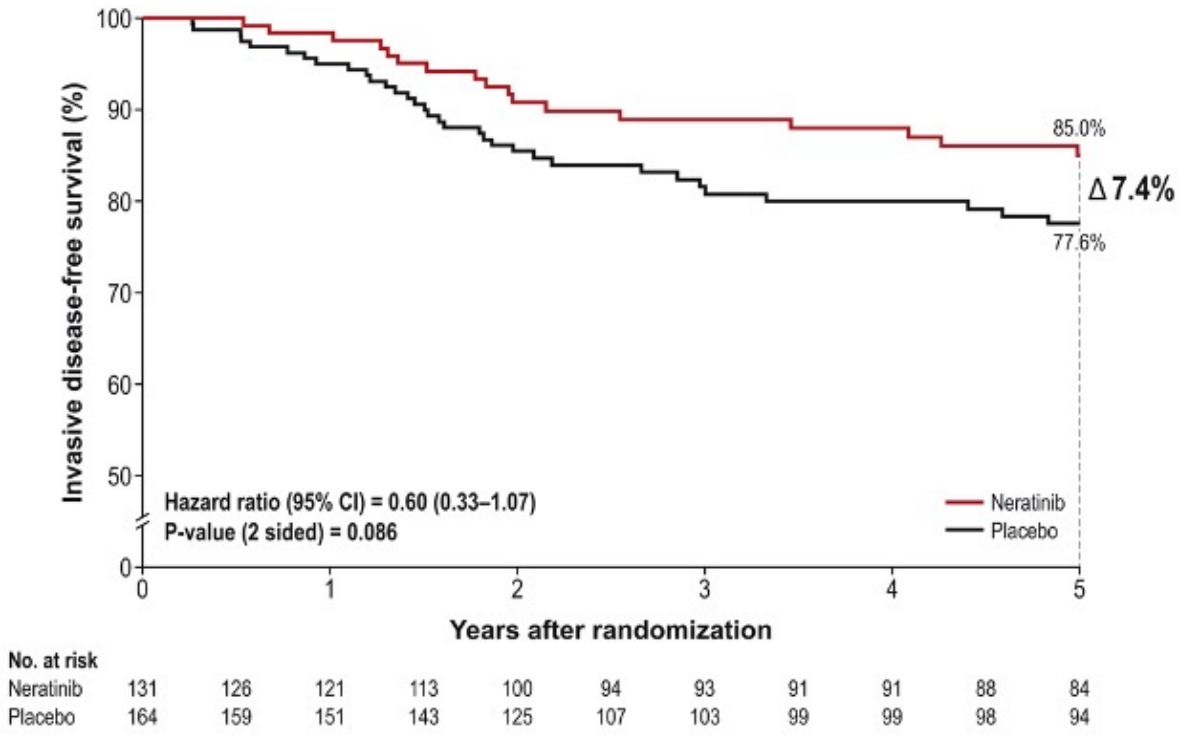


Chan et al Clin Breast Cancer 2021 Feb;21(1):80-91.e7.

Courtesy of Ian E Krop, MD, PhD

ExteNET: Outcomes in HR+, ≤1 year from trastuzumab, and with residual disease after neoadjuvant therapy

