Beyond the Guidelines: Clinical Investigator Perspectives on the Management of HER2-Positive Breast Cancer

Thursday, December 10, 2020
8:30 PM – 10:00 PM ET

Faculty

Carey K Anders, MD
Erika Hamilton, MD
Sara Hurvitz, MD
Mark D Pegram, MD
Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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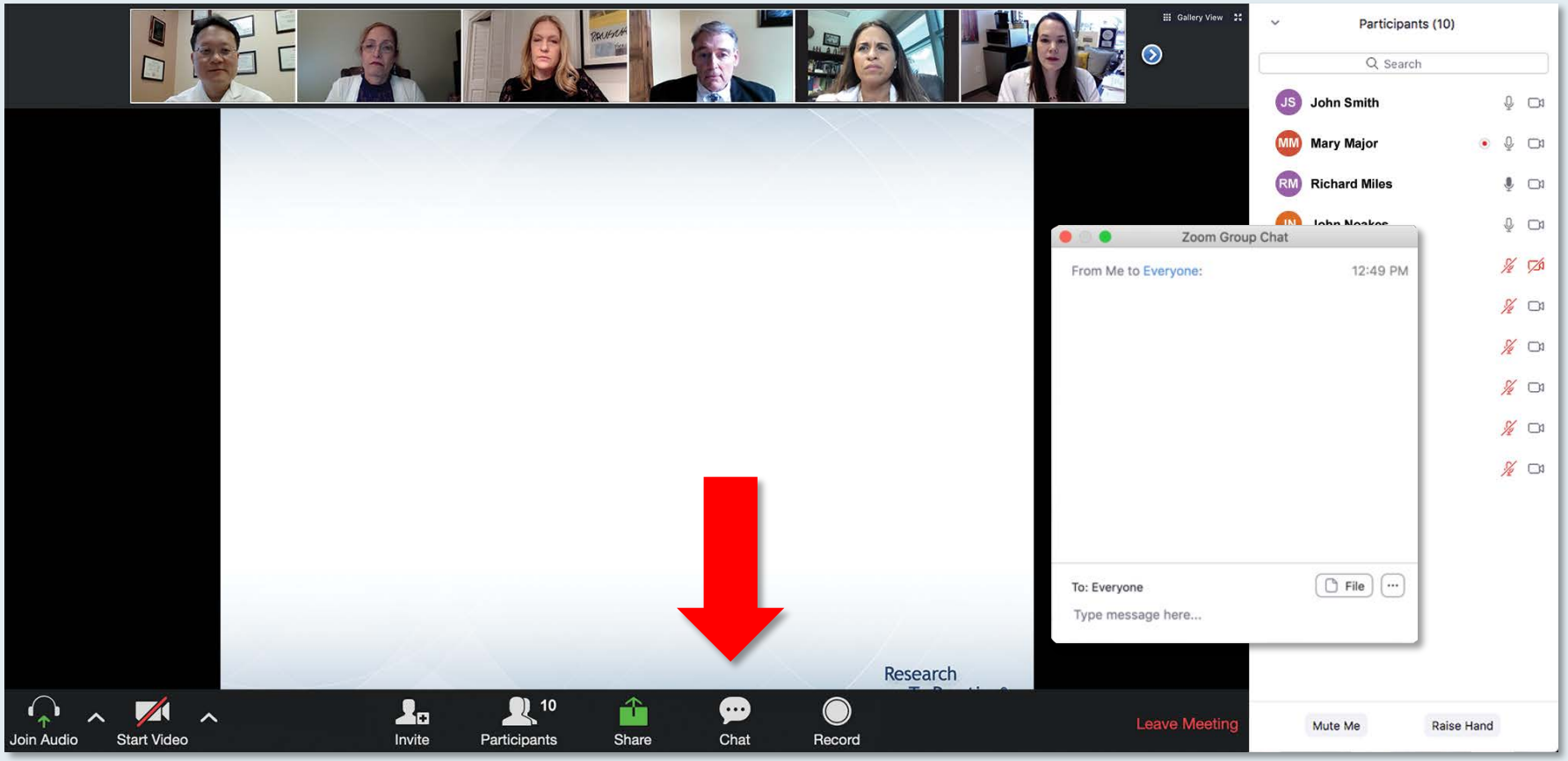

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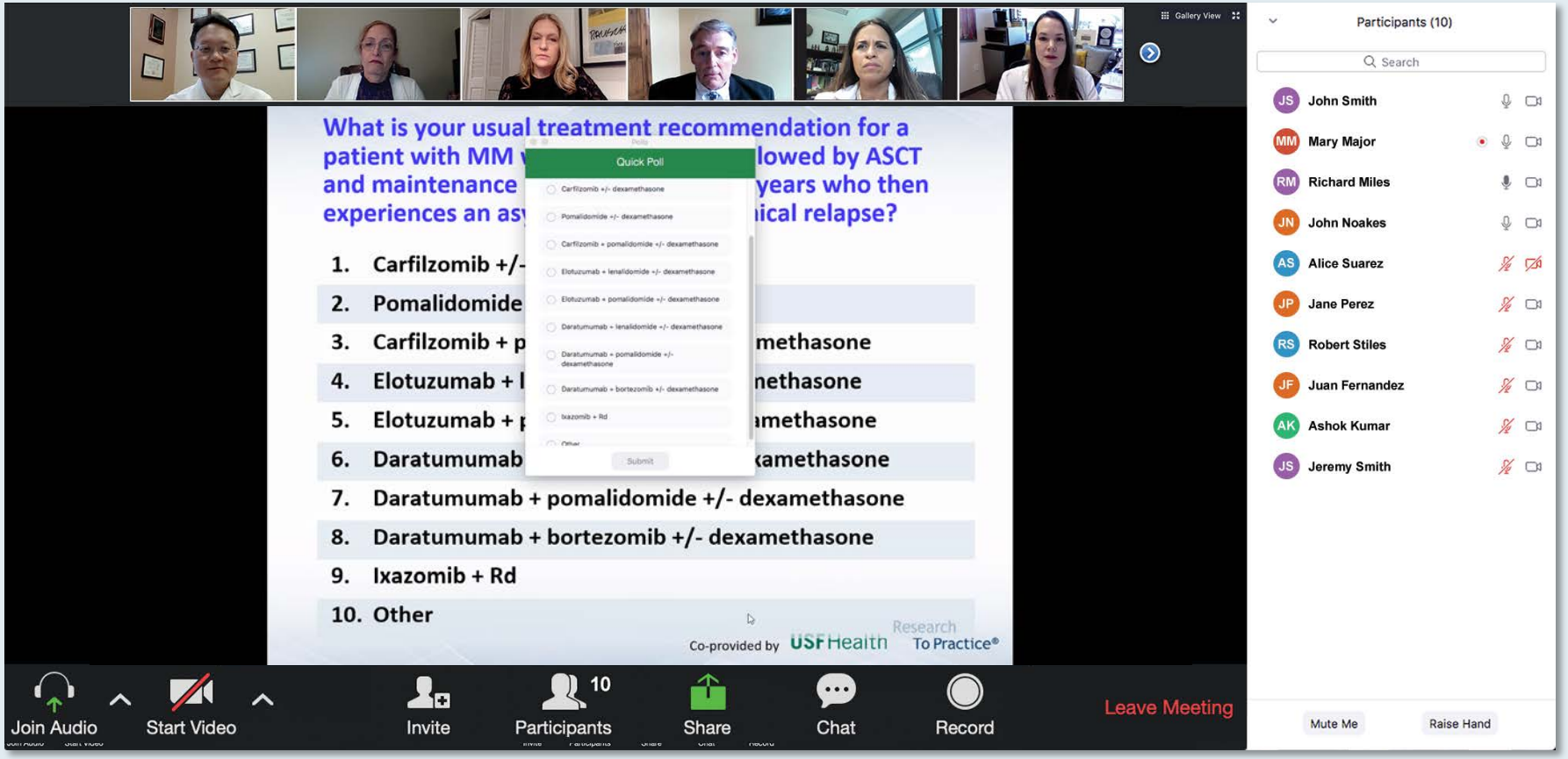

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Friday, December 11, 2020
8:30 PM – 10:00 PM ET

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Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, MD, PhD

Moderator

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Year in Review: Clinical Investigators Provide Perspectives on the Most Relevant New Publications, Data Sets and Advances in Oncology

Hepatobiliary and Pancreatic Cancers

Tuesday, December 15, 2020
5:00 PM – 6:00 PM ET

Faculty

Tanios Bekaii-Saab, MD
Lipika Goyal, MD, MPhil

Moderator

Neil Love, MD

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Meet The Professor
Multiple Myeloma

Wednesday, December 16, 2020
12:00 PM – 1:00 PM ET

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Chronic Lymphocytic Leukemia

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

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IMMUNE CHECKPOINT INHIBITION IN BREAST CANCER

DR SYLVIA ADAMS

PERLMUTTER CANCER CENTER

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JULES BORDET
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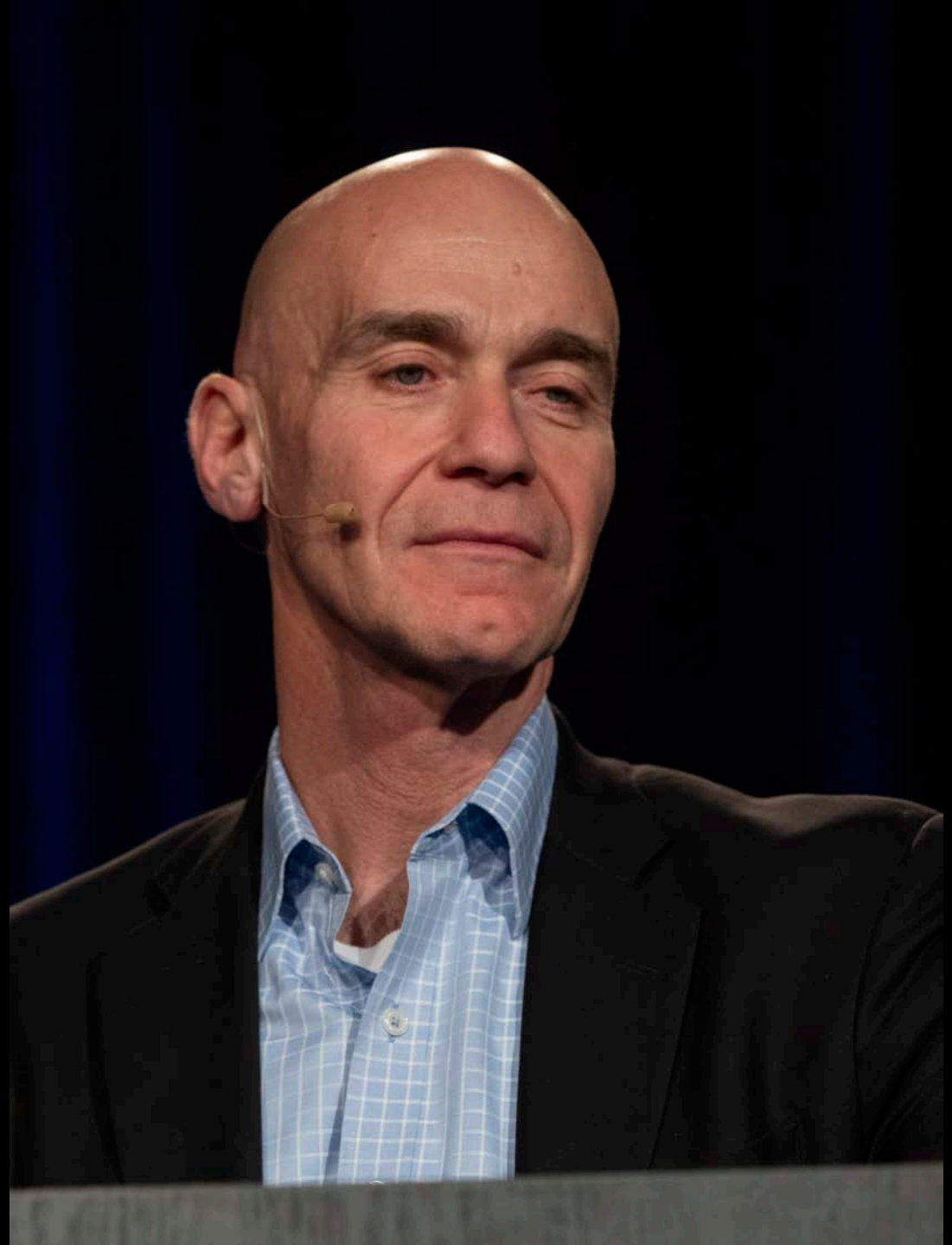
Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive Breast Cancer
Martine J Piccart-Gebhart, MD, PhD
Scientific Director




KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC
KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC


Management of Triple-Neg
Thursday, December 12, 2019
7:30 PM – 9:00 PM
San Antonio, Texas
Moderator
Neil Love, MD
Faculty
Erika Hamilton, MD


Sparano et al. N Engl J Med 2019;380(25):2395-2405.
Integrated Risk: Potential Clinical Utility of Integrated RS and Clinical Risk for Guiding Treatment in Women ≤ 50 Years
Integrated RS and Clinical Risk (CR)
Low Integrated Risk (58%)
< 5% Distant Recurrence
High Integrated Risk (31%)
> 10% Distant Recurrence
Tamoxifen alone adequate
No Chemotherapy
Consider chemotherapy or OFS + AI as an alternative to chemotherapy
Chemotherapy and consider OFS + AI in addition to chemotherapy
Prediction: Hazard Ratio for Chemotherapy Benefit as a Function of Continuous RS and Age (SEER)
Cox proportional hazards regression with propensity weighting (N=70,087)
Age ≤ 50 Years
Age > 50 Years


A 65-year-old postmenopausal woman completes 5 years of adjuvant anastrozole for an ER-positive, HER2-negative IDC but develops asymptomatic biopsy-proven bone and liver metastases 2 years later. Which systemic treatment would you most likely recommend?


Gene Expression Assays in Breast Cancer
Unsupervised analysis
Breast cancer is heterogeneous
Distinct subtypes
Prognosis varies by subtype (PAM50)
Supervised analysis
Several other prognostic assays (21-gene, 70-gene, others)
Lack of concordance in prognostic classification
Luminal A
Luminal B
ERBB2
Basal
Normal
C
D
E
F
G
Sorlie et al PNAS 2003; 100(14): 8418-8423
Bartlett JM et al. J Natl Cancer Inst. 2016;108(9)

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Neil Love, MD

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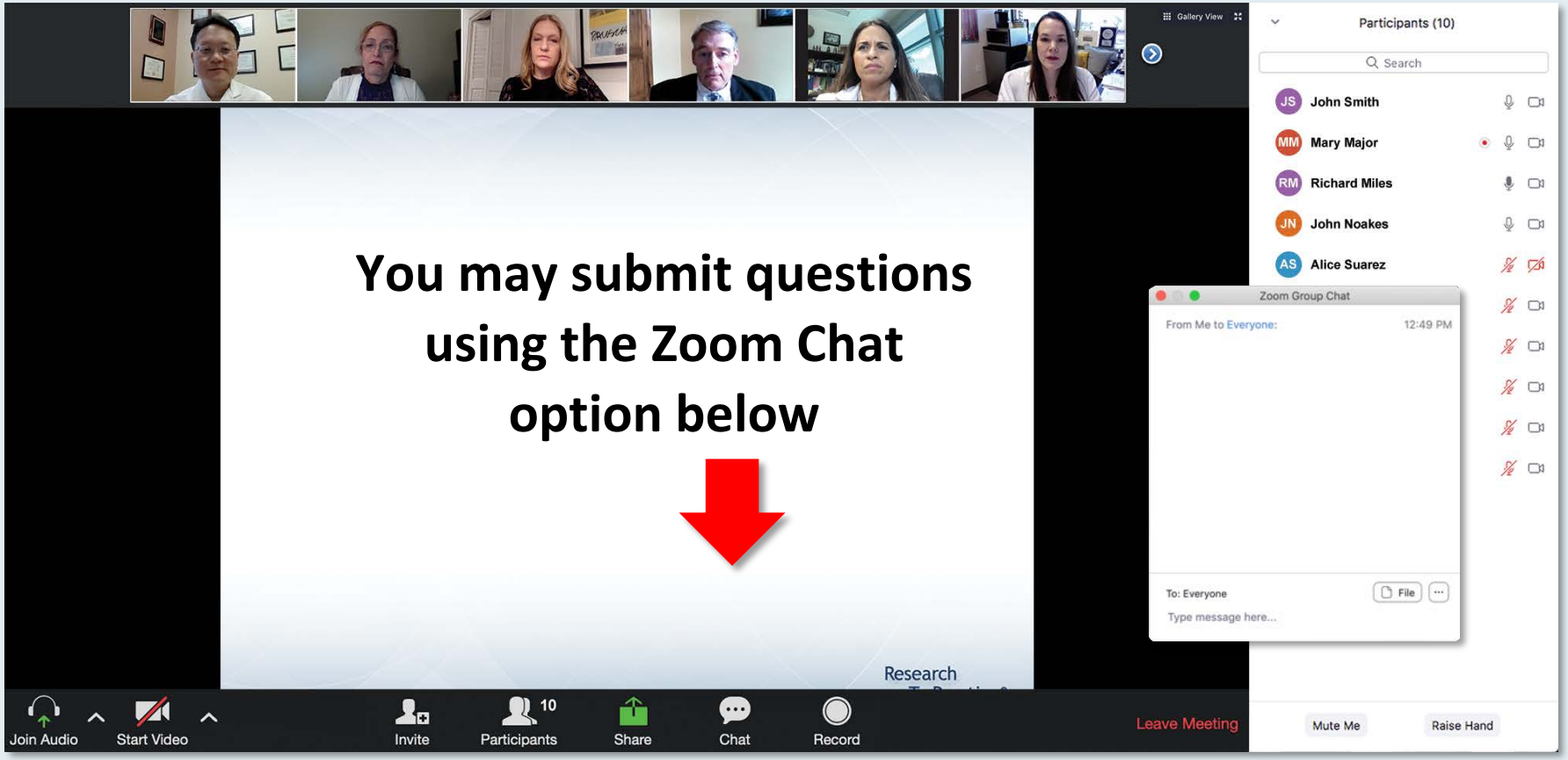

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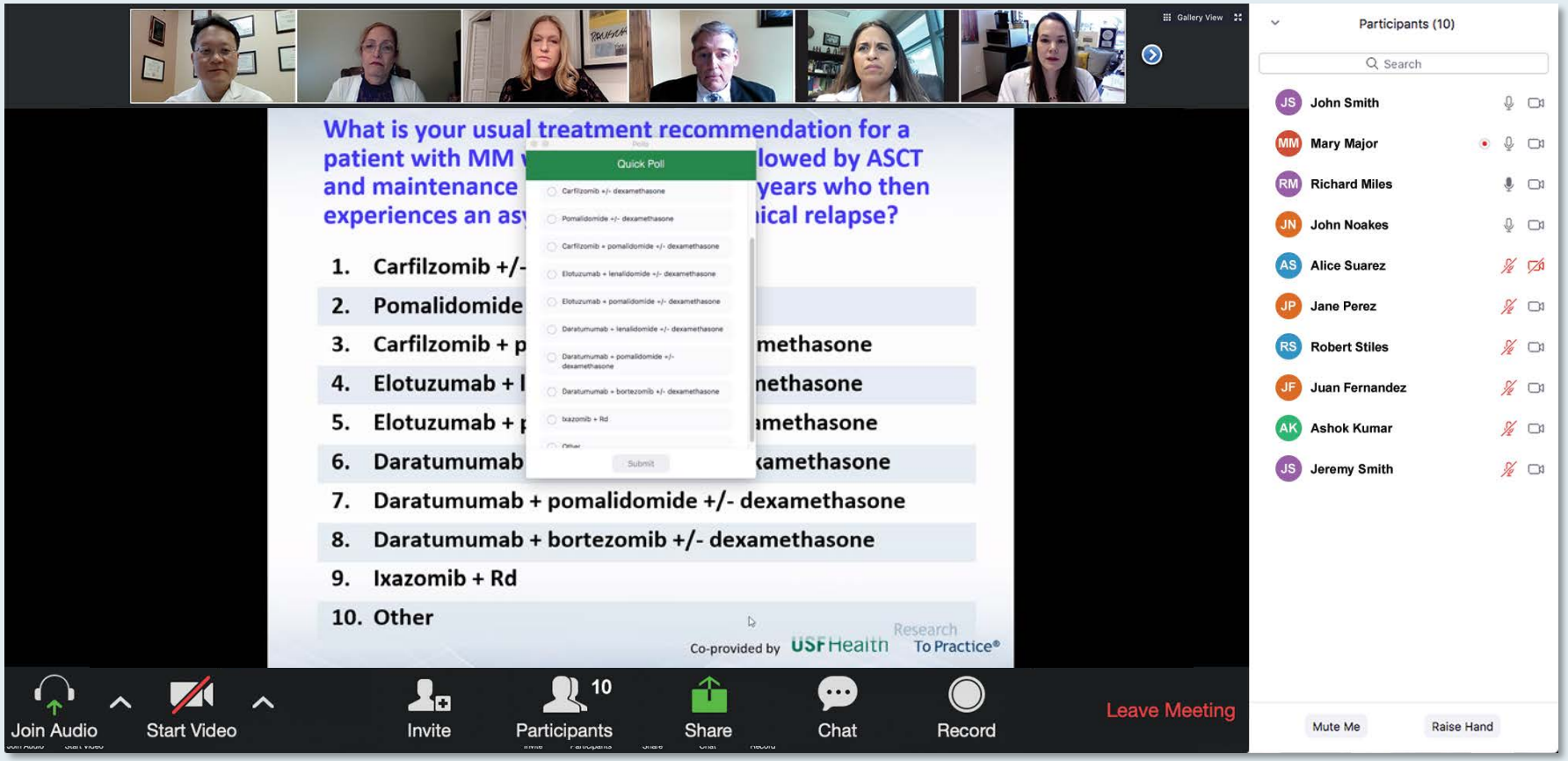

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IMMUNE CHECKPOINT INHIBITION IN BREAST CANCER

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Presentation Library

HER2-Positive Breast Cancer, Thursday, December 10, 2020

Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer (BC) Receiving Neoadjuvant Systemic Therapy
Mark D Pegram, MD

Download Slides

Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive BC
Sara M Tolaney, MD, MPH

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Optimizing the Management of HER2-Positive Metastatic BC (mBC)
Sara Hurvitz, MD

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Treatment of HER2-Positive Brain Metastases
Carey K Anders, MD

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Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy
Erika Hamilton, MD

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HER2-Positive Breast Cancer Survey Participants

1. Carey K Anders, MD
2. Aditya Bardia, MD, MPH
3. Joanne L Blum, MD
4. Adam M Brufsky, MD, PhD
5. Howard A Burris III, MD
6. Harold J Burstein, MD, PhD
7. Lisa A Carey, MD
8. Charles E Geyer Jr, MD
9. Matthew Goetz, MD
10. Erika Hamilton, MD
11. Sara Hurvitz, MD
12. Virginia Kaklamani, MD, DSc
13. Hannah M Linden, MD
14. Eleftherios P Mamounas, MD, MPH
15. P Kelly Marcom, MD
16. Jennifer M Matro, MD
17. Kathy D Miller, MD
18. Rita Nanda, MD
19. Ruth O'Regan, MD
20. Joyce O'Shaughnessy, MD
21. Mark D Pegram, MD
22. Lajos Pusztai, MD, DPhil
23. Joseph Sparano, MD
24. Sandra M Swain, MD
25. Sara M Tolaney, MD, MPH