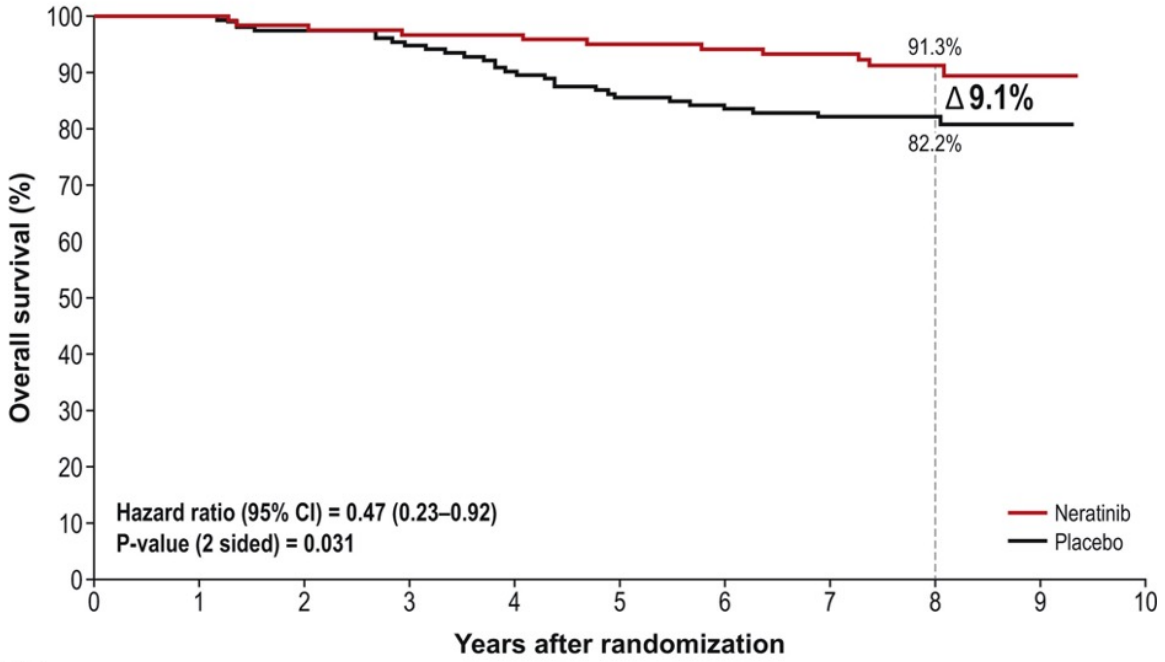
iDFS at 5yrs



No. at risk

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

Overall Survival



No. at risk

Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

Chan et al Clin Breast Cancer 2021 Feb;21(1):80-91.e7.

Courtesy of Ian E Krop, MD, PhD

ExteNET: Cumulative incidence of CNS disease as 1st site of recurrence

Population or Subgroup	CNS Events (No. Patients)		Cumulative Incidence of CNS Recurrences at 5 Years, % (95% CI)	
	Neratinib	Placebo	Neratinib	Placebo
$HR^+/\leq$ 1-year population	4 (670)	12 (664)	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Nodal status				
Positive	4 (540)	10 (539)	0.8 (0.3-2.0)	2.2 (1.1-3.8)
Negative	0 (130)	2 (125)	0 (NE)	1.9 (0.4-6.0)
Prior trastuzumab regimen				
Concurrent	2 (411)	8 (415)	0.6 (0.1-1.9)	2.3 (1.1-4.3)
Sequential	2 (259)	4 (249)	0.9 (0.2-3.0)	1.8 (0.6-4.3)
Adjuvant or neoadjuvant therapy				
Adjuvant	3 (508)	6 (472)	0.7 (0.2-2.0)	1.5 (0.6-3.0)
Neoadjuvant	1 (162)	6 (192)	0.7 (0.1-3.3)	3.7 (1.5-7.4)
pCR status[a]				
No	1 (131)	5 (164)	0.8 (0.1-4.0)	3.6 (1.3-7.8)
Yes	0 (17)	1 (21)	0 (NE)	5.0 (0.3-21.2)

Chan et al Clin Breast Cancer 2021 Feb;21(1):80-91.e7.