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Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer (BC) Receiving Neoadjuvant Systemic Therapy — Dr Pegram

Module 2: Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive BC — Dr Tolaney

Module 3: Optimizing the Management of HER2-Positive Metastatic BC (mBC) — Dr Hurvitz

Module 4: Treatment of HER2-Positive Brain Metastases — Dr Anders

Module 5: Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hamilton

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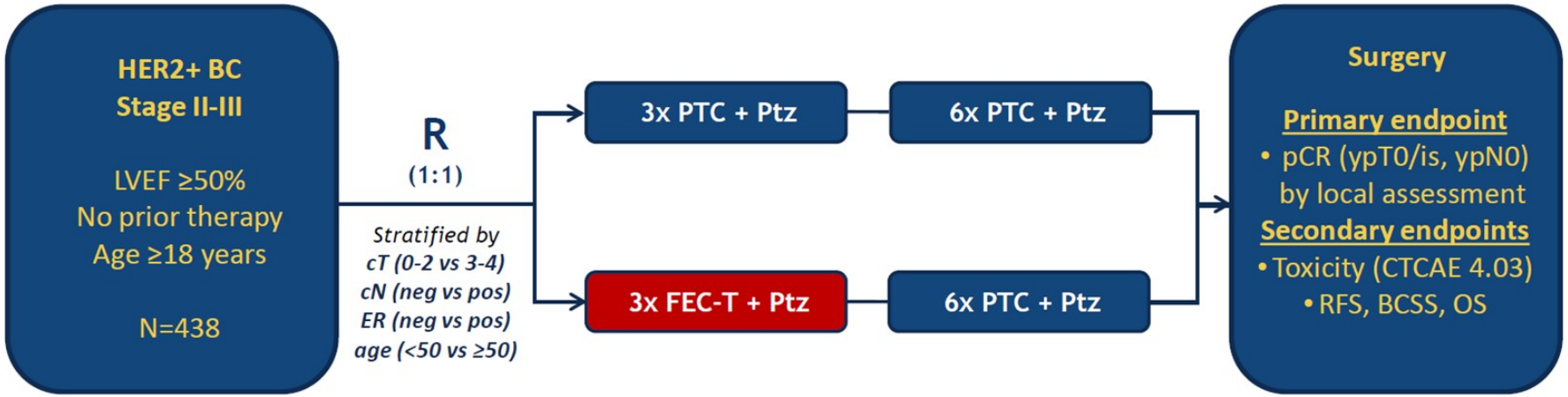
Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer Receiving Neoadjuvant Systemic Therapy

Mark D. Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Associate Director for Clinical Research
Associate Dean for Clinical Research Quality
Director, Clinical/Translational Research Unit
Stanford University School of Medicine

Three year follow-up of neoadjuvant chemotherapy with or without anthracyclines with dual HER2 antibody blockade

TRAIN-2: study design



- PTC+Ptz cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P: P = paclitaxel 80mg/m^2; T = trastuzumab 6mg/kg (loading dose 8mg/kg); C = carboplatin AUC = 6mg·min/ml; Ptz = pertuzumab, 420mg (loading dose 840mg)
- FEC-T+Ptz cycle of 3 weeks: F = 5-fluorouracil 500mg/m^2; E = epirubicin 90mg/m^2; C = cyclophosphamide 500mg/m^2;T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)
- Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumors

van Ramshorst et al, *Lancet Oncol* 2018; van Ramshorst et al, *Eur J Cancer* 2017

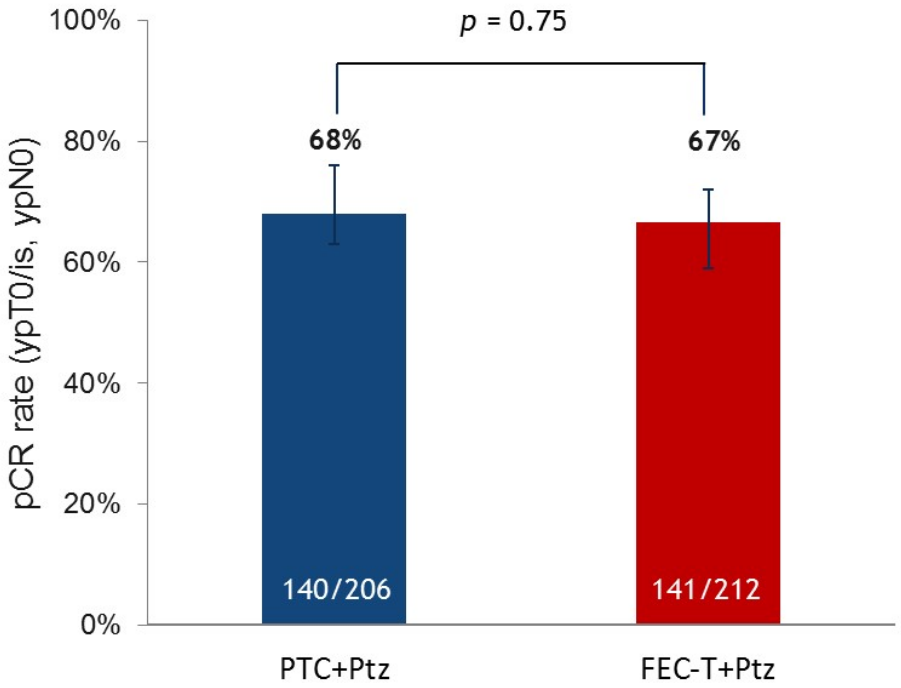
ClinicalTrials.gov identifier: NCT01996267

Presented By Anna van der Voort at ASCO 2020

Courtesy of Mark D Pegram, MD

TRAIN-2: primary endpoint pCR

- High pathological complete response rates with and without anthracyclines
- Main outcome was consistent across levels of prespecified subgroups
  - cT (0-2 vs 3-4)
  - cN (negative vs positive)
  - HR (negative vs positive)
  - age (<50 vs ≥50)



van Ramshorst et al, *Lancet Oncol* 2018

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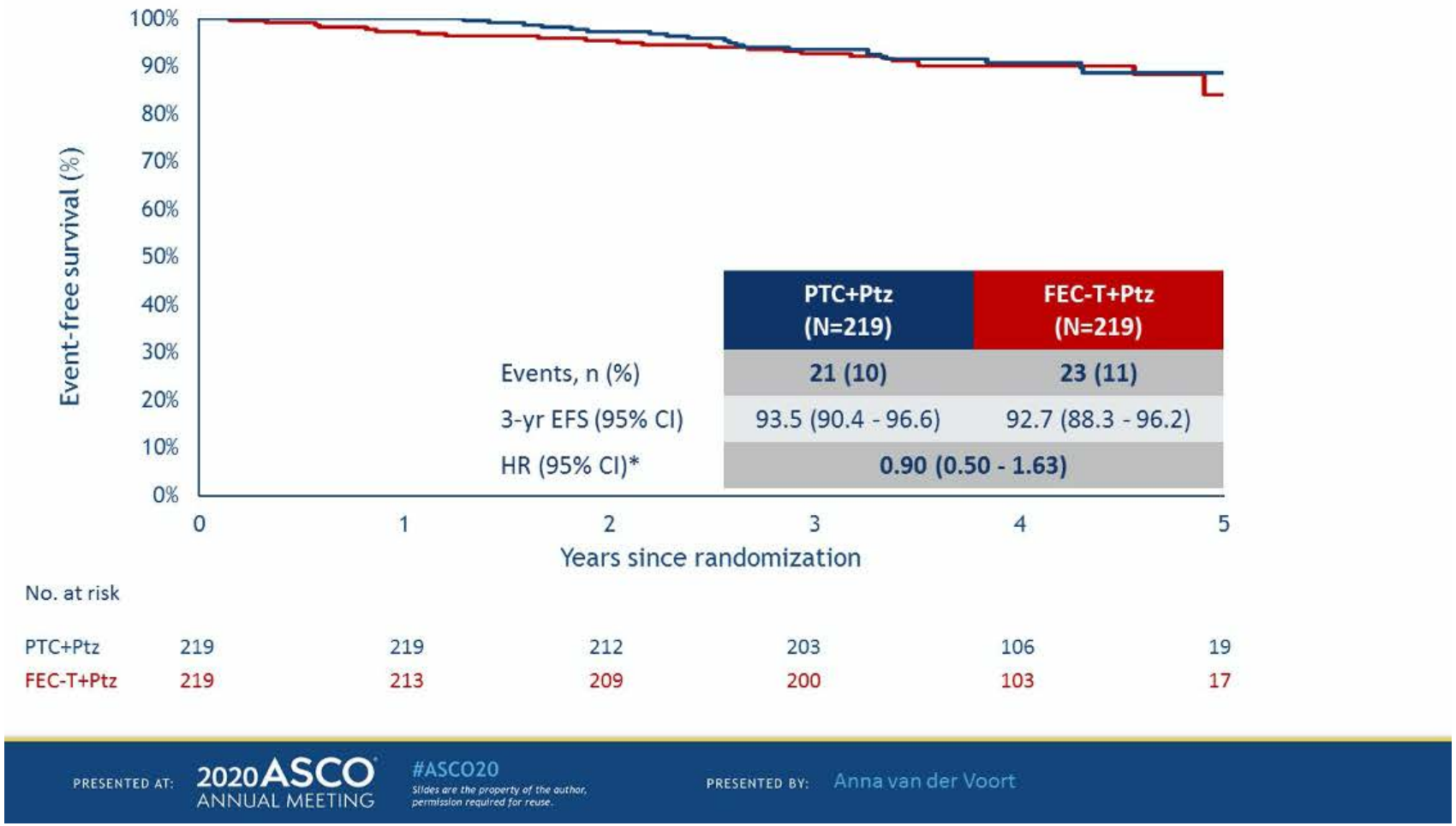
ASCO 2020 Update time-to-event analysis (EFS)



EFS by nodal status – no hint of advantage of anthracyclines even in high risk subgroups (cN2/3; HR=0.75 w/ trend favoring non-anthracycline)

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Courtesy of Mark D Pegram, MD

Safety: cardiotoxicity

	PTC+Ptz (n=218) n (%)	FEC-T+Ptz (n=220*) n (%)	p-value
LVEF decrease ≥10% or LVEF <50%	49[#] (22%)	80 (36%)	0.0016
LVEF decrease ≥10% and LVEF <50%	7 (3%)	17 (8%)	0.044

LVEF was measured every 3 months for 1 year

* one patient was allocated to PTC+Ptz but received neoadjuvant FEC-T+PTZ

[#] one patient developed grade 2 LVEF decline during adjuvant treatment with anthracyclines

LVEF decline did not recover to normal during follow-up in about one third of the patients

Presented By Anna van der Voort at ASCO 2020

Courtesy of Mark D Pegram, MD

Safety: new malignancies

	PTC+Ptz (n=218*) n (%)	FEC-T+Ptz (n=220#) n (%)
Acute leukemia†	0	2 (1%)
Female genital cancer	0	2 (1%)
Lung carcinoma	1 (<1%)	0
Melanoma	1 (<1%)	0
Papillary thyroid carcinoma	0	2 (1%)
Tongue carcinoma	1 (<1%)	0
Non-melanoma skin cancer	2 (1%)	5 (2%)
Total	**5 (2%)**	**11 (5%)**

* two patients in the PTC+Ptz arm received adjuvant adjuvant anthracyclines
# one patient was allocated to PTC+Ptz but received FEC-T+Ptz
† acute leukemia was chemotherapy associated in both patients

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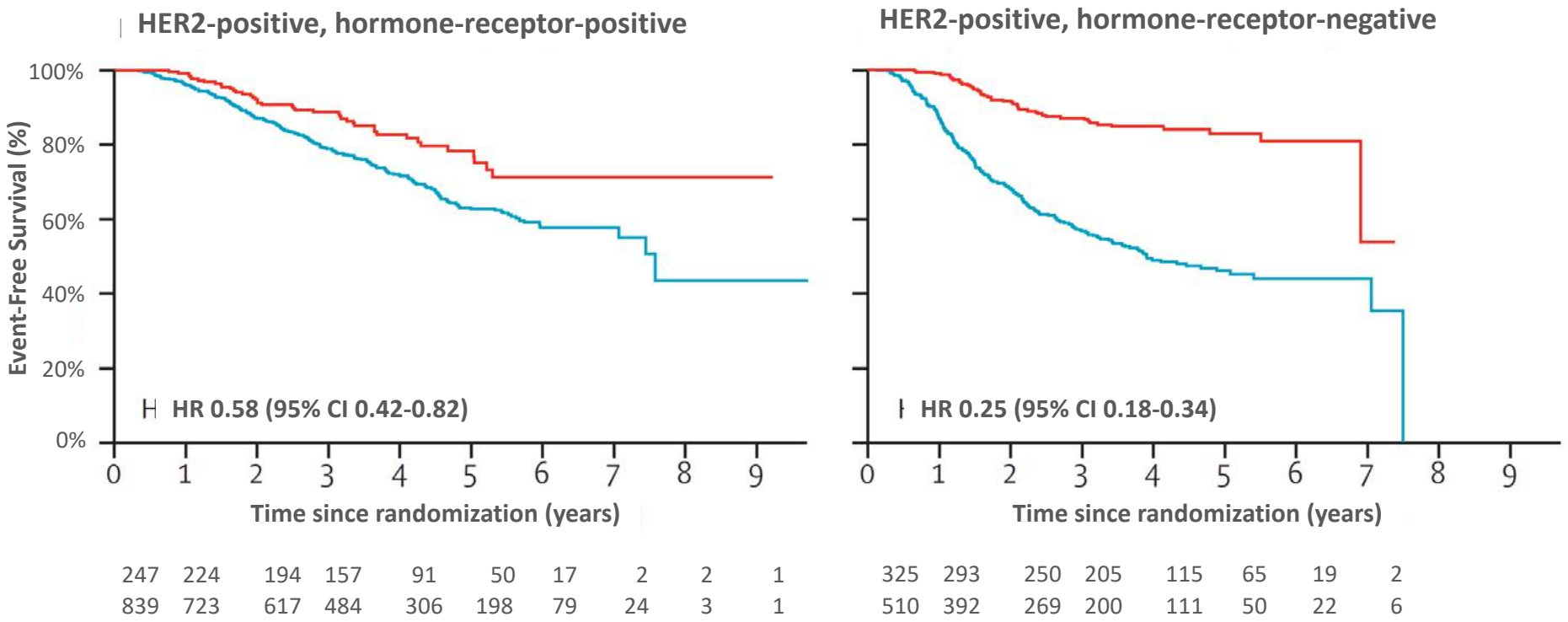
Among neoadjuvant-treated HER2+ patients, even though pCR portends a more favorable prognosis, risk of relapse still exists



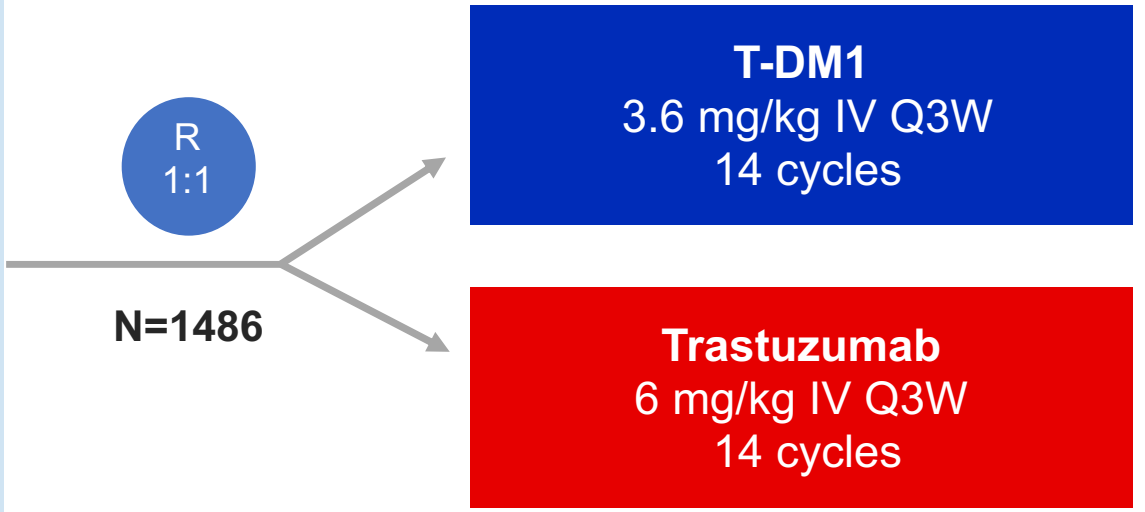
Red line: pCR
Blue line: non-pCR

Cortazar, et al., FDA Meta-analysis. *Lancet* 2014

Courtesy of Mark D Pegram, MD

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

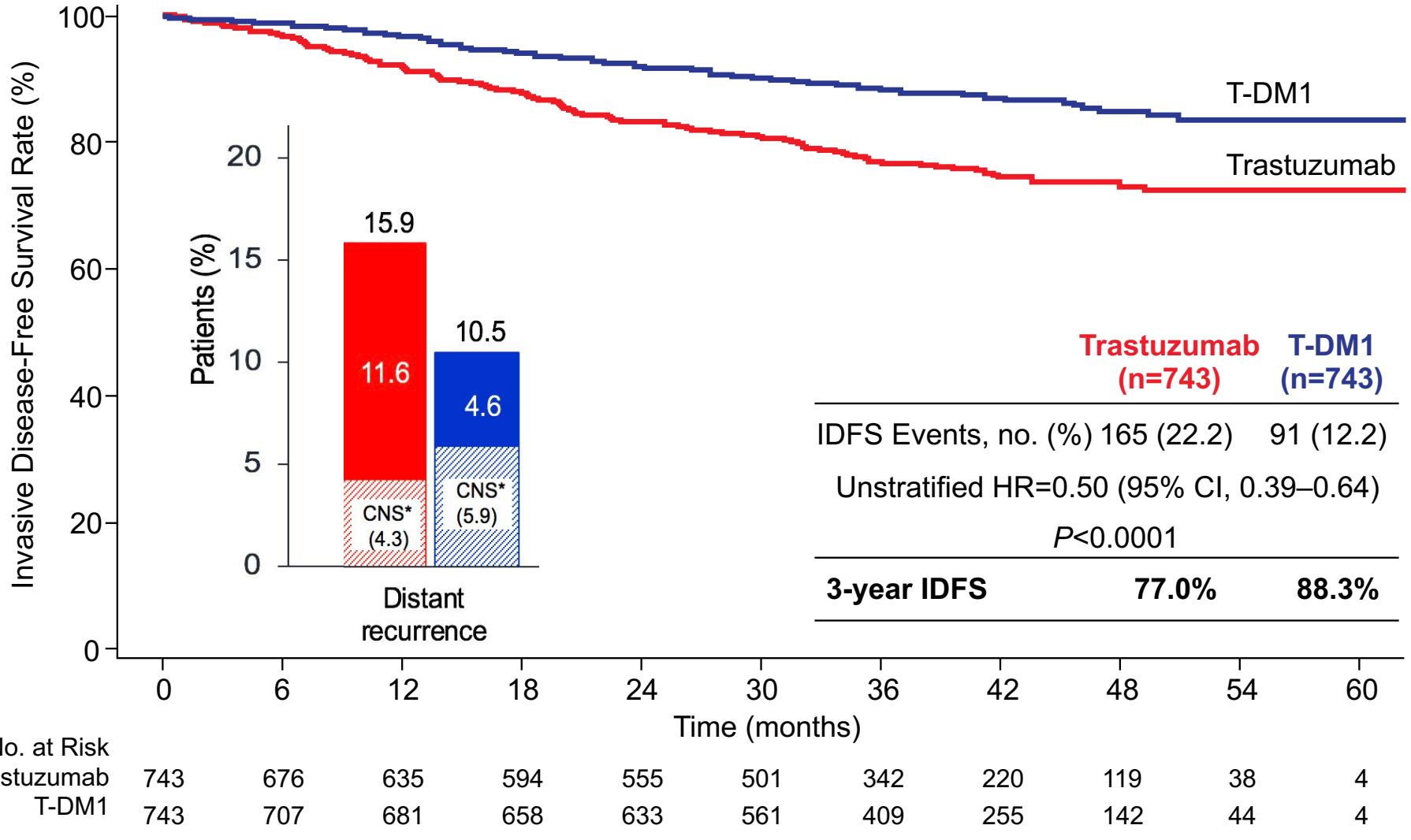
Stratification factors:

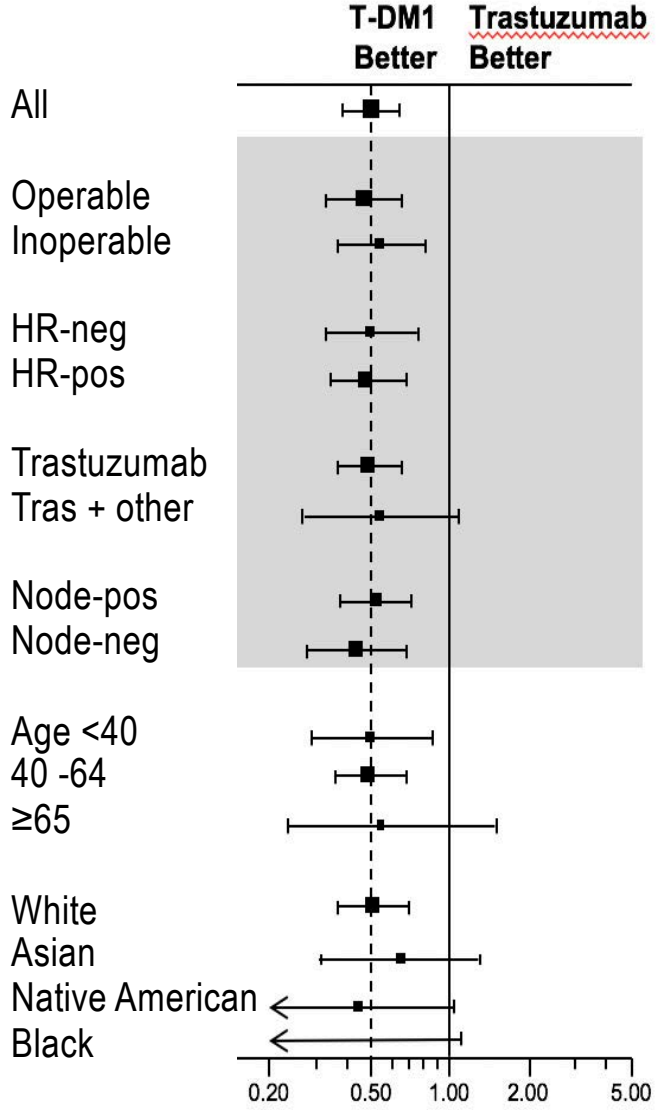
- Clinical presentation: **Inoperable (stage cT4 or cN2–3) vs operable** (stages cT1-3N0-1)
- **Hormone receptor**: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: **Trastuzumab vs trastuzumab plus other** HER2-targeted therapy
- **Pathological nodal status** after neoadjuvant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

Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

Courtesy of Mark D Pegram, MD

Invasive Disease-Free Survival





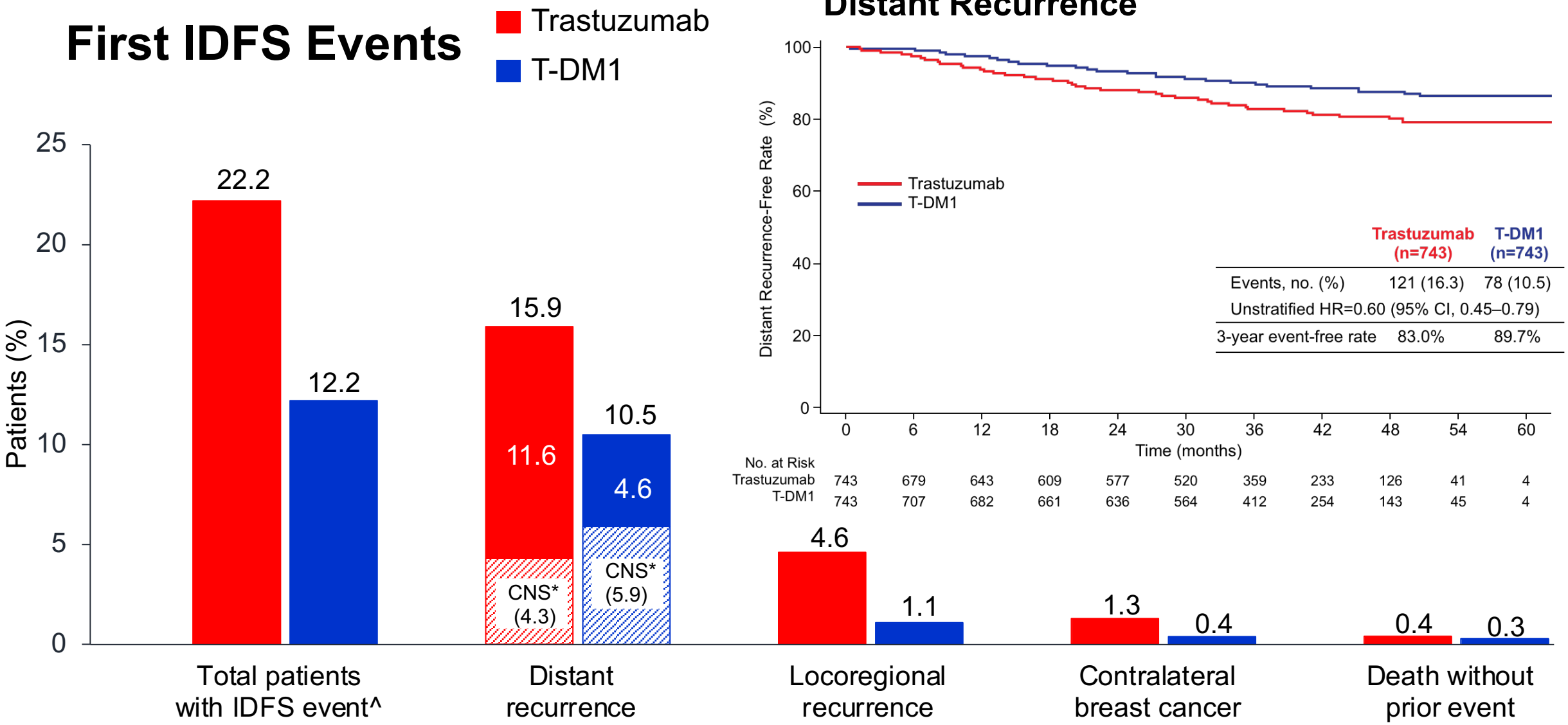
By comparison, 3 year DFS, B31/N9831 Joint Analysis: 87% vs. 75%

Echoes of "The results are simply stunning"? -- Gabriel N. Hortobagyi, N Engl J Med 2005; 353:1734-1736

Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

Courtesy of Mark D Pegram, MD

First IDFS Events



Distant Recurrence

	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	121 (16.3)	78 (10.5)
Unstratified HR=0.60 (95% CI, 0.45–0.79)		
3-year event-free rate	83.0%	89.7%

No. at Risk											
Trastuzumab	743	679	643	609	577	520	359	233	126	41	4
T-DM1	743	707	682	661	636	564	412	254	143	45	4

^Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.

***CNS metastases as component of distant recurrence (isolated or with other sites).** Trastuzumab T-DM1

Von Minckwitz G, et al. N Engl J Med 2019; 380:617-628

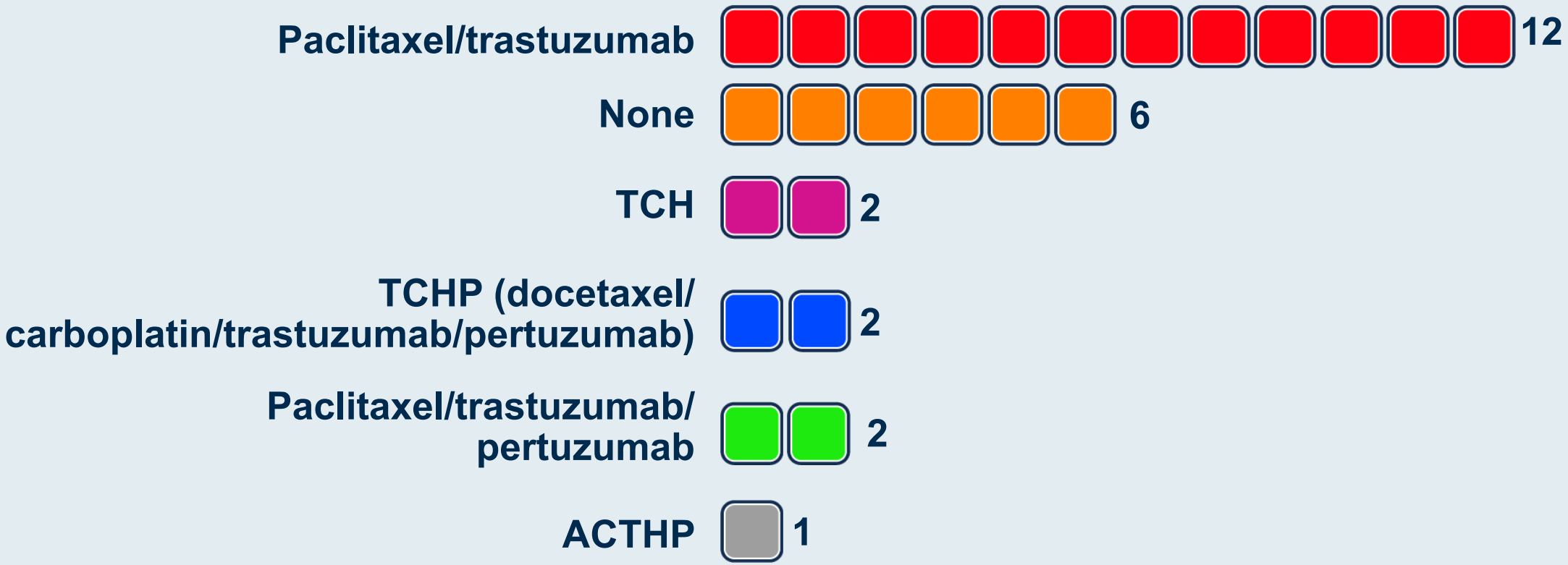
Courtesy of Mark D Pegram, MD

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 65-year-old patient with a 1.5-cm, ER-negative, HER2-positive, 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 (docetaxel/carboplatin/trastuzumab/pertuzumab)
8. Other

Which neoadjuvant systemic therapy, if any, would you generally recommend for a patient with an ER-negative, HER2-positive IDC with the following characteristics?

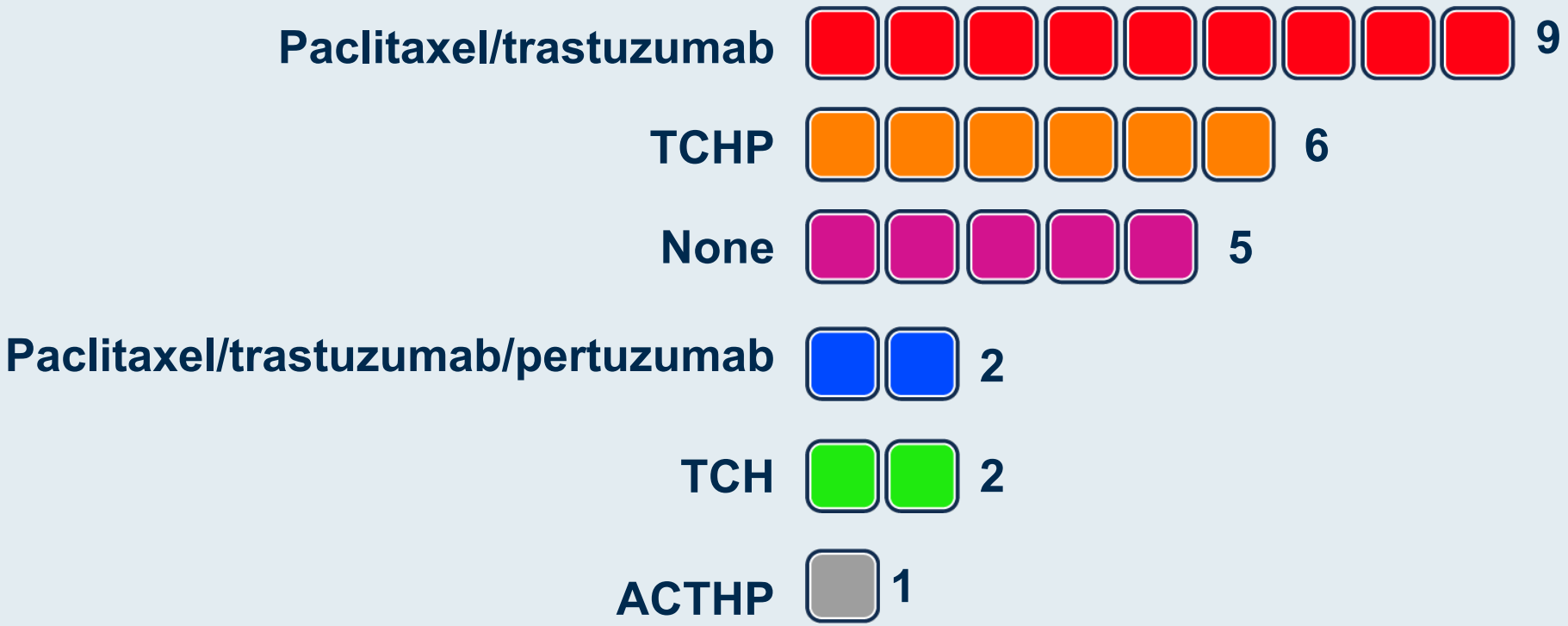
Age: 65, Tumor size: 1.5 cm, Nodal status: Node-negative



Survey of 25 Breast Cancer Clinical Investigators

Which neoadjuvant systemic therapy, if any, would you generally recommend for a patient with an ER-negative, HER2-positive IDC with the following characteristics?

Age: 35, Tumor size: 1.5 cm, Nodal status: Node-negative



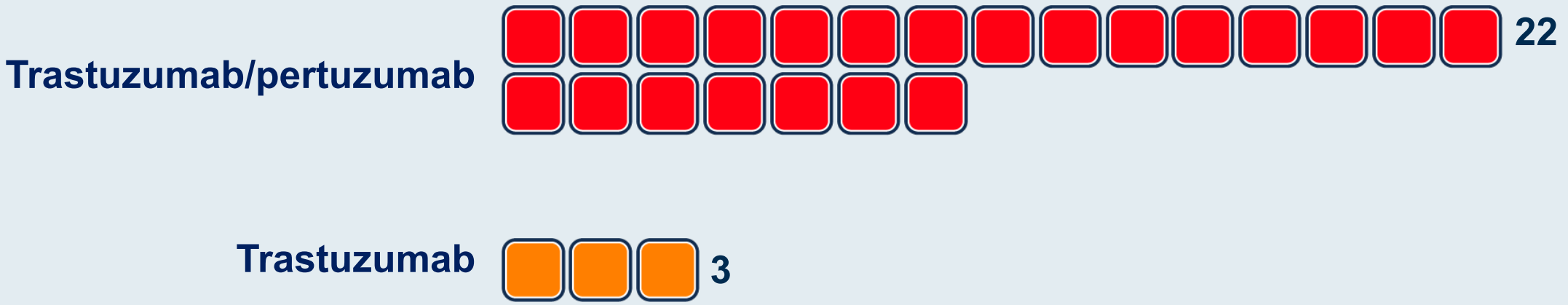
Survey of 25 Breast Cancer Clinical Investigators

A 65-year-old woman presents with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven 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

A 65-year-old woman presents with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven 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?



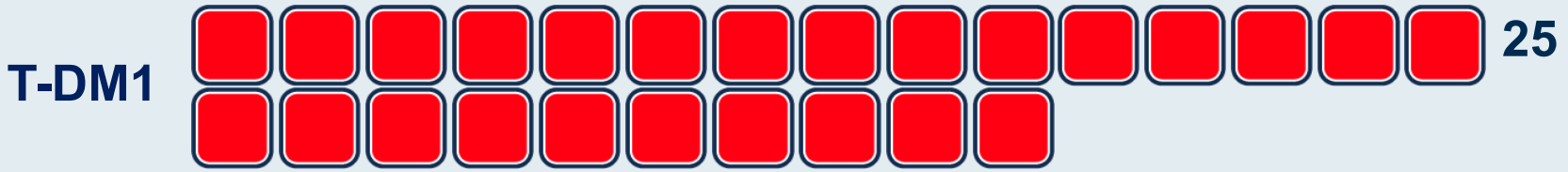
Survey of 25 Breast Cancer Clinical Investigators

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

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

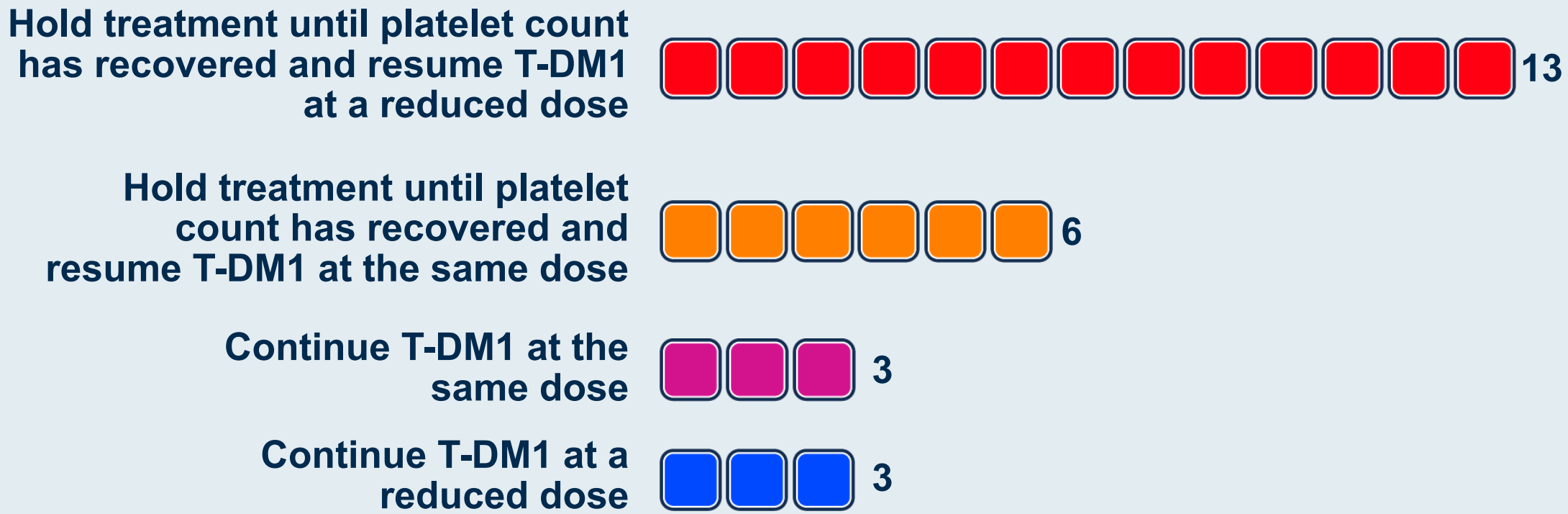
RTP
RESEARCH
TO PRACTICE

A 65-year-old woman presents with a 3.4-cm, ER-negative, HER2-positive IDC with biopsy-proven 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 0.5 cm of residual tumor in the breast and no disease in the nodes?



Survey of 25 Breast Cancer Clinical Investigators

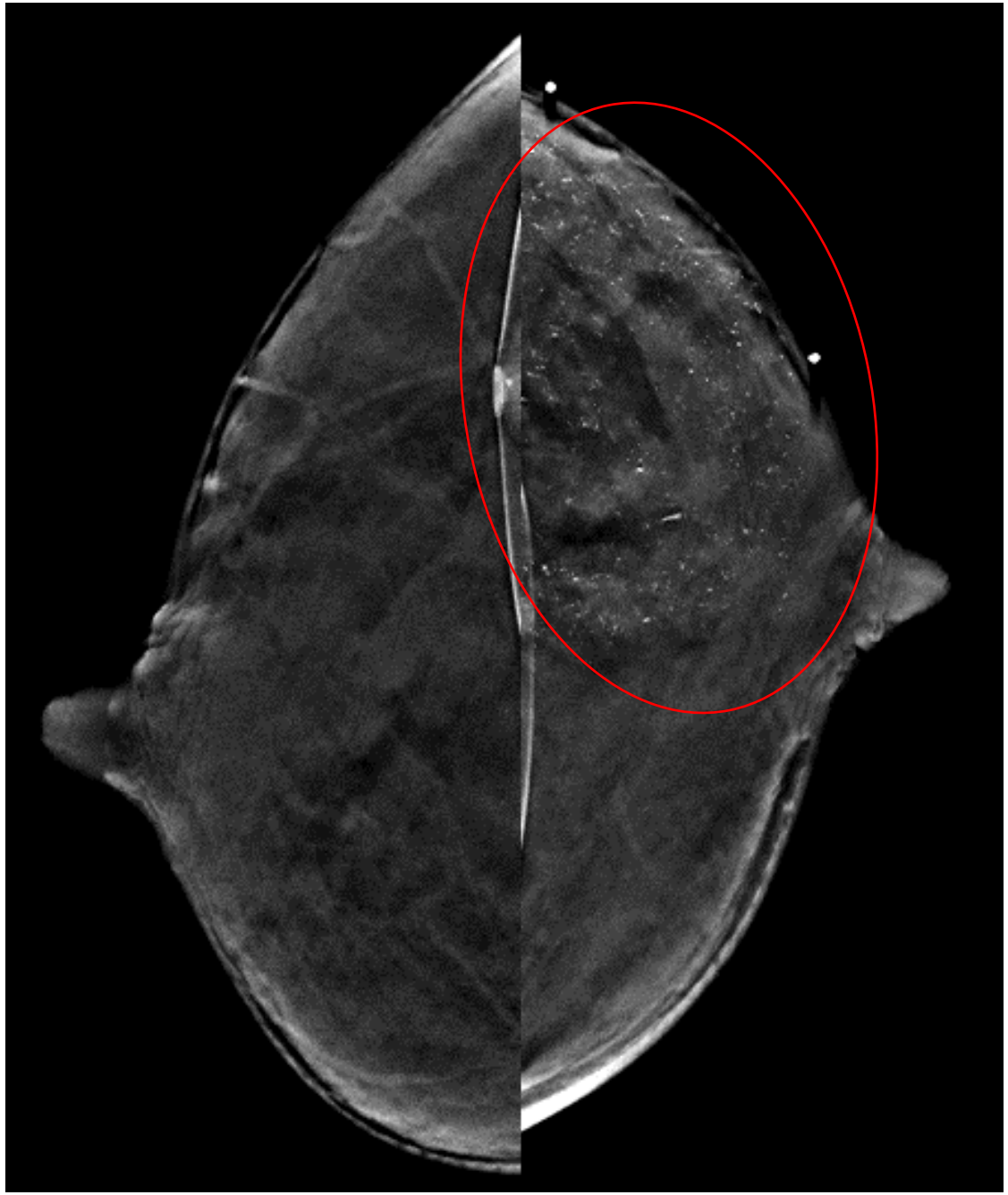
A 65-year-old woman presents with a 3.5-cm, ER-negative, HER2-positive, node-negative IDC, receives neoadjuvant TCHP and at surgery is found to have 2 cm of scattered residual disease in the breast. She begins adjuvant T-DM1, but after 6 cycles her platelet count drops to 70,000/mm^3. What would you recommend?