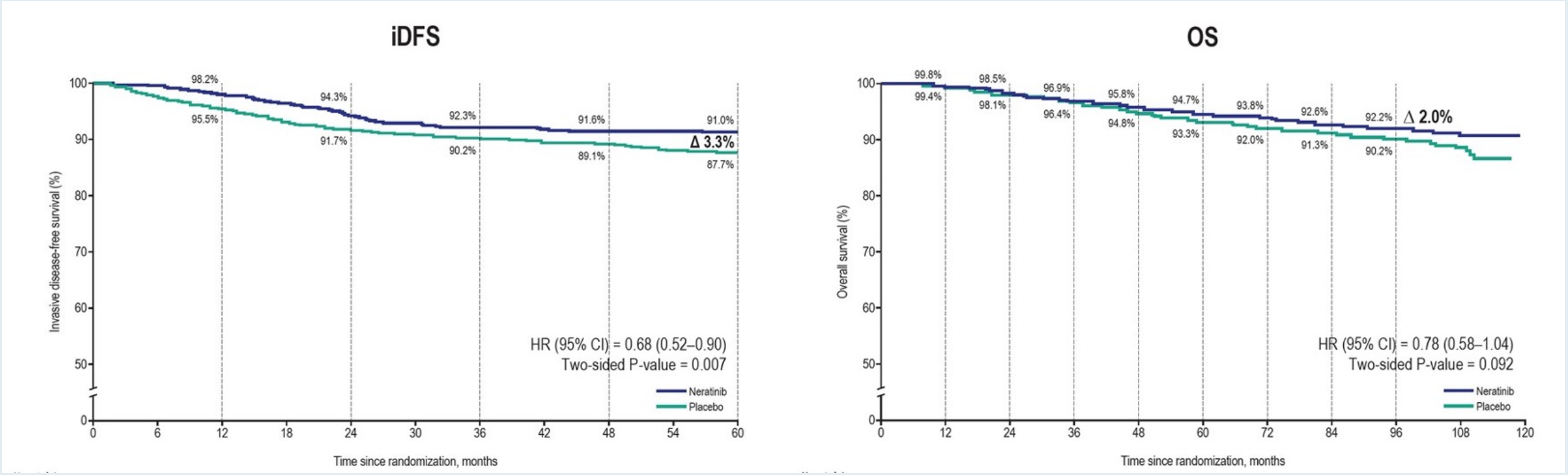
Courtesy of Ian E Krop, MD, PhD

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

Moy B et al.

ASCO 2021;Abstract 540.