Survey of 25 Breast Cancer Clinical Investigators

Case Presentation – Dr Pegram: 42-year-old woman

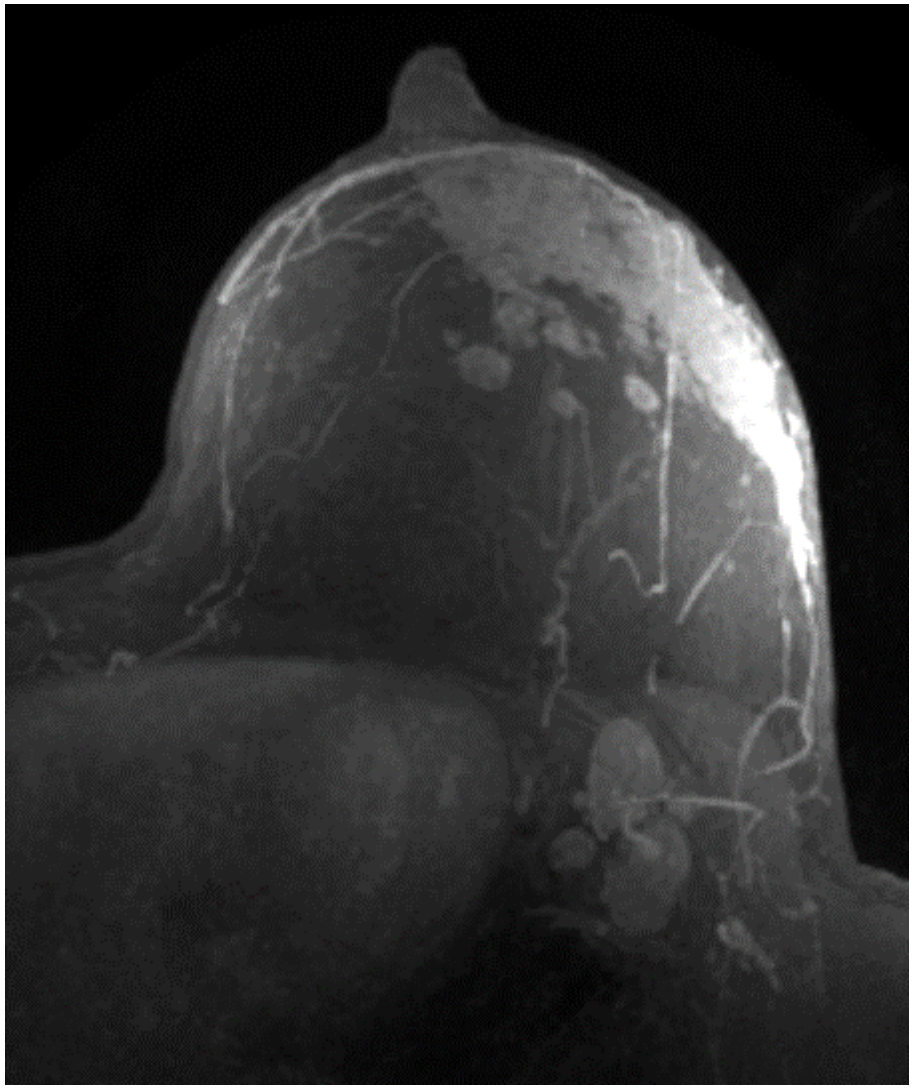
- 42-year-old female noticed diffuse palpable abnormalities in lateral left breast and left axilla over 6-month period while breastfeeding



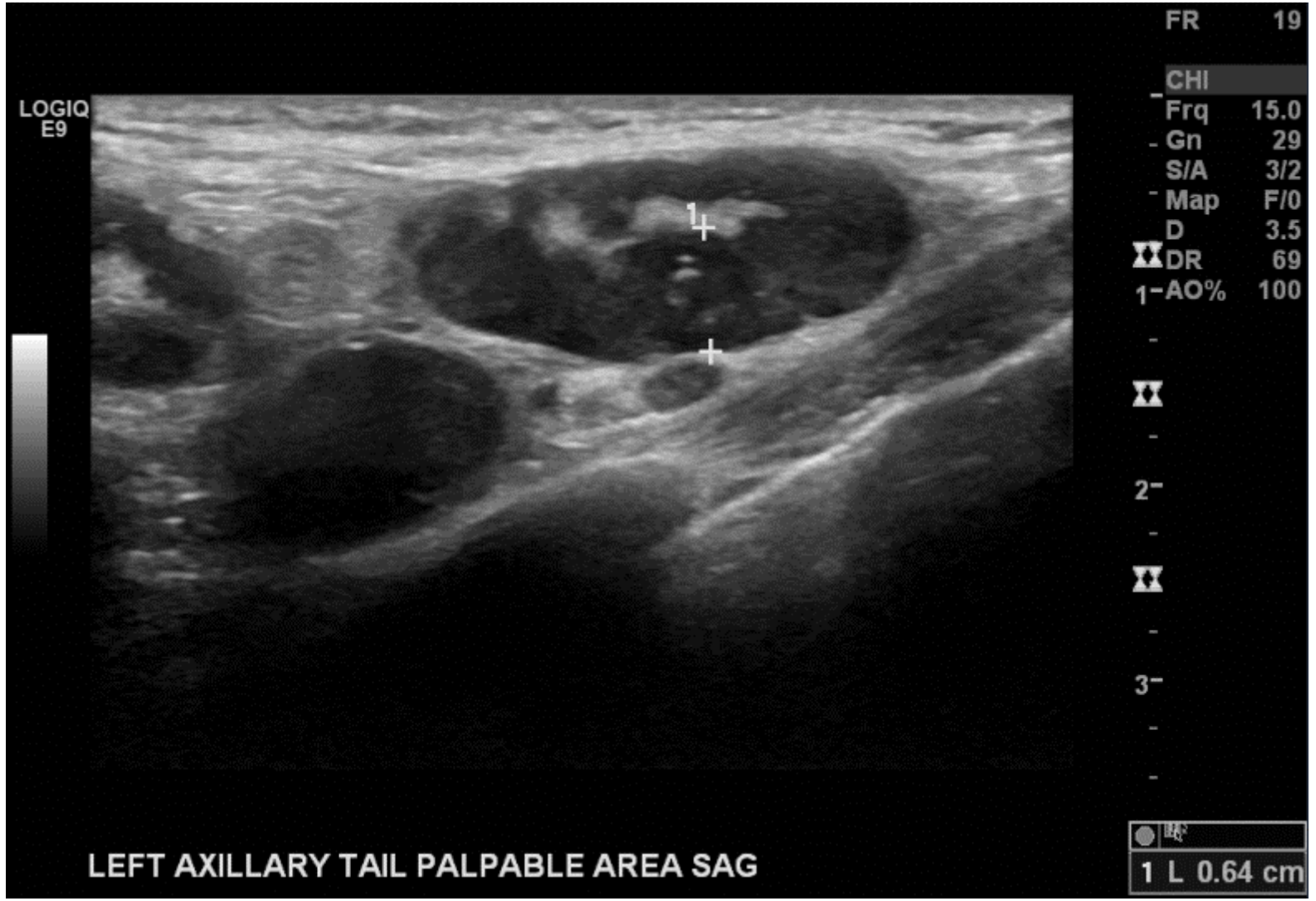
Courtesy of Mark D Pegram, MD

MRI shows abnormal clumped NME spanning the upper outer and entire lower outer quadrant, abnormal lymph nodes

5/25/18 MRI

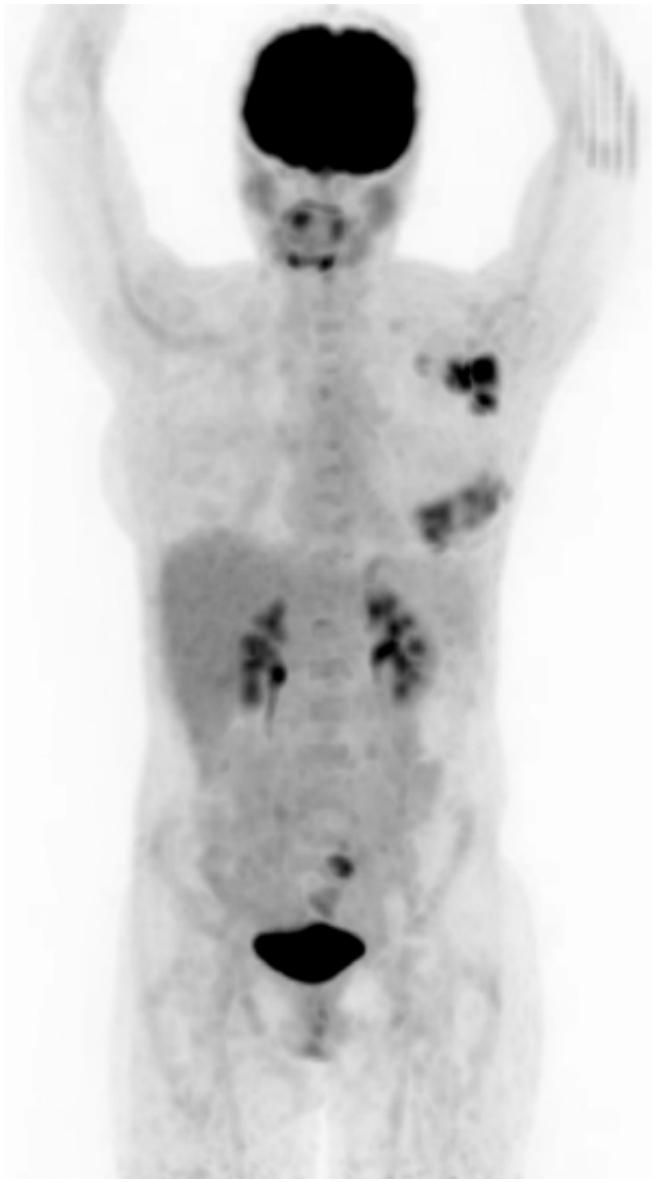


Courtesy of Mark D Pegram, MD



Courtesy of Mark D Pegram, MD

FDG PET/CT shows axillary nodal and breast disease, no distant disease



Courtesy of Mark D Pegram, MD

Case Presentation – Dr Pegram: 42-year-old woman (cont)

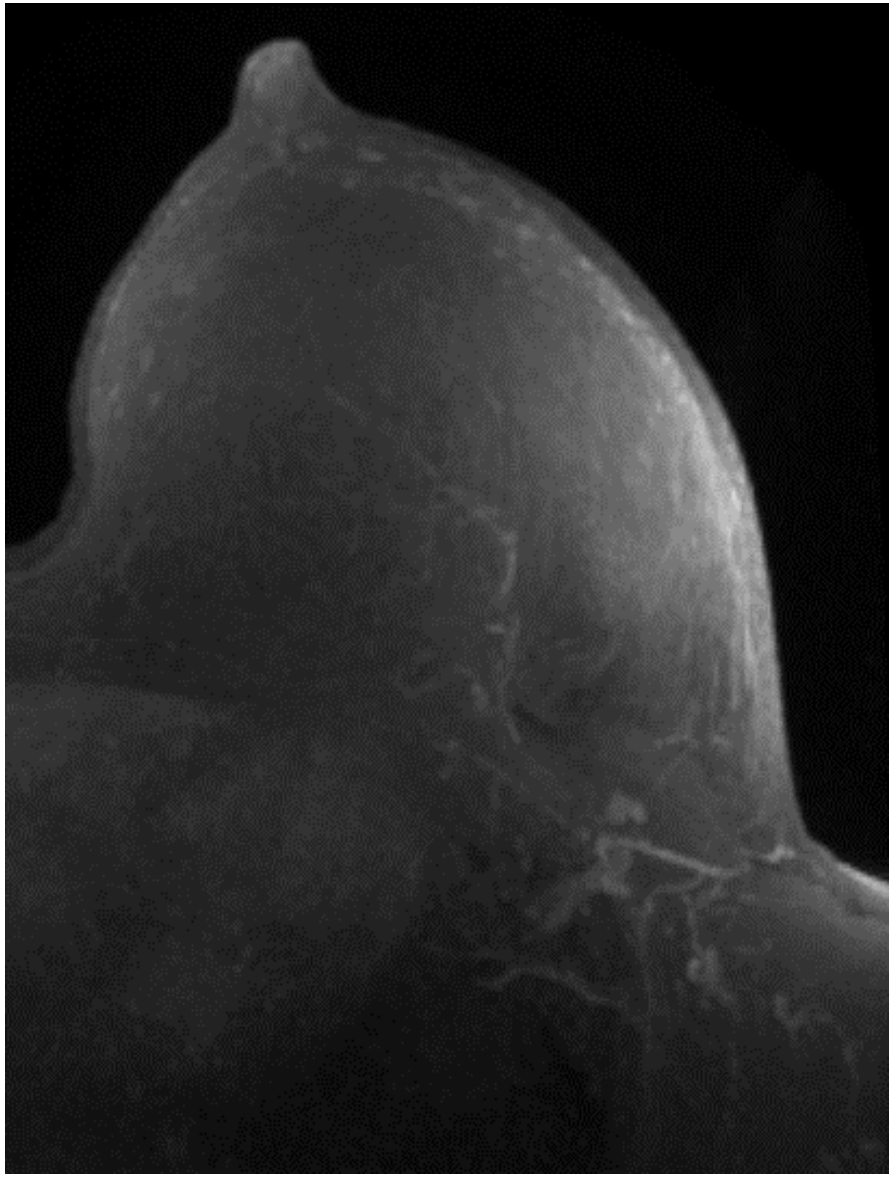
9/11/18 to 12/26/18: Completed neoadjuvant TCHP x 6 cycles

3/25/19: Left breast nipple sparing mastectomy, left SLN, TE/ADM reconstruction

Courtesy of Mark D Pegram, MD

post NACT MRI shows resolution of disease

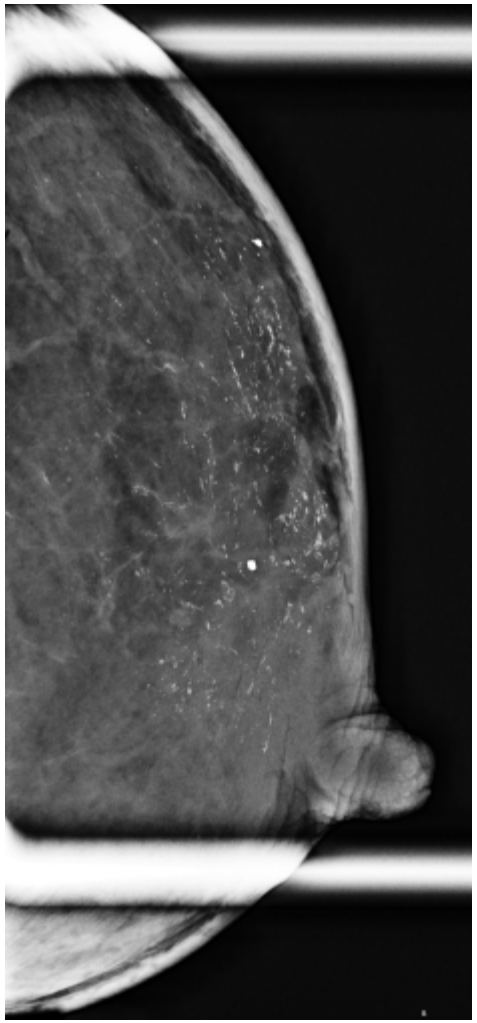
1/4/19 post NACT MRI

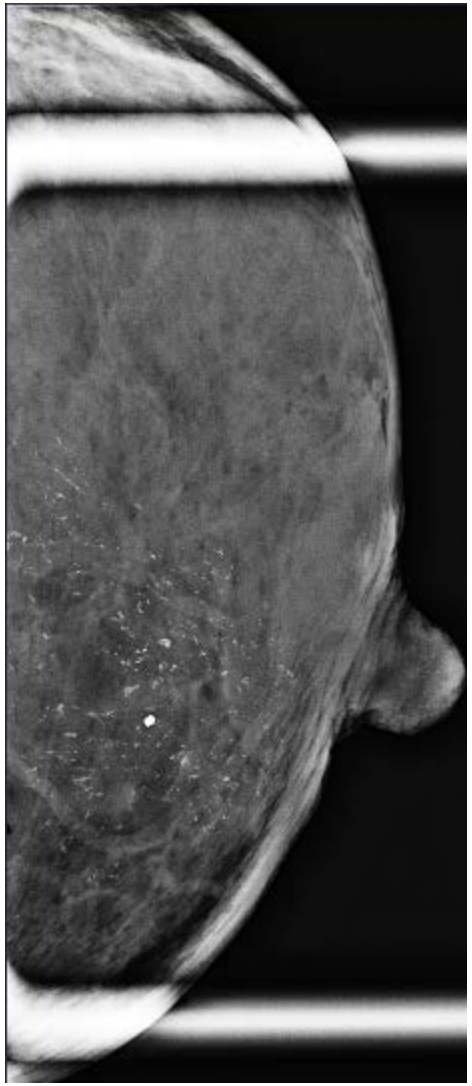


Courtesy of Mark D Pegram, MD

2/14/19 diagnostic mammogram shows stable distribution and extent of calcs

2/14/19 diagnostic mammogram





Courtesy of Mark D Pegram, MD

Case Presentation – Dr Pegram: 42-year-old woman (cont)

Left breast, mastectomy

- Residual invasive ductal carcinoma with treatment effect, 7.8 cm, 5% tumor cellularity
- Residual DCIS
- Extensive lymphovascular invasion
- Invasive carcinoma present at posterior margins, other close margins

Left axillary sentinel lymph nodes

- Metastatic carcinoma in two of three lymph nodes (2/3)

Left axillary lymph nodes

- Metastatic carcinoma in three of eleven lymph nodes (3/11)

Pathologic Stage: ypT3 N2a

Case Presentation – Dr Pegram: 42-year-old woman (cont)

- 5/6/19: Revision of left mastectomy flap
- Received T-DM1 X 14 cycles post-op
- Final reconstruction 12/2019

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer (BC) Receiving Neoadjuvant Systemic Therapy — Dr Pegram

Module 2: Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive BC — Dr Tolaney

Module 3: Optimizing the Management of HER2-Positive Metastatic BC (mBC) — Dr Hurvitz

Module 4: Treatment of HER2-Positive Brain Metastases — Dr Anders

Module 5: Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hamilton

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

ADJUVANT AND EXTENDED-ADJUVANT THERAPY FOR PATIENTS WITH LOCALIZED HER2+ BREAST CANCER

Sara M. Tolaney

Dana-Farber Cancer Institute

APHINITY UPDATED ANALYSIS: IDFS BY SUBGROUPS 74.1 MONTHS MEDIAN FU

	PERTUZUMAB	PLACEBO	DIFFERENCE	HAZARD RATIO
ITT	90.6%	87.8%	2.8%	0.76
HR+	91.2%	88.2%	3.0%	0.73
HR-	89.5%	87.0%	2.5%	0.83
Node +	87.9%	83.4%	4.5%	0.72
Node -	95.0%	94.9%	0.1%	1.02

- **BENEFIT SEEN IN HR+/HR- AND NODE POSITIVE**
- **NO BENEFIT IN NODE NEGATIVE**
- **NO OS BENEFITS YET SEEN**

Piccart M et al, SABCS 2019

Courtesy of Sara M Tolaney, MD, MPH

WHEN DO WE THEN GIVE PERTUZUMAB?

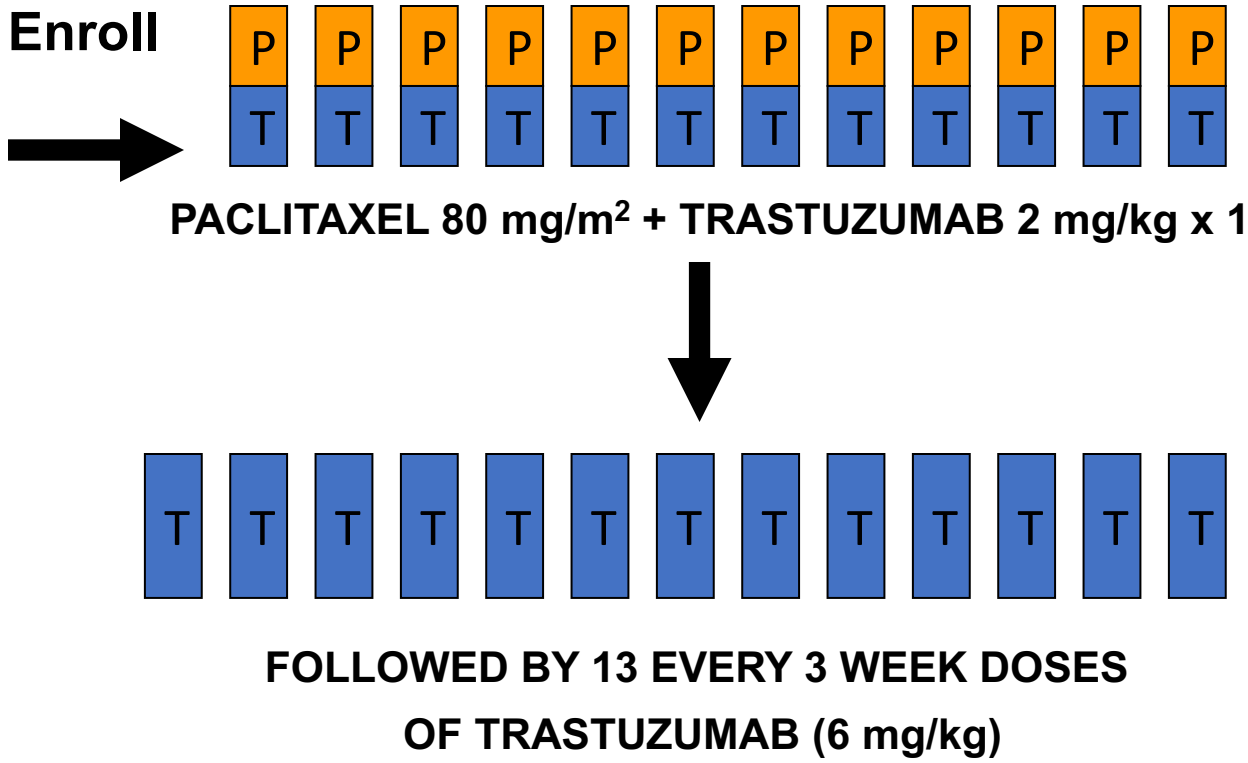
- Most patients with HER2+ tumors >2cm or clinically node positive disease receive preoperative therapy
- The addition of pertuzumab improves pCR but will not improve DFS in *all* patients (ie. not node negative patients)
- Administration of preoperative pertuzumab to all patients may result in some overtreatment, but challenging to discern which patients need pertuzumab upfront

Courtesy of Sara M Tolaney, MD, MPH

WHAT ABOUT STAGE 1 HER2+ PATIENTS?
APT TRIAL: STUDY DESIGN

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400

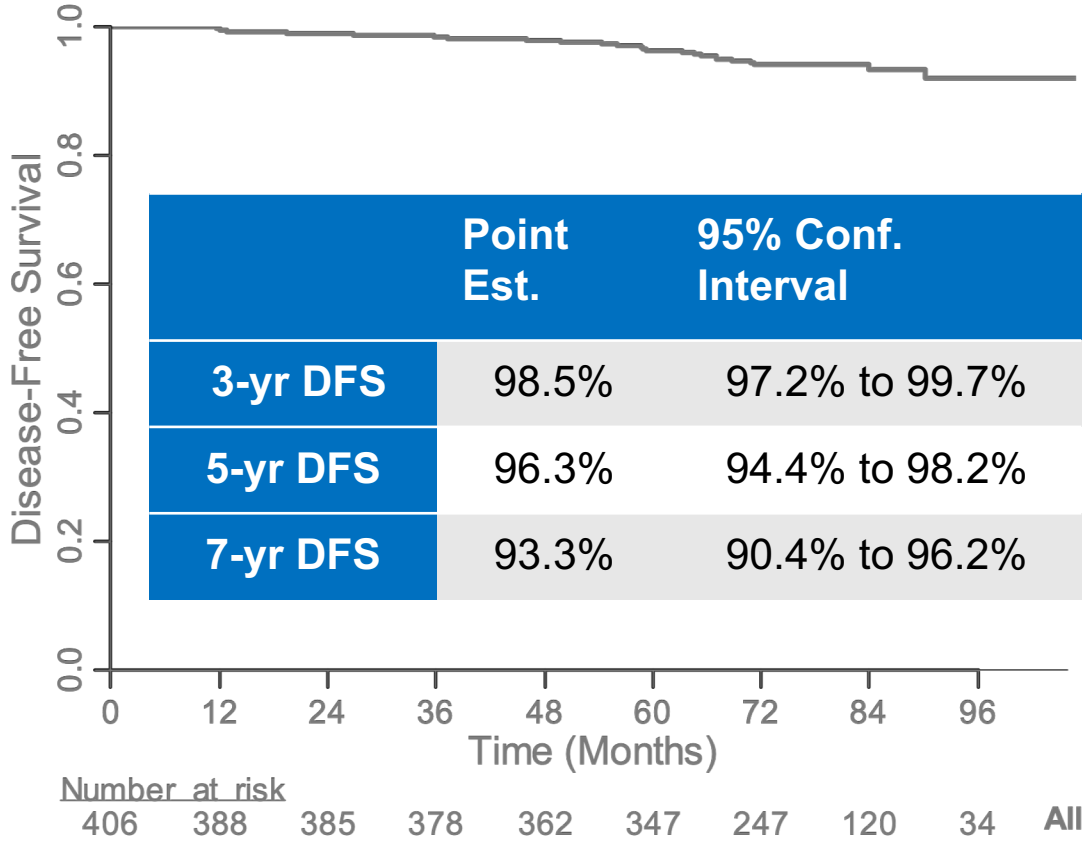


Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019

Courtesy of Sara M Tolaney, MD, MPH

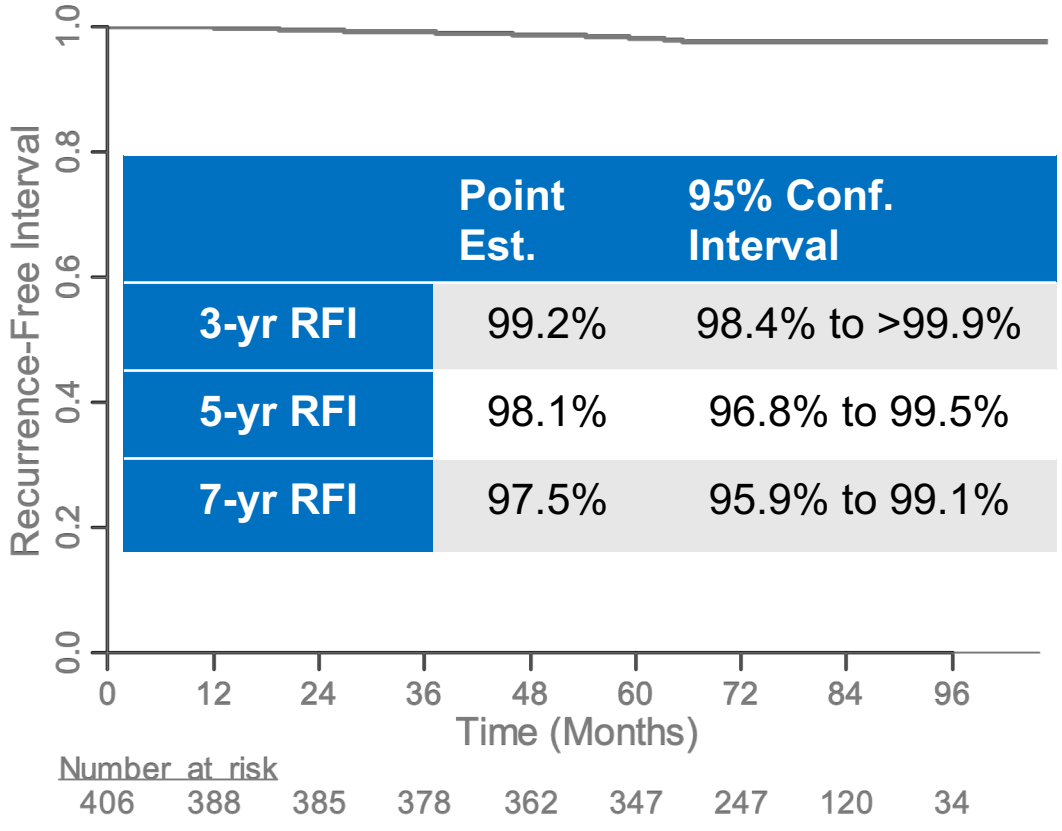
APT: OUTCOMES AT 7 YRS

DISEASE-FREE SURVIVAL



	Point Est.	95% Conf. Interval
3-yr DFS	98.5%	97.2% to 99.7%
5-yr DFS	96.3%	94.4% to 98.2%
7-yr DFS	93.3%	90.4% to 96.2%

RECURRENCE-FREE INTERVAL



	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to >99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al, JCO 2019

Courtesy of Sara M Tolaney, MD, MPH

Does T-DM1 have a role for Stage I HER2+ Disease? ATEMPT Trial

Key Eligibility Criteria

- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

N = 497

R 3:1

3

1

N = 383

T-DM1

3.6 mg/kg IV q3 wks x 17

N = 114

TH

Paclitaxel 80 mg/m^2 IV + Trastuzumab 2 mg/kg IV wkly x12 → Trastuzumab 6 mg/kg every 3 wks x13

Stratification factors:

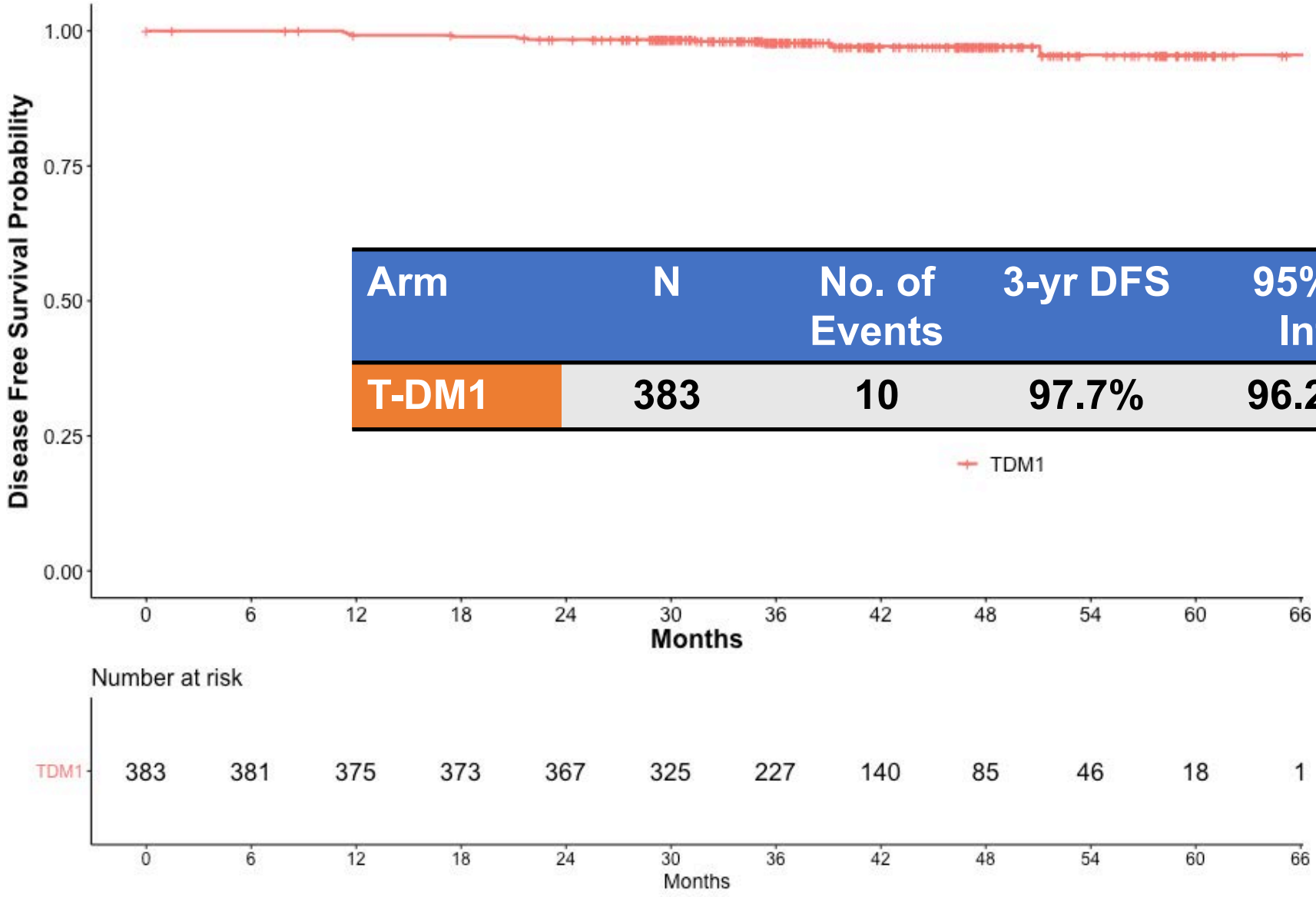
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

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

Tolaney S et al. SABCS 2019

Courtesy of Sara M Tolaney, MD, MPH

ATEMPT: DISEASE-FREE SURVIVAL FOR T-DM1



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

p<0.0001

Tolaney S et al. SABCS 2019

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 non-hematologic 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%)

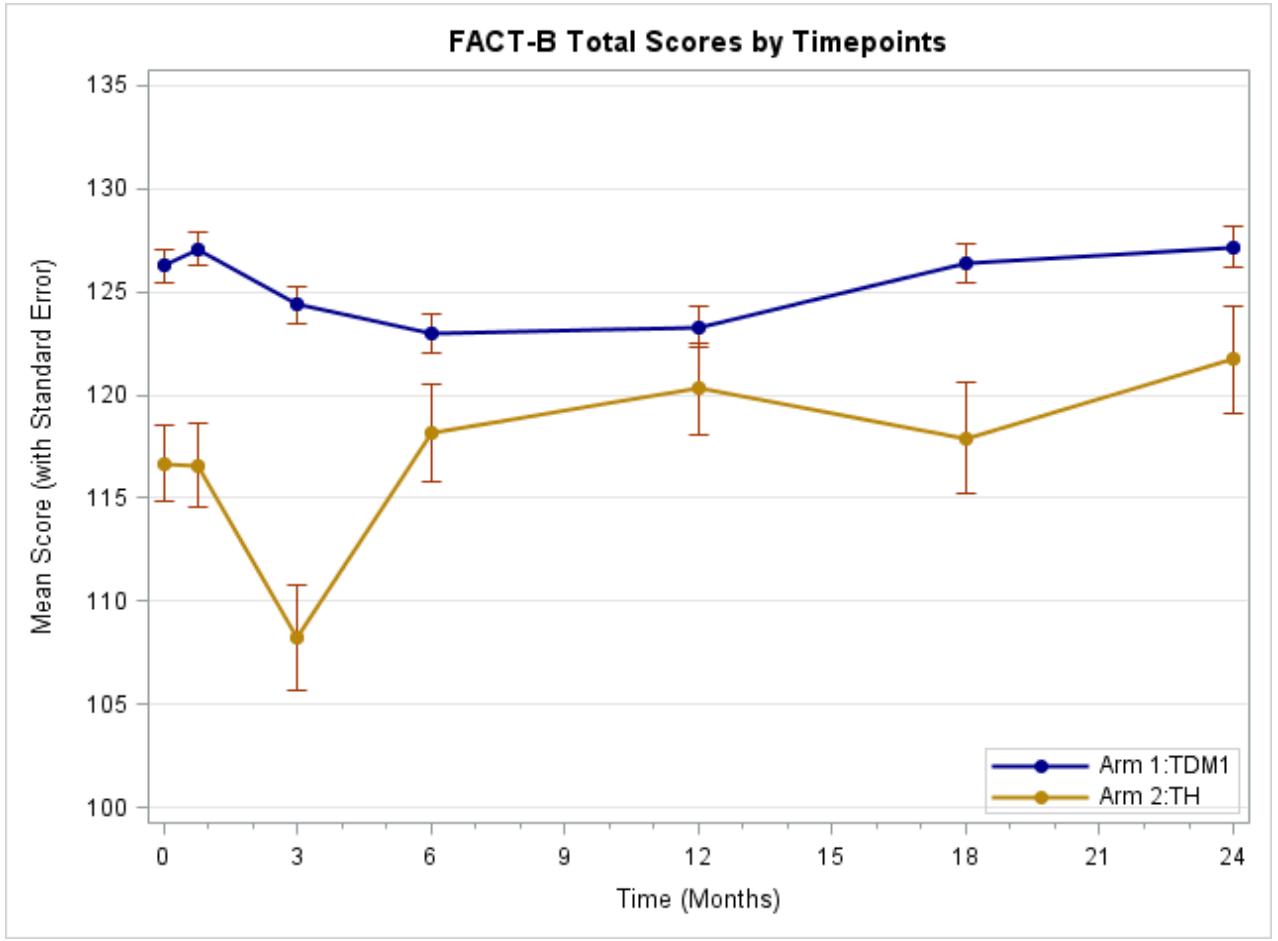
p=0.91

Tolaney S et al. SABCS 2019

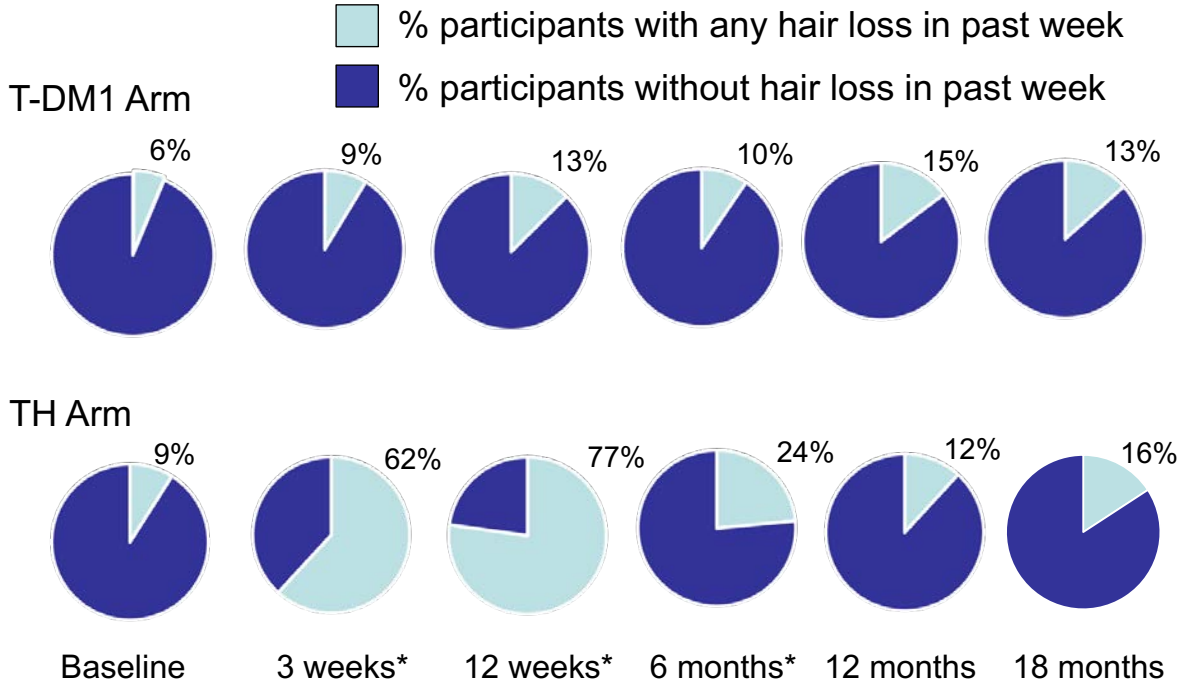
Courtesy of Sara M Tolaney, MD, MPH

ATEMPT TRIAL: PROS

QUALITY OF LIFE



Alopecia

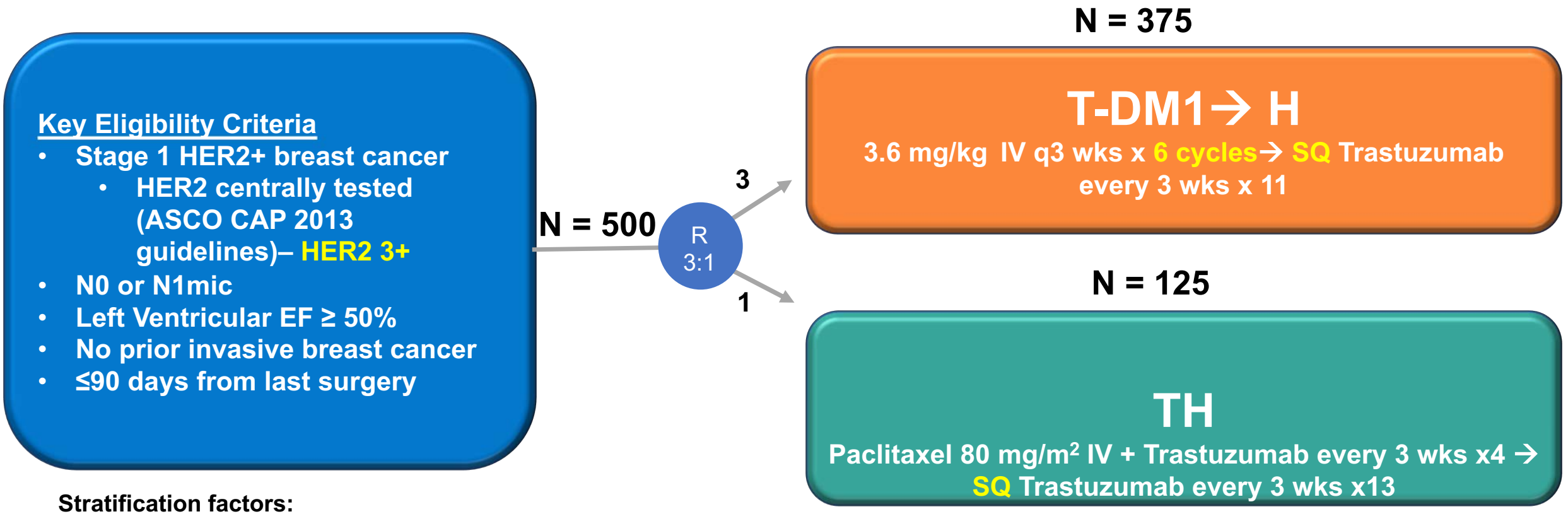


- * Indicates statistically significantly ($p<0.05$) greater hair loss at timepoint for TH vs. T-DM1

Partridge et al, SABCS 2019

Courtesy of Sara M Tolaney, MD, MPH

PLANNED STUDY: ATEMPT 2.0



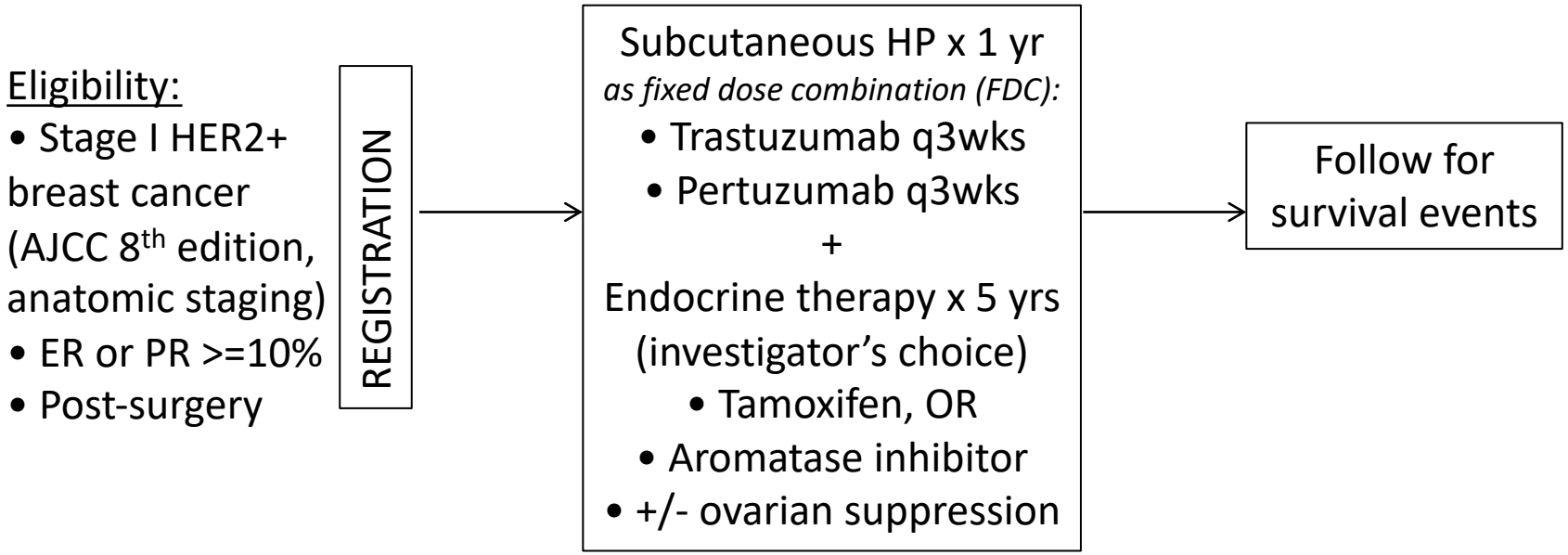
Stratification factors:

- **Age (<55, ≥55)**
- **Planned radiation (Yes/No)**
- **Planned hormonal therapy (Yes/No)**

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

Courtesy of Sara M Tolaney, MD, MPH

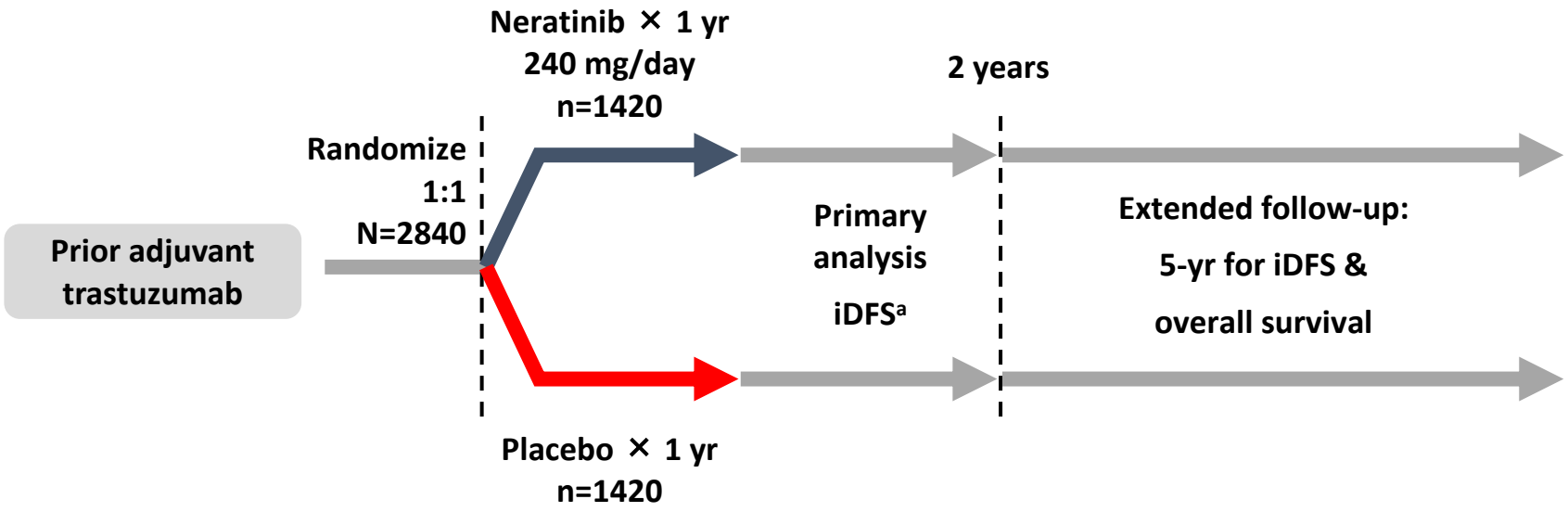
PLANNED STUDY: A SINGLE ARM PHASE II STUDY OF ADJUVANT ENDOCRINE THERAPY, SUBCUTANEOUS PERTUZUMAB, AND TRASTUZUMAB FIXED-DOSE COMBINATION FOR PATIENTS WITH ANATOMIC STAGE I HORMONE RECEPTOR-POSITIVE, HER2-POSITIVE BREAST CANCER (ADEPT)



PI: Ada Waks

Courtesy of Sara M Tolaney, MD, MPH

ADDING NERATINIB: ExteNET STUDY



Primary endpoint: invasive disease-free survival (iDFS)[a]