ExteNET: iDFS and OS – Completed Neratinib Therapy



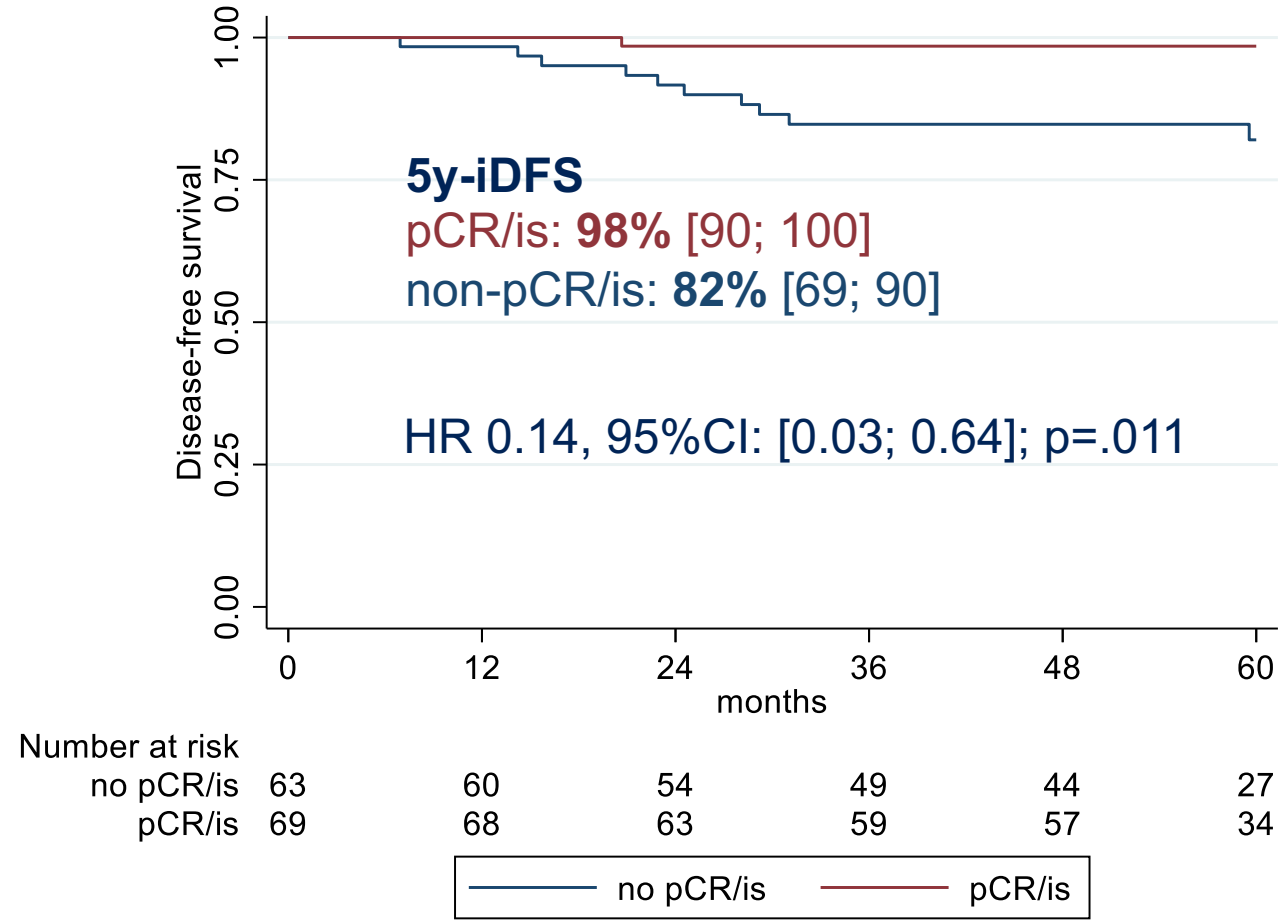
In the ITT population, the HR for OS was reduced from 0.95 to 0.78 upon completion of neratinib therapy.