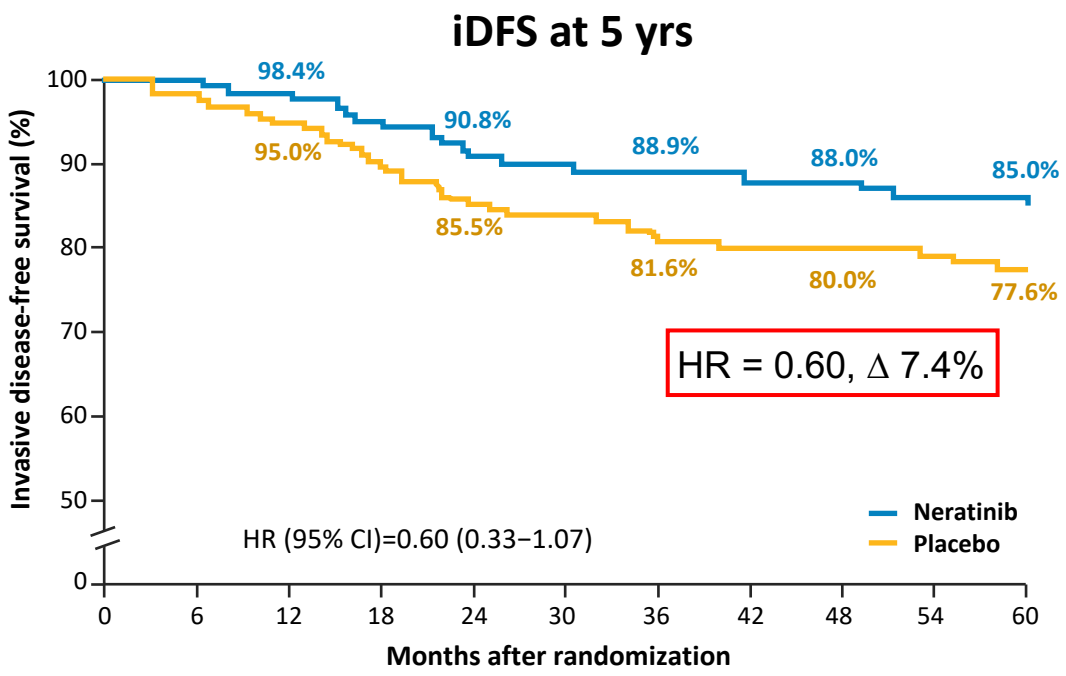
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

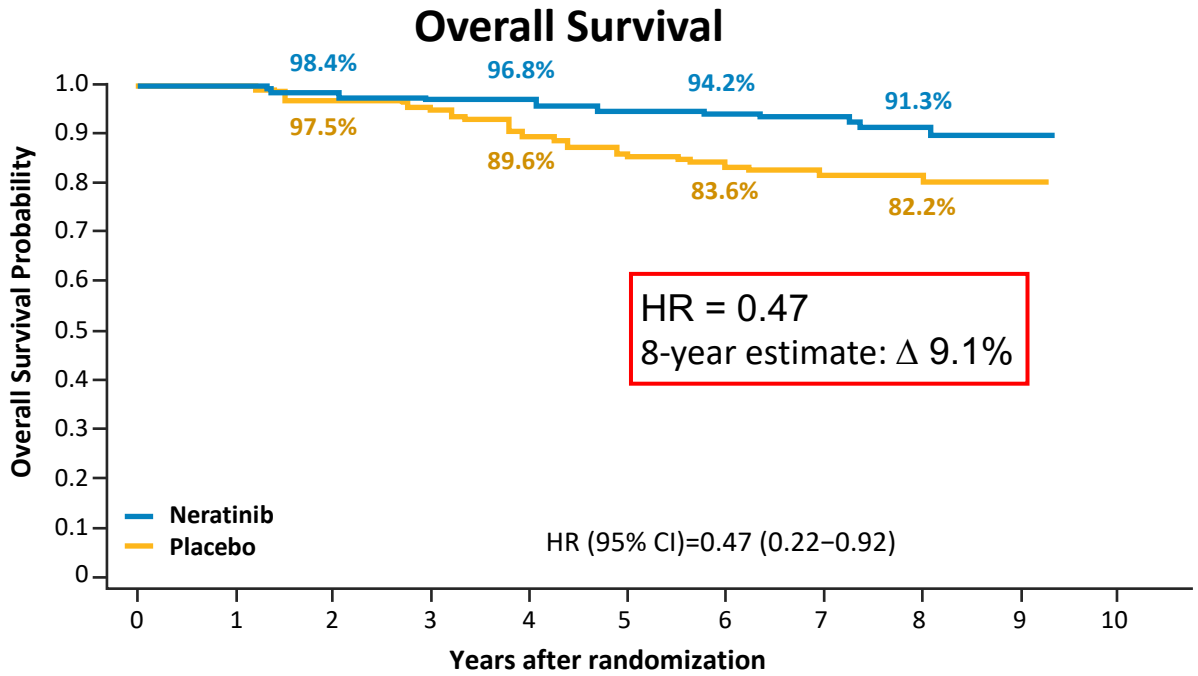
Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Study blinded: Until primary analysis; OS remains blinded

Courtesy of Sara M Tolaney, MD, MPH

ExteNET: No pCR Post Neoadjuvant Therapy HR+, ≤1 Year from Trastuzumab (N=295)





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

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, A. Clin Breast Cancer. 2020. Online ahead of print.

Courtesy of Sara M Tolaney, MD, MPH

Descriptive Analysis: Cumulative Incidence of CNS recurrences at first site of mets at 5 years HR+/≤1-year population (*n*=1334)

Subgroup	Cumulative Incidence of CNS recurrences at 5 years, %	
	Neratinib	Placebo
	%	%
All patients (*n*=1334)	0.7	2.1
Prior neoadjuvant therapy		
No (*n*=980)	0.7	1.5
Yes (*n*=354)	0.7	3.7
pCR status[1]		
No (*n*=295)	0.8	3.6
Yes (*n*=38)*	0	5

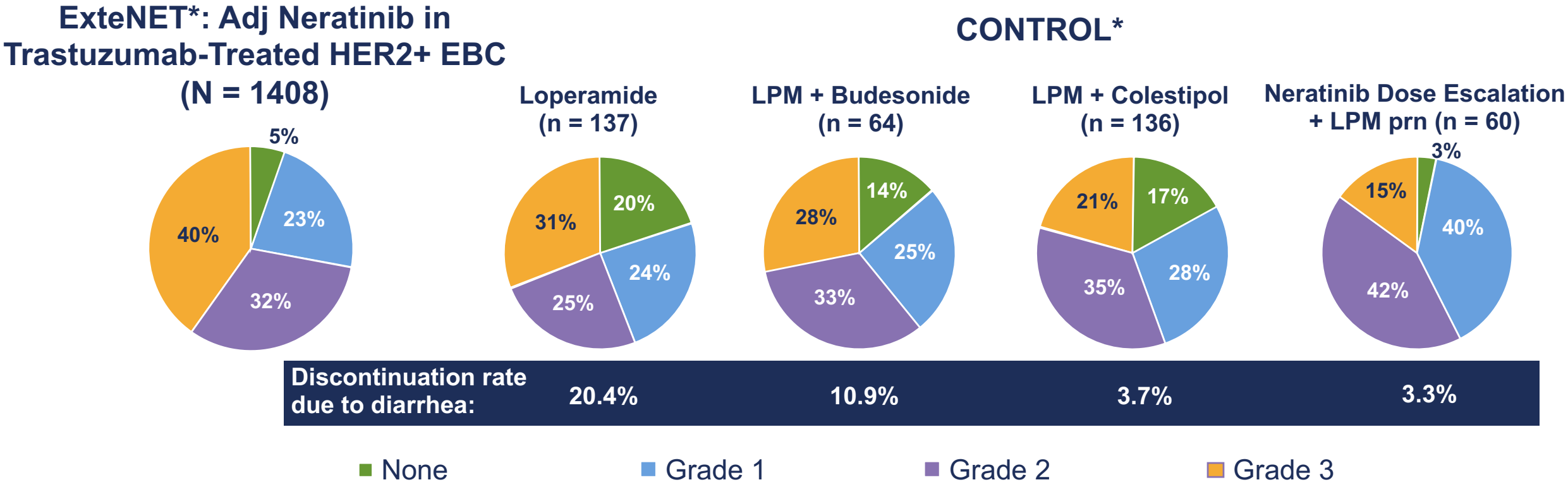
*Small Ns

1. Among the 354 patients who had received neoadjuvant therapy, 295 had no pCR, 38 patients achieved a pCR, and 21 patients had no outcome reported

CI, confidence interval; CNS, central nervous system; NE, not estimated; pCR, pathologic complete response

Courtesy of Sara M Tolaney, MD, MPH

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

WHEN SHOULD WE GIVE NERATINIB?

- Benefit seen in patients with high risk HR+ HER2+ disease (larger benefit in patients with residual disease after preoperative therapy)
- Challenge is lack of data in patients who have previously received pertuzumab and/or T-DM1
- Must also weigh potential benefit with toxicity (~40% grade 3/4 diarrhea)
    - All patients should receive prophylactic anti-diarrheals (OR can consider a dose escalation approach)

Courtesy of Sara M Tolaney, MD, MPH

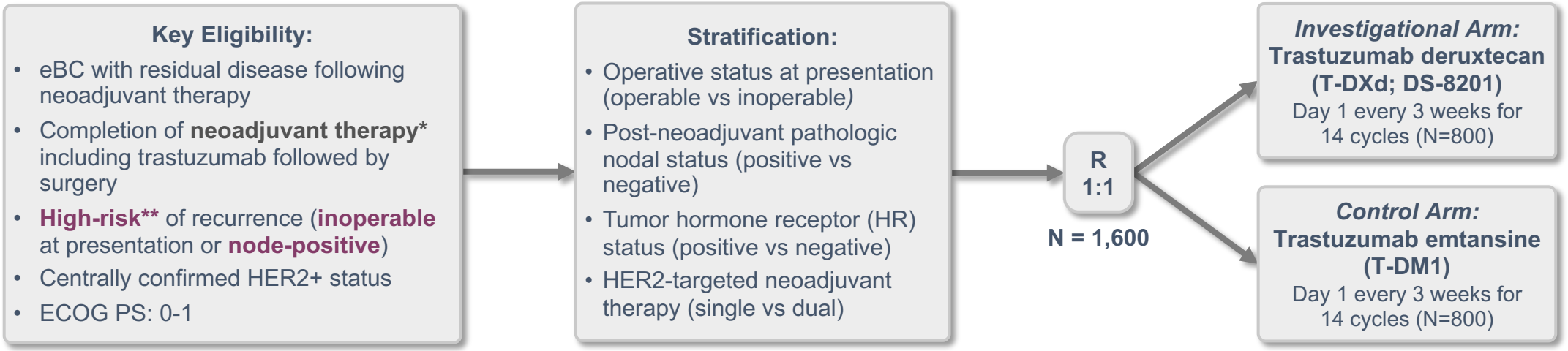
CAN WE IMPROVE UPON THE KATHERINE TRIAL OF T-DM1?

- 3 yr iDFS for N+ pts: 83%.
- No improvement in rates of CNS recurrence
- May want to consider further treatment escalation with future studies:
  - Add on strategies: T-DM1 + tucatinib (being explored in COMPASS-RD)
  - Substitution strategies: Trastuzumab deruxtecan (DS-8201a)

Courtesy of Sara M Tolaney, MD, MPH

DESTINY-Breast05 (DS8201-A-U305) Study Design

T-DXd vs. T-DM1 in high-risk HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant therapy



*Neoadjuvant therapy to include at least 16 weeks of total systemic treatment in the preoperative setting, including:

- At least 9 weeks of HER2-targeted therapy including **trastuzumab** (with or without pertuzumab) and,
- At least 9 weeks of **taxane** therapy

**High-risk definitions:

- **Inoperable:** Inoperable breast cancer at presentation with residual invasive cancer in the breast or axillary nodes following neoadjuvant therapy.
- **Node-positive:** Metastatic disease in axillary node(s) following neoadjuvant therapy irrespective of presence or absence of residual invasive cancer in the breast.

Additional Notes: Randomization within 12 weeks of surgery; adjuvant radiotherapy and/or endocrine therapy per protocol and local guidelines.

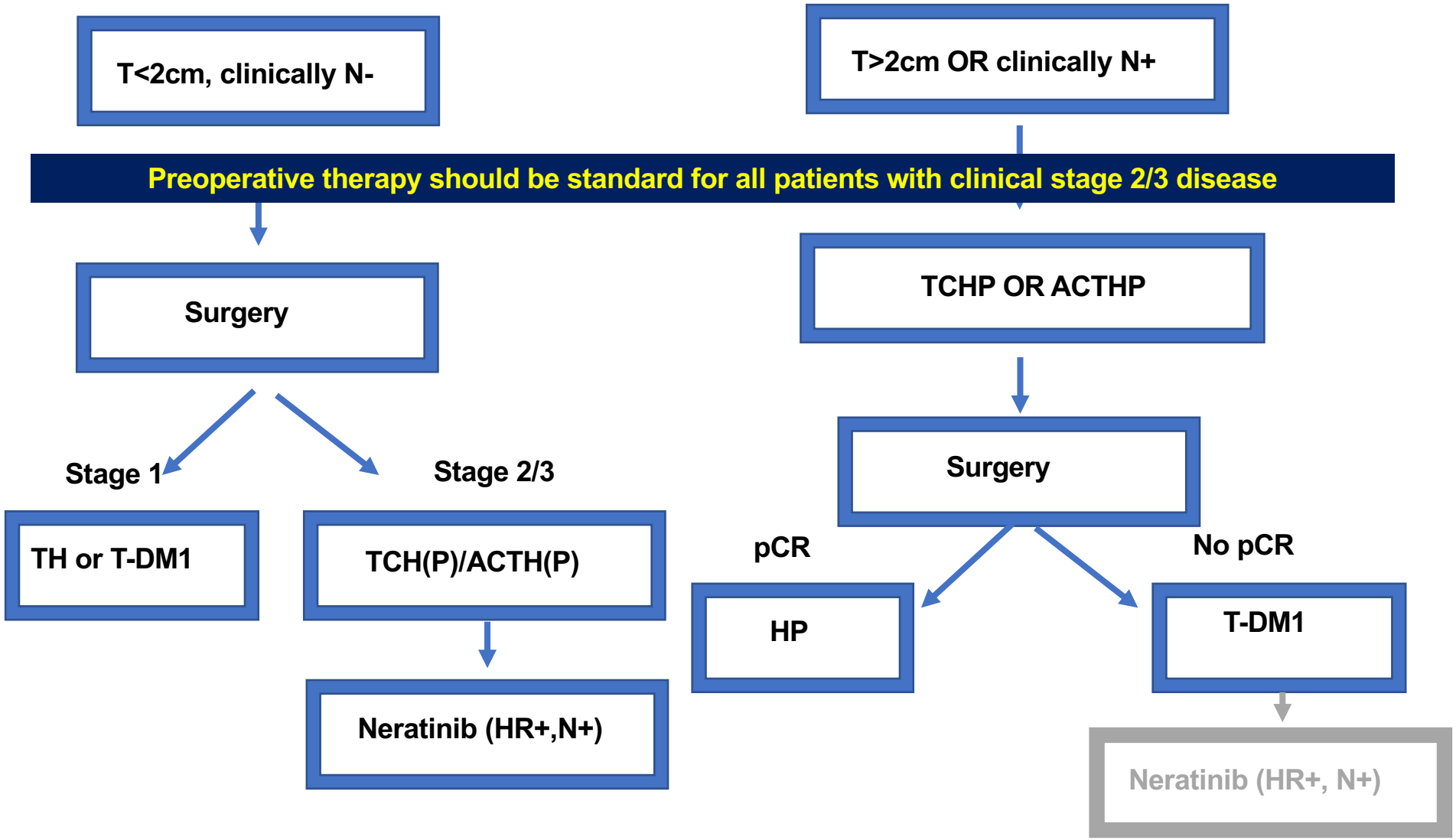
Endpoints:

- **Primary:**
  - **IDFS** (Invasive disease-free survival)
- **Secondary:**
  - **DFS** (Disease-free survival)
  - **DRFI** (Distant recurrence-free interval)
  - **BMFI** (Brain metastases-free interval)
  - **OS** (Overall survival)
  - **Adverse events**
- **Exploratory:**
  - **PROs** (Patient reported outcomes; QoL)
  - **Biomarkers** associated with efficacy/safety
  - **PK** associated with efficacy/safety

eBC=early breast cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; HER2=Human epidermal growth factor receptor 2; PK=pharmacokinetics; QoL=quality of life R=randomization

Courtesy of Sara M Tolaney, MD, MPH

Current Approach for Treatment of HER2+ breast cancer: 2020



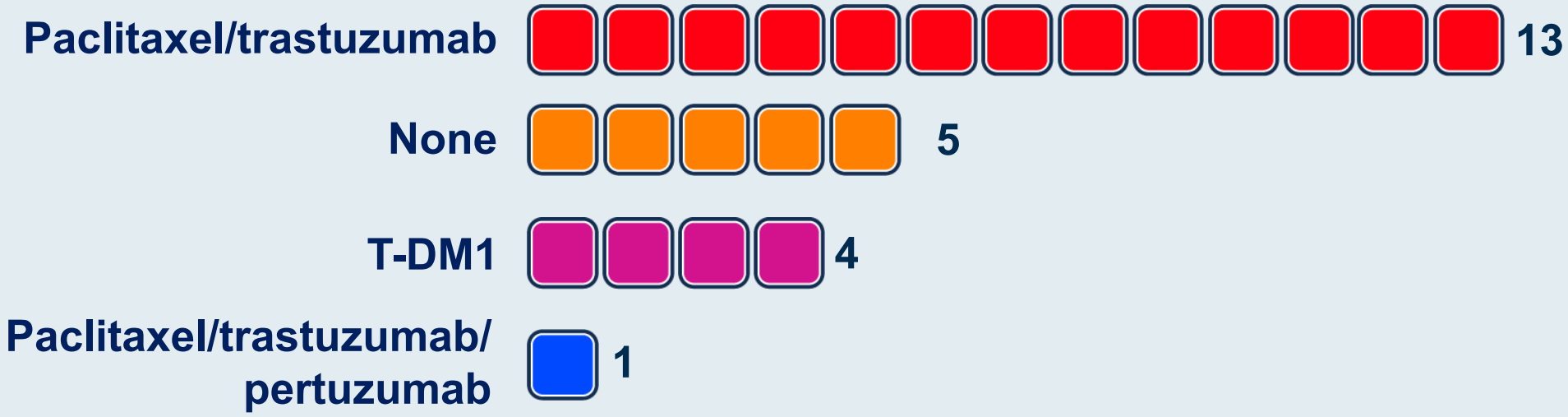
Courtesy of Sara M Tolaney, MD, MPH

An 80-year-old woman presents with a 0.6-cm, ER-negative, HER2-positive, node-negative IDC. Regulatory and reimbursement issues aside, what adjuvant systemic therapy would you recommend?

1. None
2. Paclitaxel/trastuzumab
3. Paclitaxel/trastuzumab/pertuzumab
4. TCH
5. TCHP
6. T-DM1
7. Other

Regulatory and reimbursement issues aside, what adjuvant systemic therapy would you recommend for a patient with an ER-negative, HER2-positive, node-negative IDC with the following characteristics?

Age: 80, Tumor size: 0.6 cm



Survey of 25 Breast Cancer Clinical Investigators

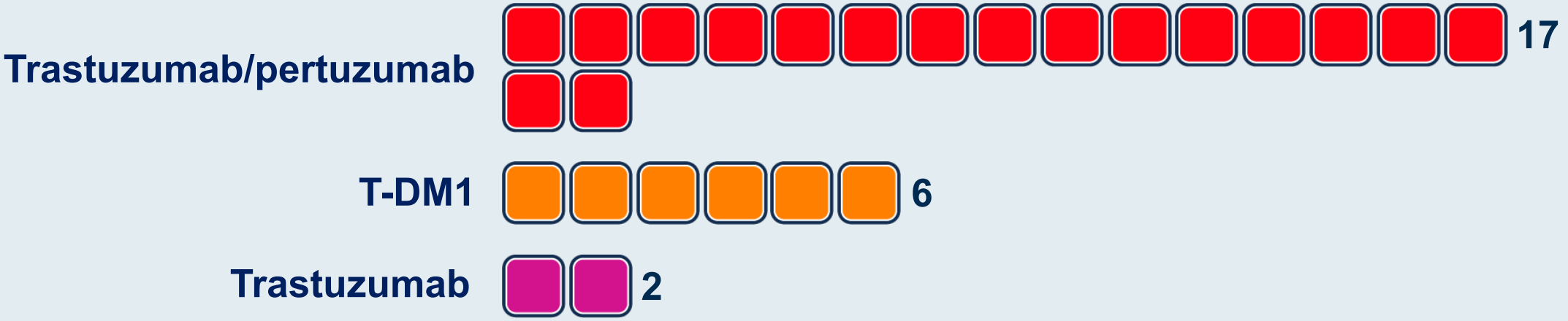
A 65-year-old woman presents with a 1.3-cm, ER-positive, HER2-positive IDC with 2 positive sentinel nodes. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

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

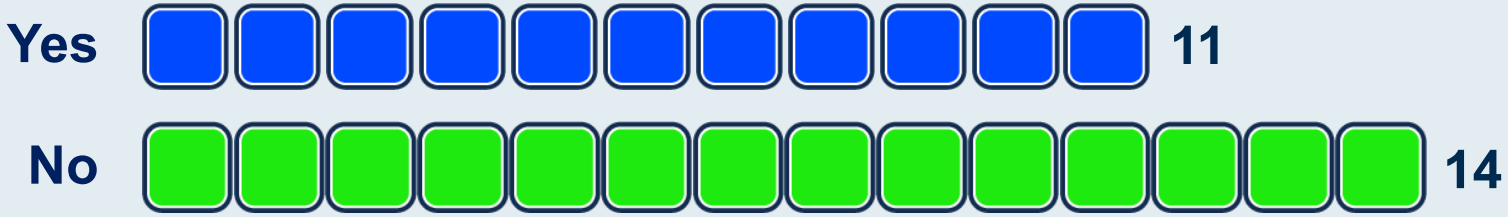
RTP
RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend for a 65-year-old patient with a 1.3-cm, HER2-positive IDC with the following characteristics?

ER-positive, 2 positive sentinel nodes

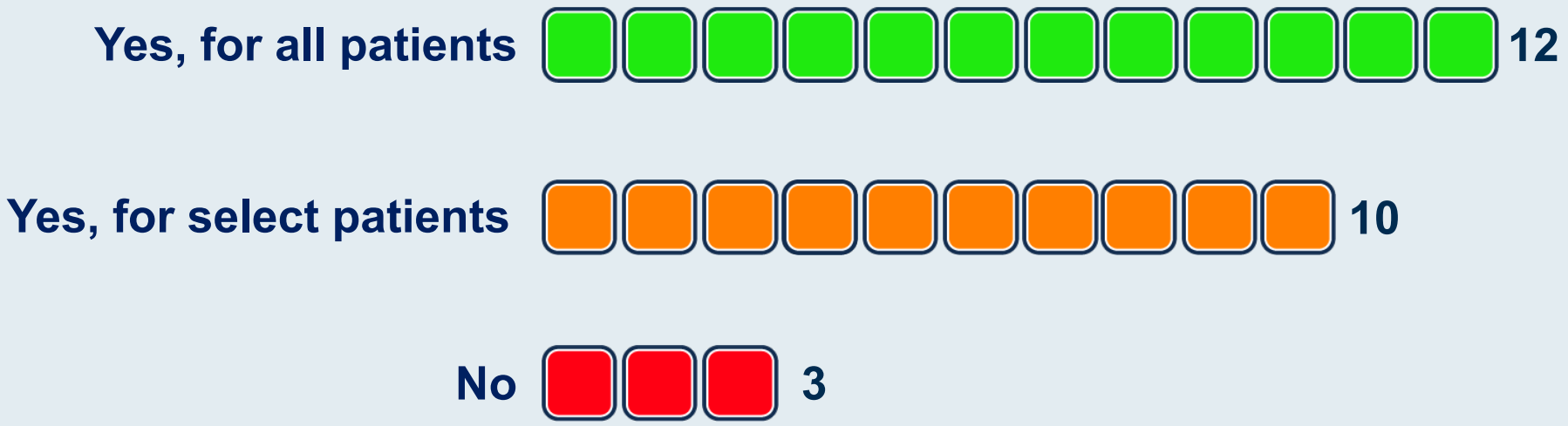


Postadjuvant neratinib?



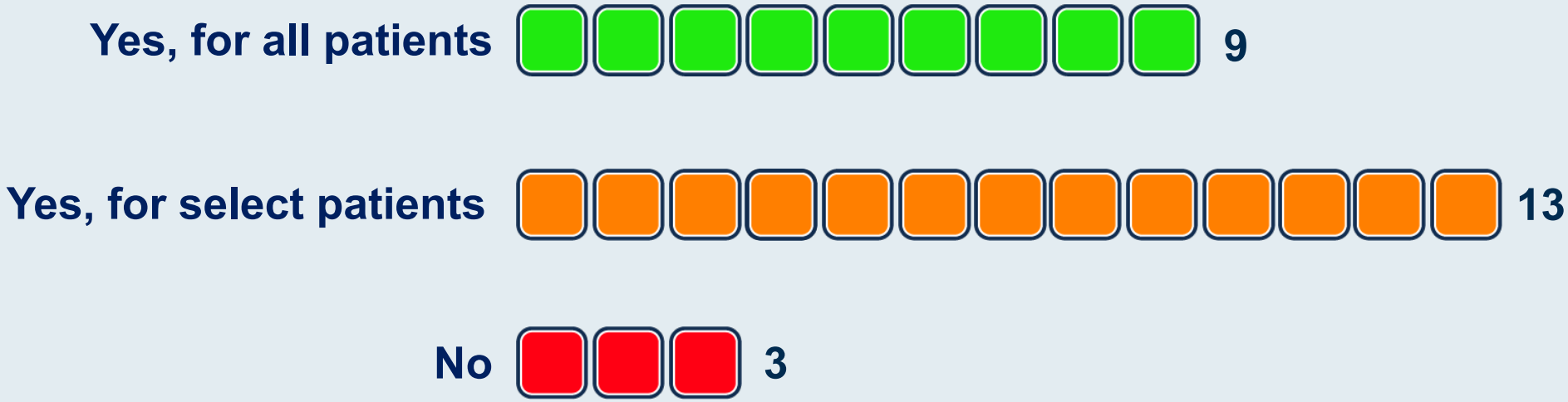
Survey of 25 Breast Cancer Clinical Investigators

Reimbursement issues aside, would you like to substitute the subcutaneous formulation of pertuzumab, trastuzumab and hyaluronidase–zzxf for standard intravenous pertuzumab and trastuzumab for patients with HER2-positive breast cancer in your practice?



Survey of 25 Breast Cancer Clinical Investigators

Reimbursement issues aside, do you believe your patients with HER2-positive breast cancer would prefer to receive the subcutaneous formulation of pertuzumab, trastuzumab and hyaluronidase–zzxf rather than standard intravenous pertuzumab and trastuzumab?



Survey of 25 Breast Cancer Clinical Investigators

Case Presentation – Dr Tolaney: 43-year-old woman with HER2-positive, ER-positive breast cancer

- 43 yo premenopausal woman presented with a palpable 4.5cm L breast mass with a palpable axillary lymph node
- Biopsy revealed grade 2 IDC, ER+, PR+, HER2 2+, FISH 3.5
- Received preop TCHP
- Underwent lumpectomy and SN biopsy: residual 2.5 cm of disease, with 2/4 SN involved; underwent completion axillary dissection with no additional positive nodes
- Received adjuvant T-DM1 x 14 cycles, and adjuvant radiation

Started recently on neratinib with dose-escalation strategy

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer (BC) Receiving Neoadjuvant Systemic Therapy — Dr Pegram

Module 2: Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive BC — Dr Tolaney

Module 3: Optimizing the Management of HER2-Positive Metastatic BC (mBC) — Dr Hurvitz

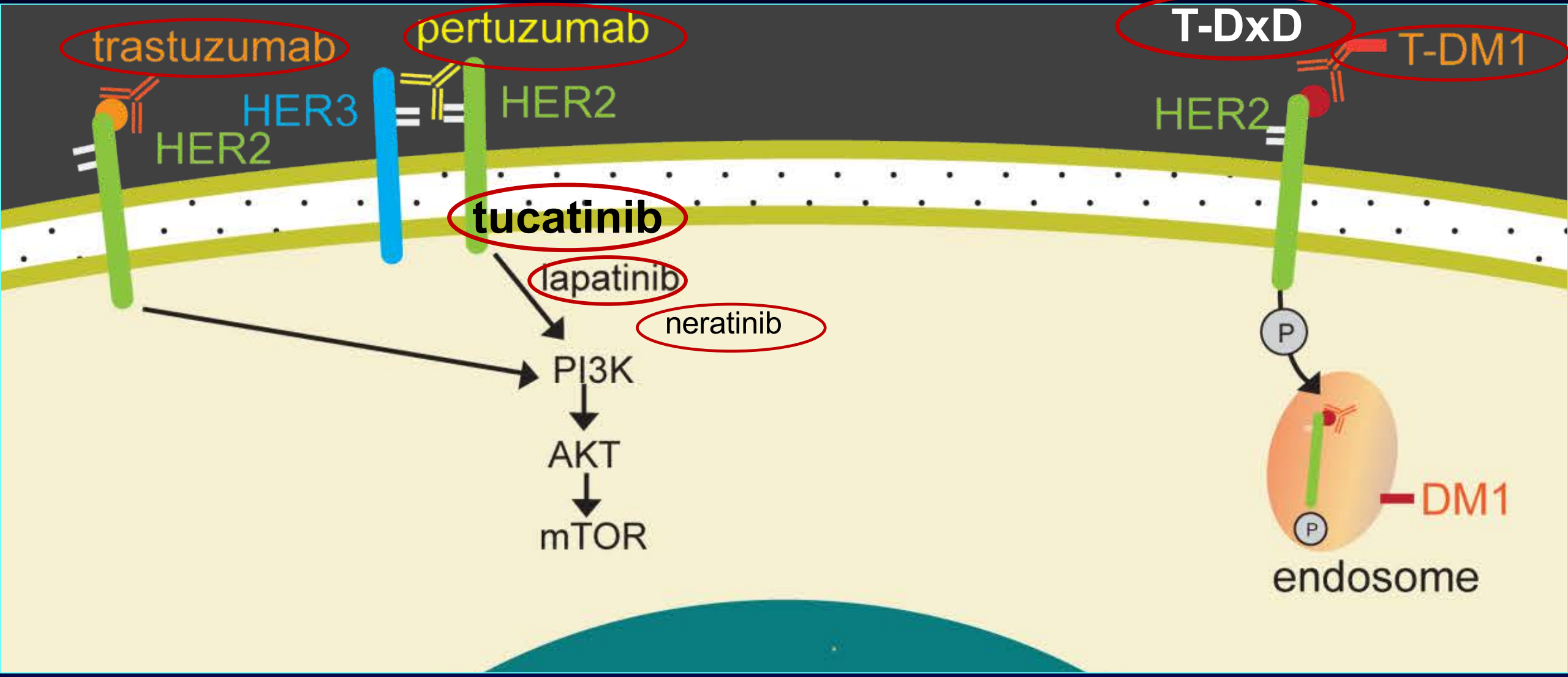
Module 4: Treatment of HER2-Positive Brain Metastases — Dr Anders

Module 5: Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hamilton

Optimizing the Management of HER2-Positive Metastatic Breast Cancer (mBC)

Sara A Hurvitz, MD, FACP
Professor of Medicine

2020: 7 FDA APPROVED HER2-DIRECTED THERAPIES

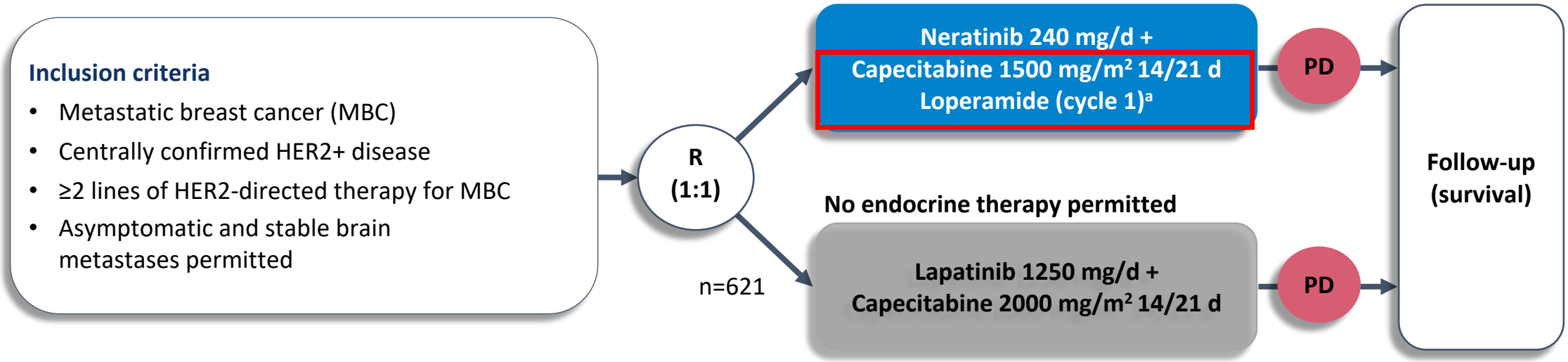


T-DM1, trastuzumab emtansine

Gajria D, et al. *Expert Rev Anticancer Ther*. 2011;11:263-275.

Courtesy of Sara Hurvitz, MD

NALA Phase III trial of neratinib: study design



Stratification variables

- Number of prior HER2 therapies for MBC
- Disease location
- HR status
- Geographic location

Endpoints

- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

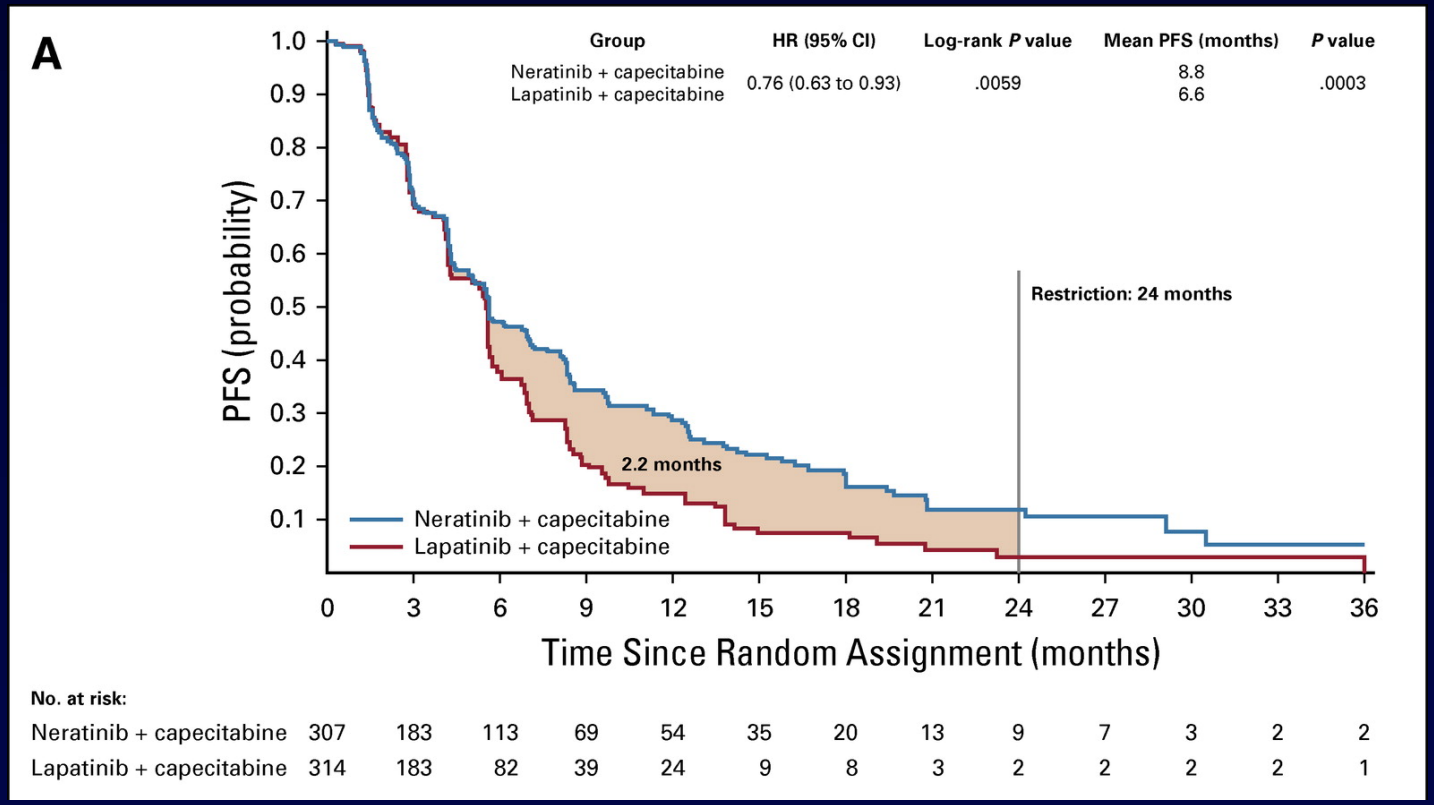
Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

Saura C, et al. ASCO Annual Meeting 2019;*Journal of Clinical Oncology* 37, no. 15_suppl (May 20, 2019) Abs 1002

Courtesy of Sara Hurvitz, MD

NALA Results

- PFS (by restricted means analysis at 24 mos)
  - 8.8 mos (neratinib) vs. 6.6 mos (lapatinib) p=0.003
- Cumulative incidence intervention CNS mets
  - 22.8% (neratinib) vs 29.2% (lapatinib); p=0.043
- Grade 3/4 diarrhea
  - 24% (neratinib) vs. 13% (lapatinib)



Saura C, et al. *Journal of Clinical Oncology* 2020:38(27):3138-3149.

Courtesy of Sara Hurvitz, MD

CONTROL: Incidence of Treatment-Emergent Diarrhea by Worst Grade in ADJUVANT setting

	LOP (n=137)	LOP + budesonide (n=64)	LOP + colestipol (n=136)	LOP prn + colestipol (n=104)	LOP prn + neratinib dose escalation (n=60)
Treatment-emergent diarrhea incidence, N (%)					
No diarrhea	28 (20)	9 (14)	23 (17)	5 (5)	2 (3)
Gr 1	33 (24)	16 (25)	38 (28)	33 (32)	24 (40)
Gr 2	34 (25)	21 (33)	47 (35)	31 (30)	25 (42)
Gr 3	42 (31)	18 (28)	28 (21)	35 (34)	9 (15)
Gr 4	0	0	0	0	0

Budesonide 9 mg qd; colestipol 2g BID;
loperamide escalation: 120 mg x 7d →160 mg x 7 d then 240 mg

Courtesy of Sara Hurvitz, MD

Chan A, et al. Presented at the 2019 San Antonio Breast Cancer Symposium. Abstract #P5-14-03.

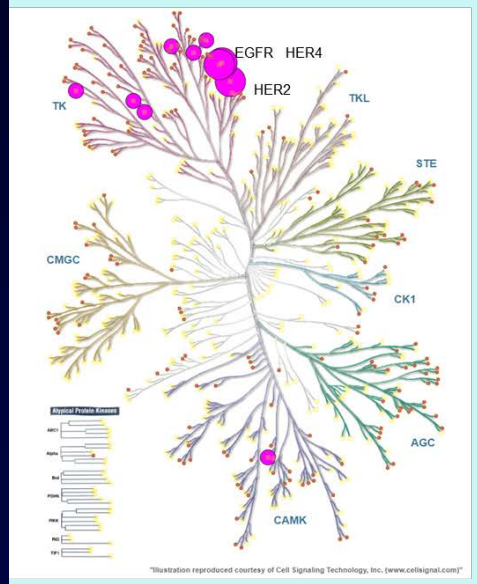
Neratinib Approval - 2.25.2020

Neratinib approved in combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer *who have received two or more prior anti-HER2 based regimens in the metastatic setting*.

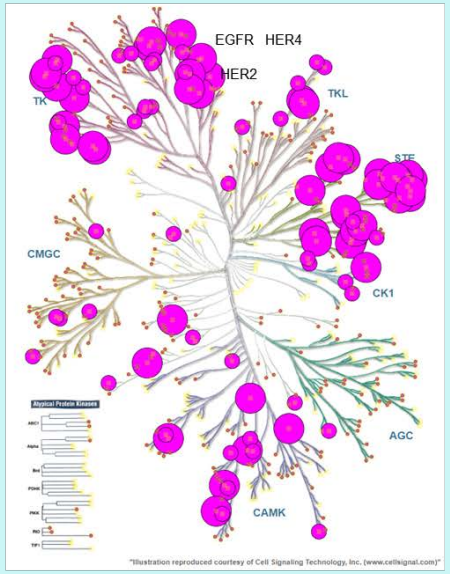
Neratinib PI.

Courtesy of Sara Hurvitz, MD

Tucatinib: HER2 Selective Kinase Inhibitor



Tucatinib



Neratinib

- IC50 < 1uM (large circle)
- 1uM < IC50 < 10uM (medium circle)
- IC50 > 10uM (small circle)

Kinome scan data from the Library of Integrated Network-based Cellular Signatures (https://lincs.hms.harvard.edu/kinomescan/)

- Kinome analysis shows limited activity in a panel of 237 protein kinases at 1 or 10 μM
  - Activity is restricted to HER2 related kinases EGFR and HER4
- Tucatinib is selective for HER2 vs. EGFR in biochemical assays

Compound	Biochemical Selectivity (Kinase Assays)	
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)
Tucatinib	6.9	449
Neratinib	5.6	1.8
Lapatinib	109	48

- *Lapatinib and neratinib inhibit EGFR and HER2 with similar potencies*

- Less EGFR-associated toxicity than other HER2-targeted TKIs
- CNS penetration
- Well tolerated and active in combinations (eg, with T-DM1, capecitabine, or trastuzumab)

Agent	Cellular Selectivity, IC_{50} (nM)	
	HER2	EGFR
Tucatinib	8	4000
Neratinib	7	8
Lapatinib	49	31

Courtesy of Sara Hurvitz, MD

HER2CLIMB Trial Design

Key Eligibility Criteria

- Measurable or non-measurable HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- Brain MRI at baseline
  - No evidence of brain metastases, or
  - Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

N=202

Placebo + Trastuzumab + Capecitabine
Treatment (21-day cycle)

Placebo (Pbo) +
Trastuzumab 6 mg/Kg Q3W (loading dose 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID (Days 1-14)

*Stratification Factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region of world (US or Canada or rest of world)

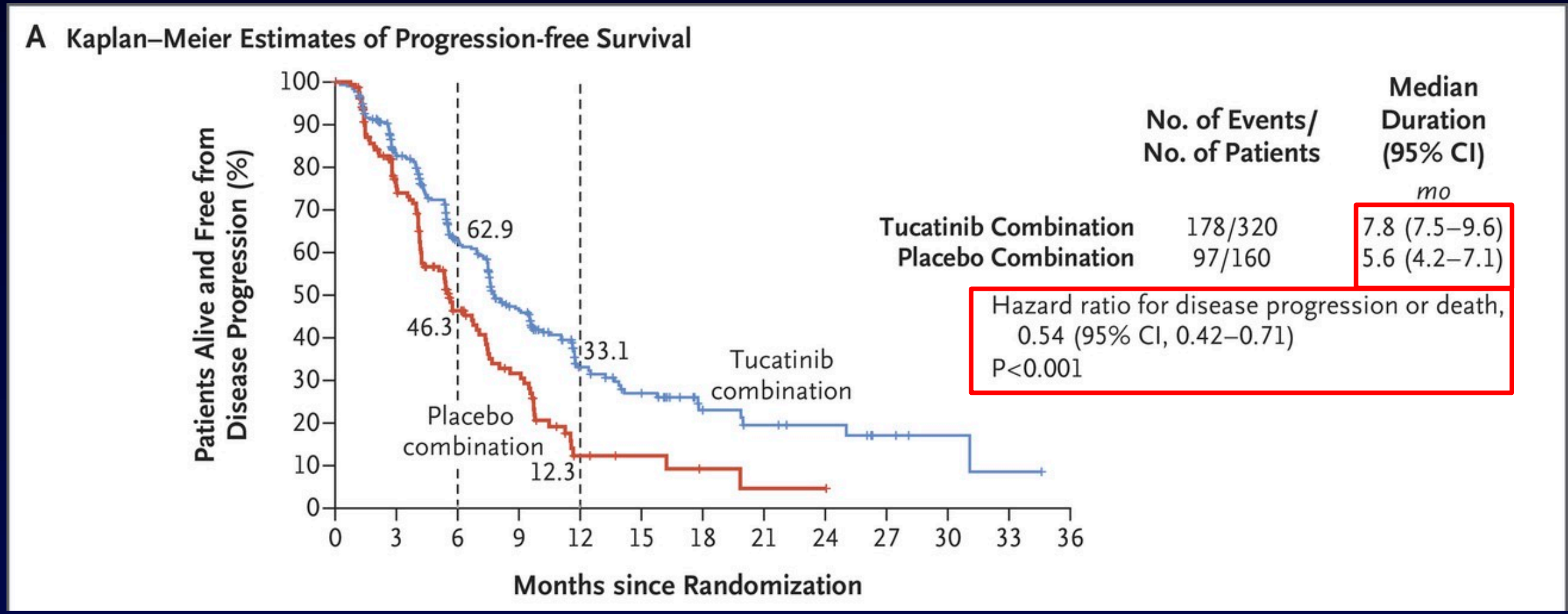
Baseline Characteristics of Note

- **60% HR positive**
- **48% CNS Metastases**
- **36% de novo metastatic breast cancer**
- **Median 3 prior lines of therapy in metastatic setting (range 1-14)**