Moy B et al. ASCO 2021;Abstract 540.

RTP RESEARCH TO PRACTICE

WSG-ADAPT HER2+/HR-

iDFS:
non-pCR vs pCR



Patients with
no further CT after pCR

Arm A	Arm B
9 (29.0%)	30 (79.0%)

Courtesy of Ian E Krop, MD, PhD

Neoadjuvant THP (DAPHNe Study)
Waks A, et al. (N=97)

RCB class	All patients (n=97)	ER+ and/or PR+ (n=65)	ER- and PR- (n=32)
0 (pCR)	**55(56.7%)**	**28(43.1%)**	**27(84.4%)**
1	9(9.3%)	8(12.3%)	1(3.1%)
2	26(26.8%)	24(36.9%)	2(6.3%)
3	2(2.1%)	2(3.1%)	0
Non-pCR → more neoadjuvant therapy	5(5.2%)	3(4.6%)	2(6.3%)

Courtesy of Ian E Krop, MD, PhD

Administration of additional adjuvant cytotoxic chemotherapy (N=92)

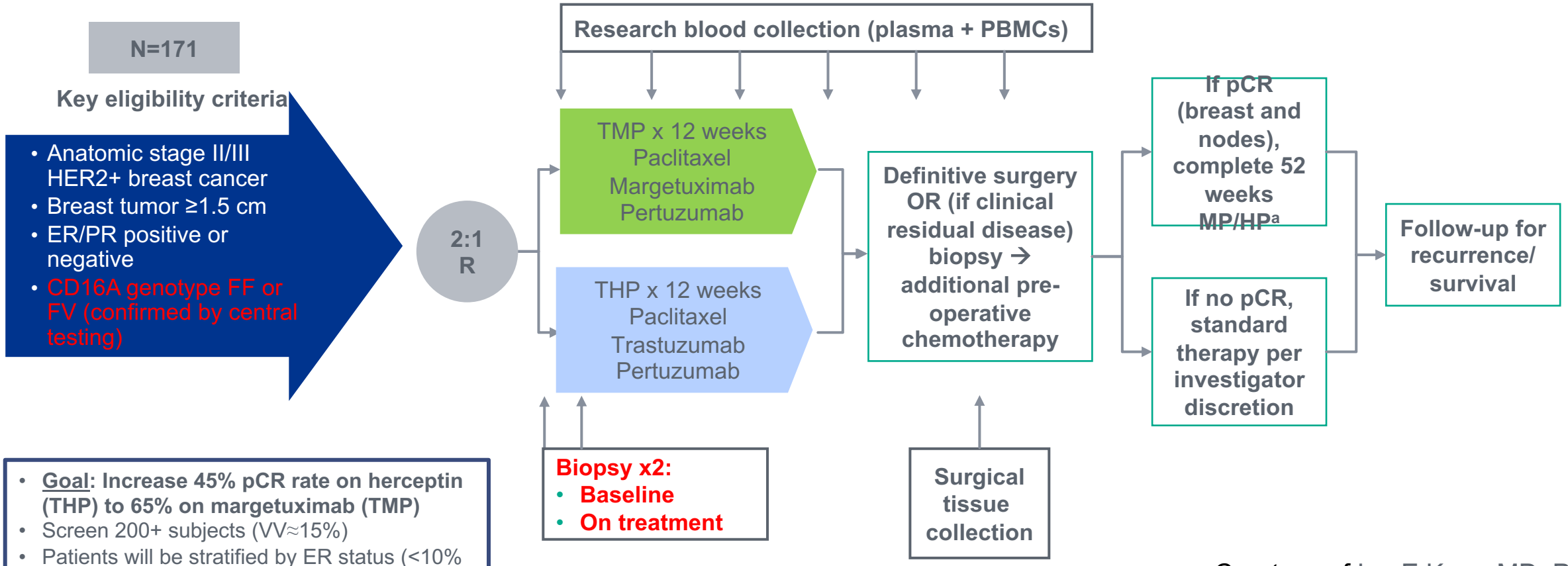
Pathologic surgical outcome	Adjuvant chemotherapy received?	No. of patients (%, 95% CI)
pCR (RCB 0) (n=55)	Yes	1(1.8%) (0.1-9.7)
	No	54(98.2%) (90.3-100.0)
Non-pCR, all RCB classes (RCB 1, 2, 3) (n=37)	Yes	16(43.2%) (27.1-60.5)
	No	21(56.8%) (39.5-72.9)

Notes: Trastuzumab emtansine (T-DM1) was NOT considered "cytotoxic chemotherapy" for this analysis. 5 pts who received additional neoadjuvant AC were excluded (pre-specified) from this analysis.

Among patients who experienced pCR following neoadjuvant THP, the rate of adherence to de-escalated adjuvant HP antibody-only therapy was 98.2% (95% CI 90.3%-100.0%).

Courtesy of Ian E Krop, MD, PhD

MARGetuximab or Trastuzumab (MARGOT): A Phase 2 Study Comparing Neoadjuvant TMP vs THP in Patients With Stage II/III HER2+ Breast Cancer



- **Goal: Increase 45% pCR rate on herceptin (THP) to 65% on margetuximab (TMP)**
- Screen 200+ subjects (VV≈15%)
- Patients will be stratified by ER status (<10% vs >10%) and clinical anatomic stage (II vs III)

Courtesy of Ian E Krop, MD, PhD

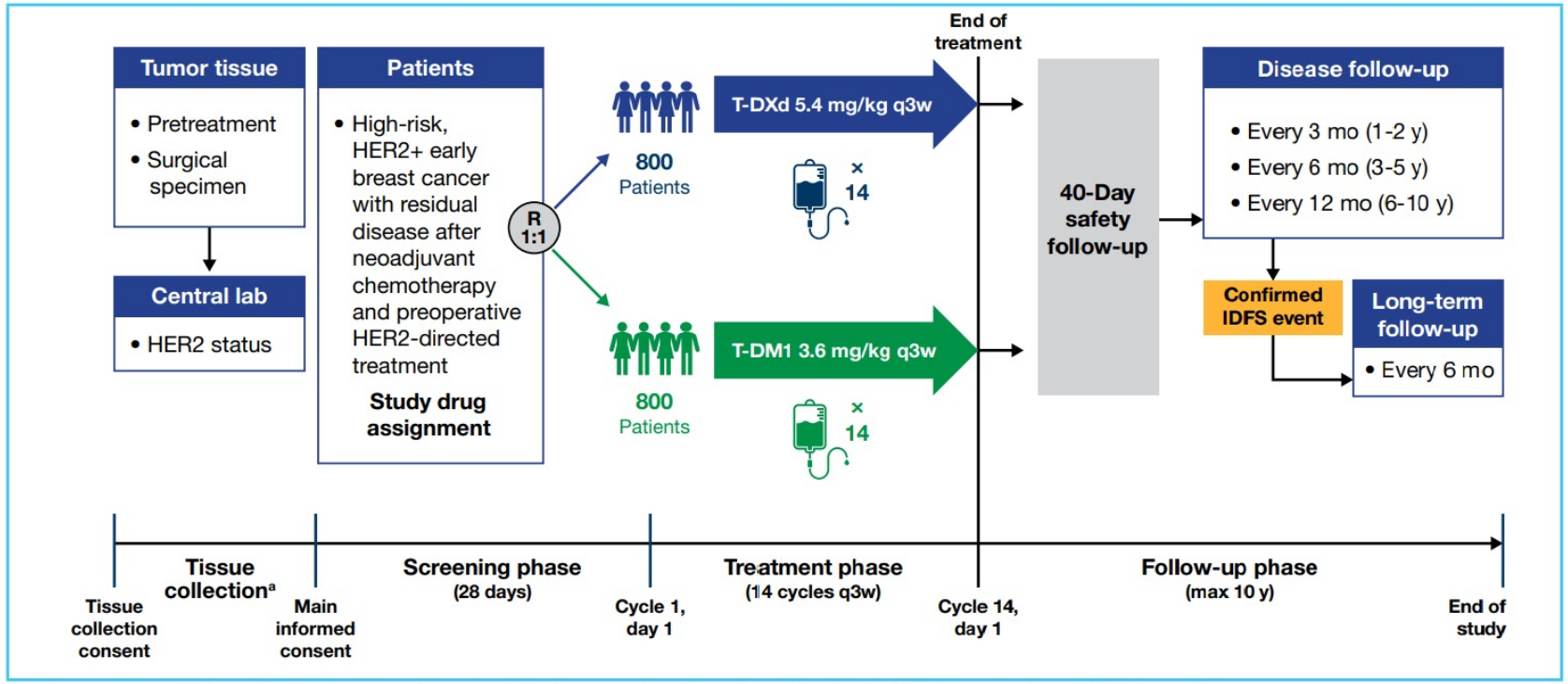
[a]Concurrent endocrine treatment allowed if HR+. Adjuvant radiation per standard institutional practice.

CD, cluster of differentiation; ER, estrogen receptor; FPI, first patient in; H, trastuzumab; HER2+, human epidermal growth factor receptor 2 positive; HR, hormone receptor; M, margetuximab; P, pertuzumab; PBMC, peripheral blood mononuclear cells; pCR, pathological complete response (defined as RCB [residual cancer burden]=0); PR, progesterone receptor; T, paclitaxel.

tbcrc Translational Breast Cancer Research Consortium

DESTINY-Breast05 phase 3 trial

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)



HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

– **Inoperable** breast cancer at presentation

– Operable breast cancer at presentation with **node–positive (ypN1-3) disease** after neoadjuvant therapy

Geyer et al. SABCS 2020 OT-03-01

Courtesy of Ian E Krop, MD, PhD

Expert Second Opinion: ER-Positive and Triple-Negative Breast Cancer

Wednesday, June 23, 2021
5:00 PM – 6:00 PM ET

Faculty

Matthew P Goetz, MD
Hope S Rugo, MD
Melinda Telli, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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