Courtesy of Sara Hurvitz, MD

https://clinicaltrials.gov/ct2/show/NCT02614794

Progression-free Survival



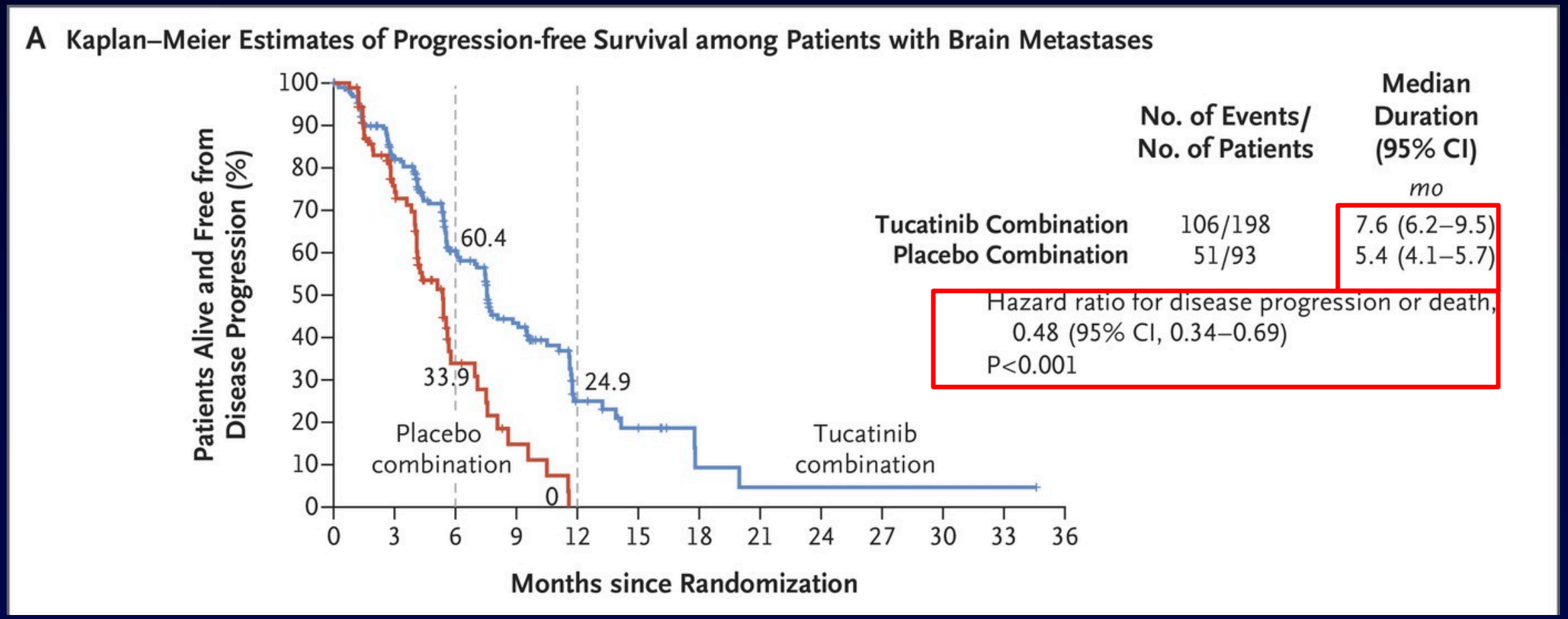
- ORR: 41% (tucatinib) vs. 23% (placebo)

The NEW ENGLAND JOURNAL of MEDICINE

RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Courtesy of Sara Hurvitz, MD

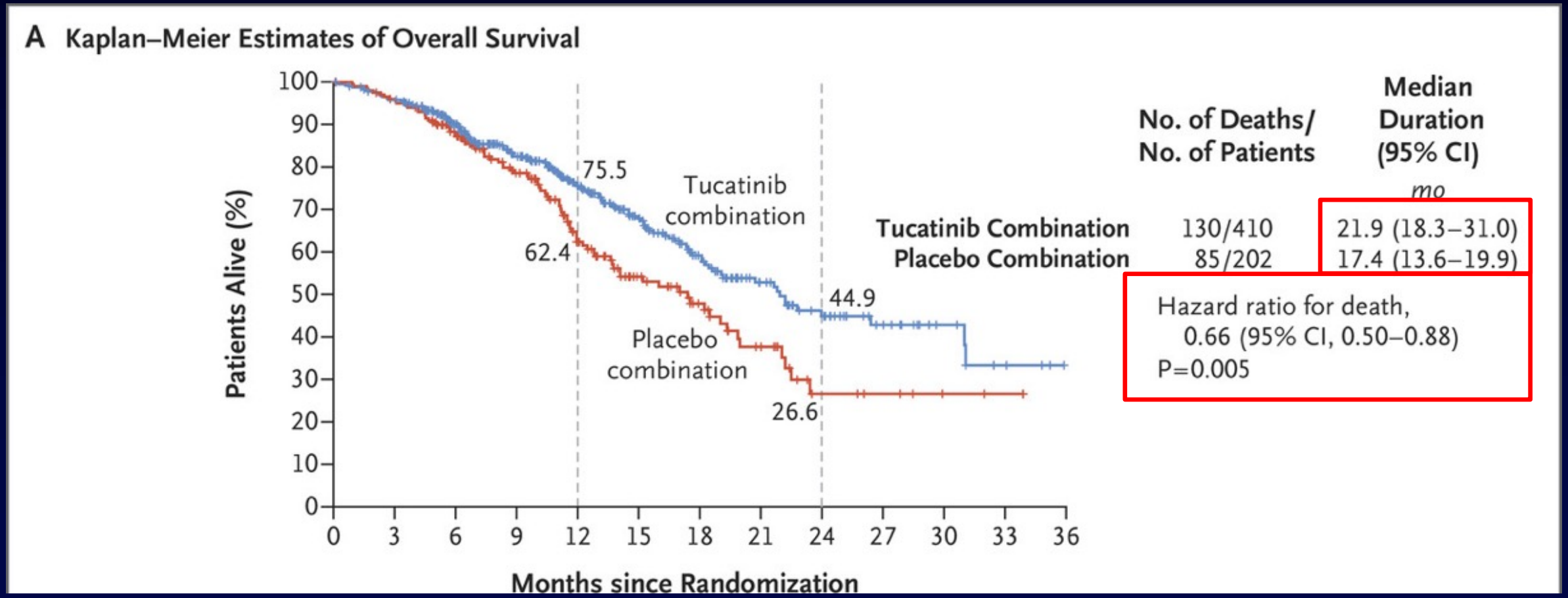
Progression-free Survival among the Patients with Brain Metastases



The NEW ENGLAND JOURNAL of MEDICINE
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Courtesy of Sara Hurvitz, MD

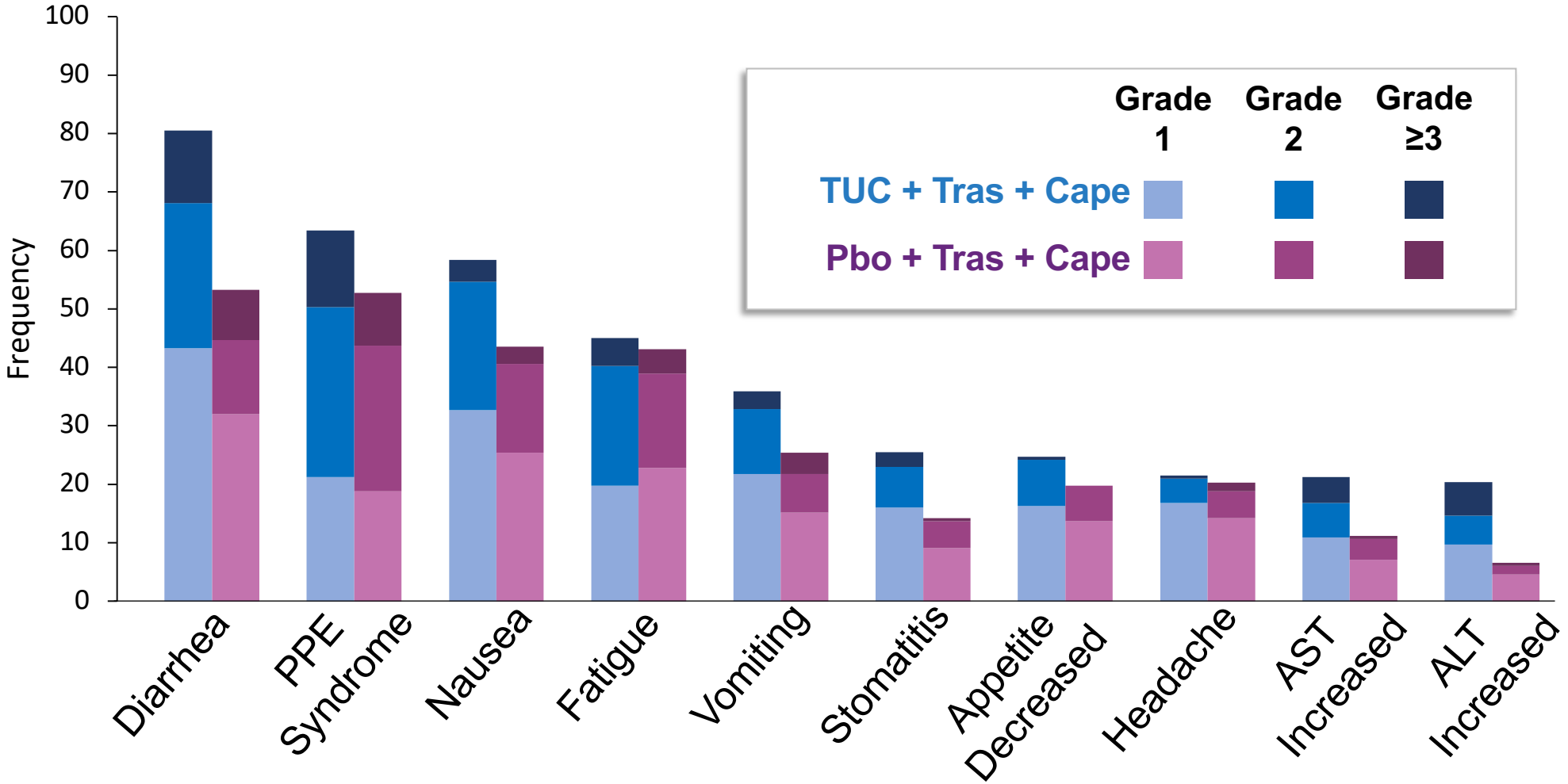
Overall Survival in the Total Population



The NEW ENGLAND JOURNAL of MEDICINE
RK Murthy et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914609

Courtesy of Sara Hurvitz, MD

Most Common Adverse Events (≥20% in the Tucatinib Arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

Courtesy of Sara Hurvitz, MD

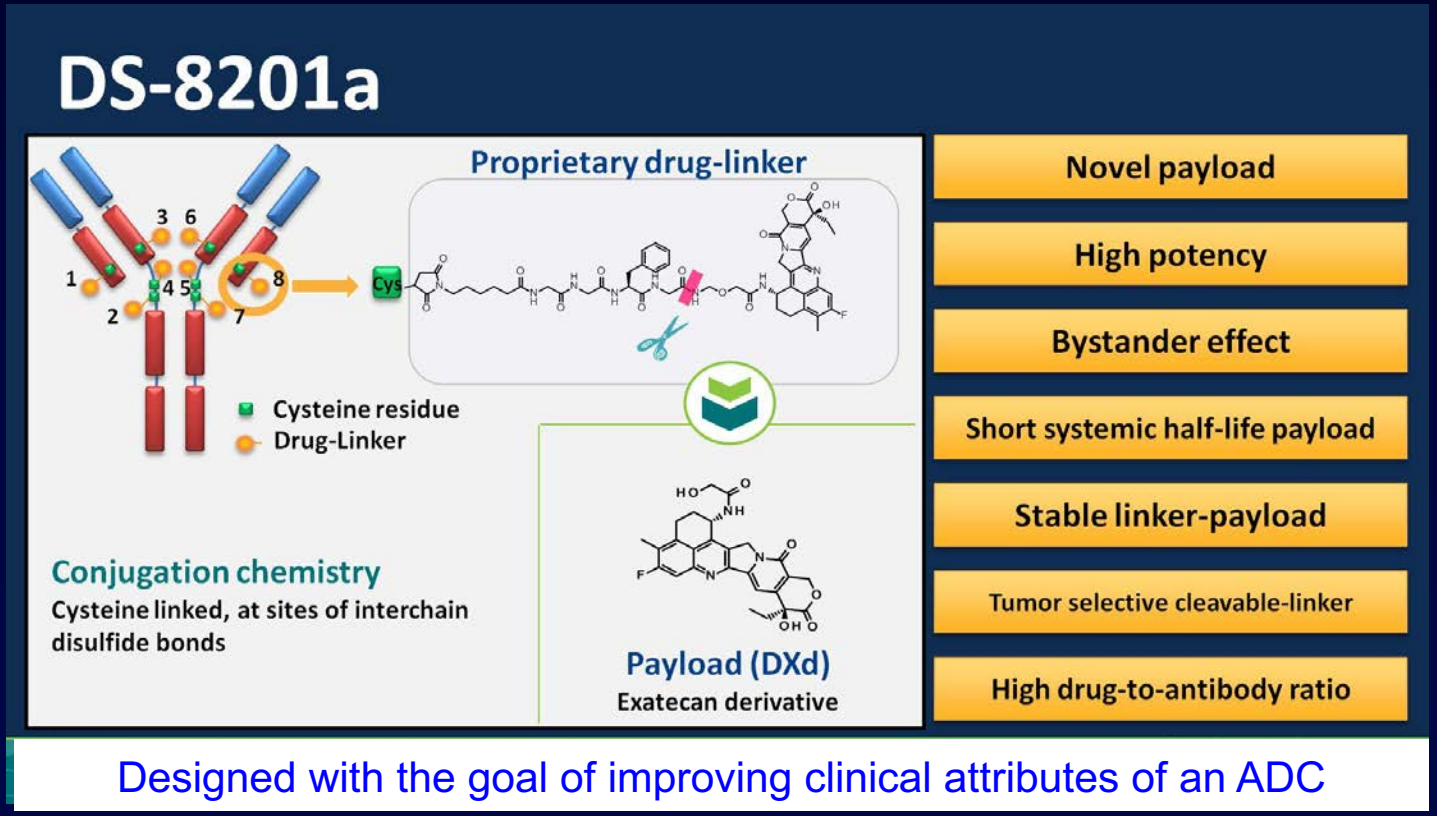
Tucatinib Approval

On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab/capecitabine for treatment of advanced, unresectable or metastatic HER2+ BC, including patients with brain metastases, who have received ≥ 1 previous HER2-targeted therapy in the metastatic setting

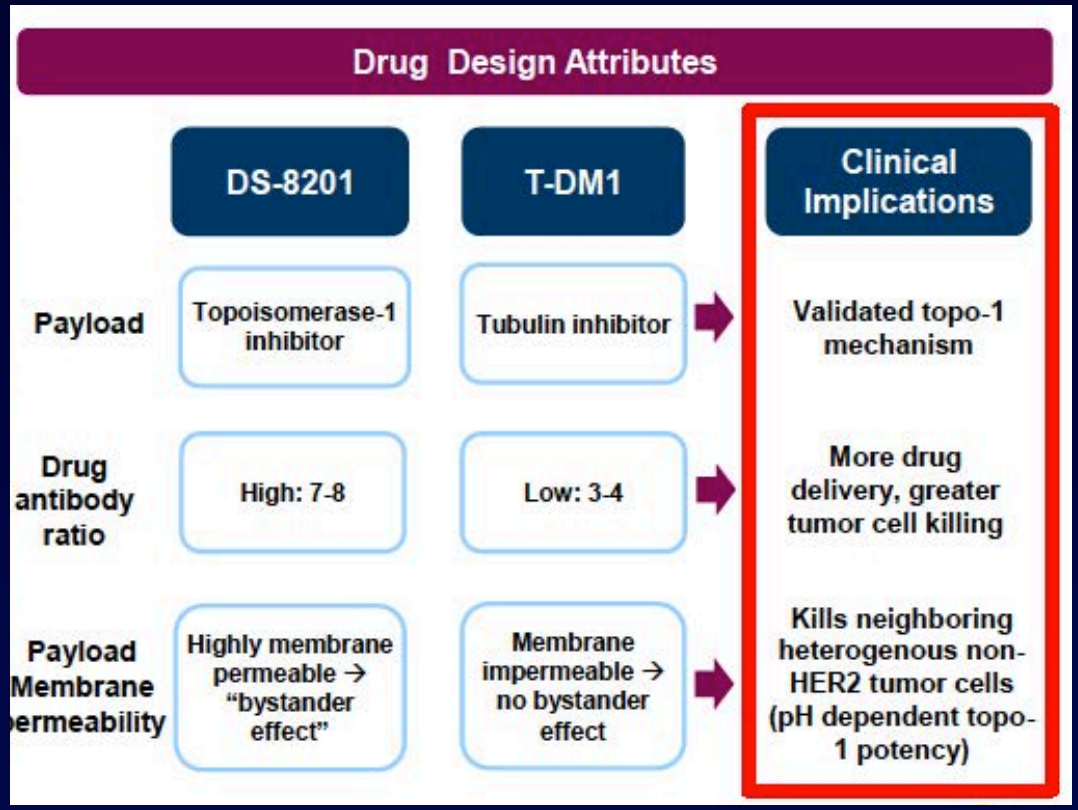
Tucatinib PI.

Courtesy of Sara Hurvitz, MD

Trastuzumab Deruxtecan (DS-8201a): Structure and Mechanism of Action



Designed with the goal of improving clinical attributes of an ADC



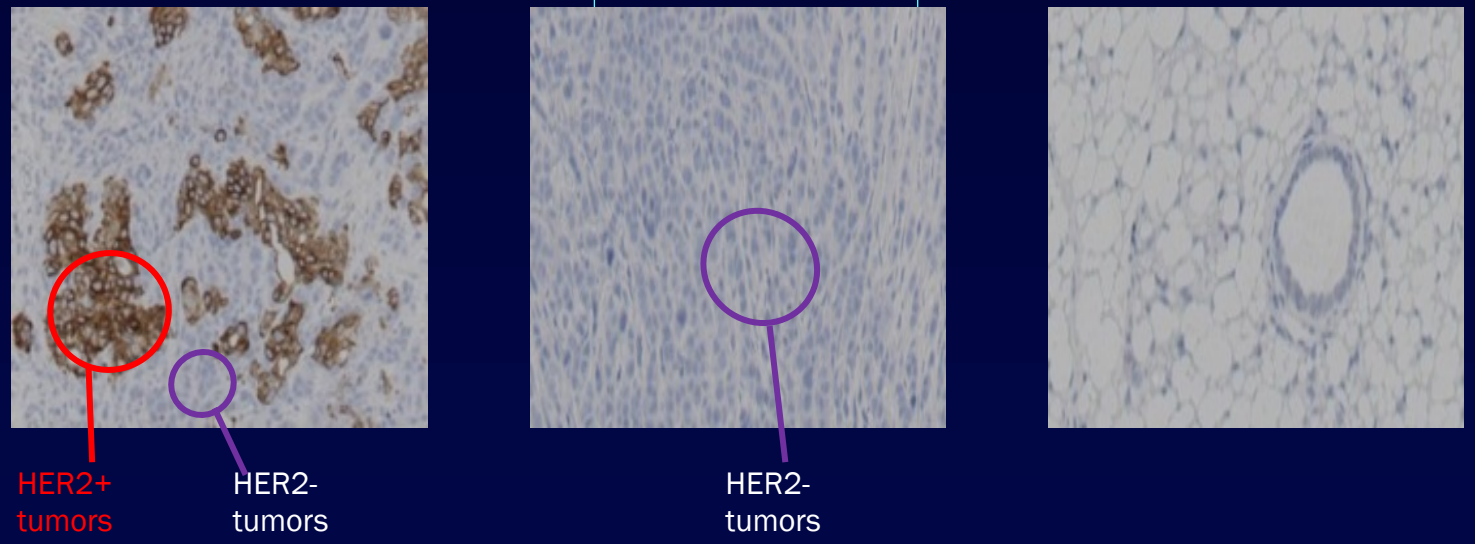
Doi et al. *J Clin Oncol*. 2017;35. DOI: 10.1200/JCO.2017.35.15_suppl.108

Courtesy of Sara Hurvitz, MD

Bystander effect of T-DXd

Bystander effect (Preclinical, after 14 day treatment)

Control	T-DM1, 10 mg/kg	DS-8201a, 3.0 mg/kg
Co-culture of HER2+ and HER2- tumors in vivo	*Activity against HER2+ tumors only*	*Activity against HER2+ and HER2- tumors*

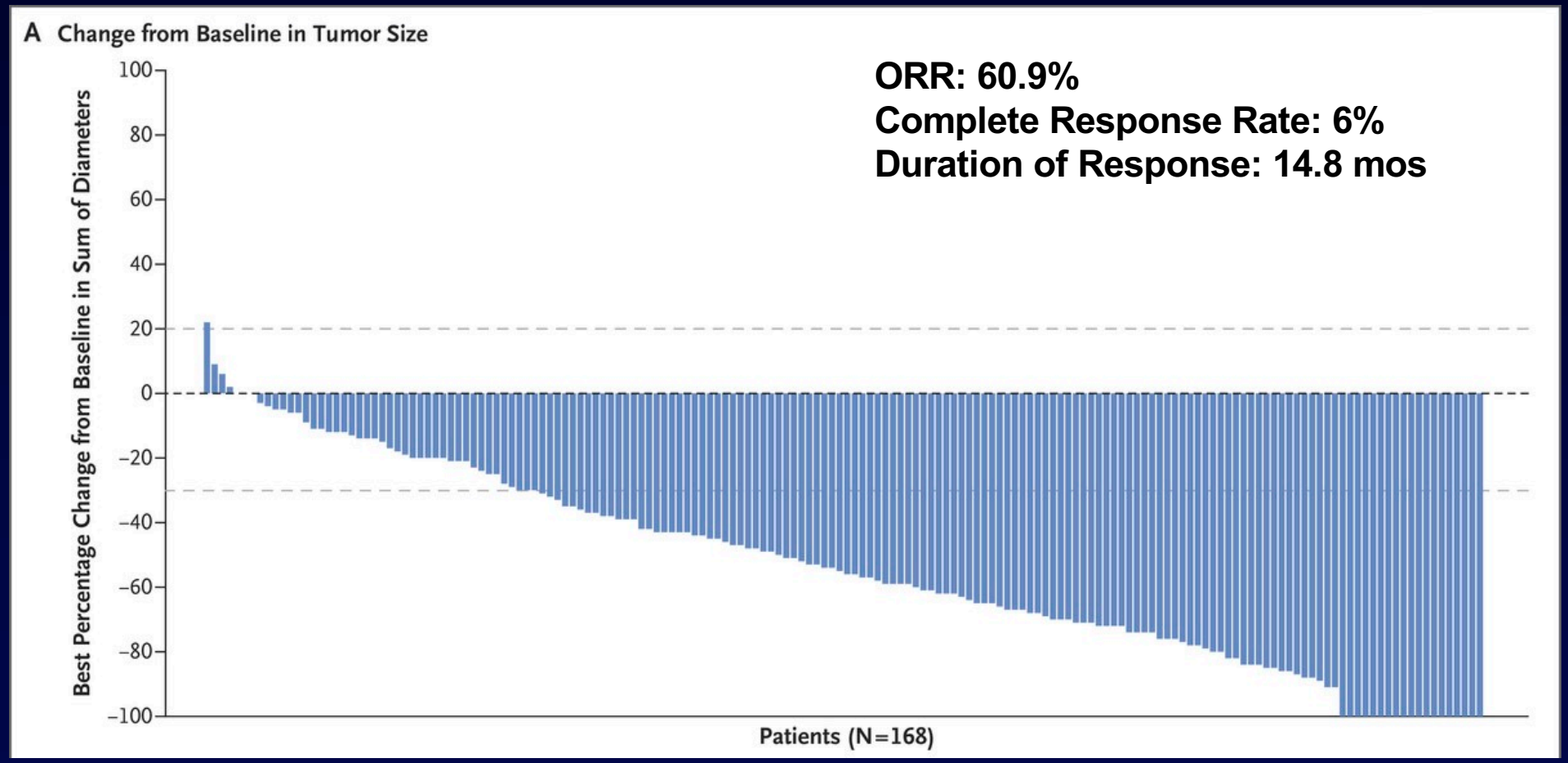


DS-8201a: Ability to kill neighboring tumor cells

Ogitani-Y *et al.*, Cancer Science 2016; 107:1039–1046

Courtesy of Sara Hurvitz, MD

Response to Trastuzumab Deruxtecan, According to Tumor Size and Subgroup Analyses.



The NEW ENGLAND JOURNAL of MEDICINE

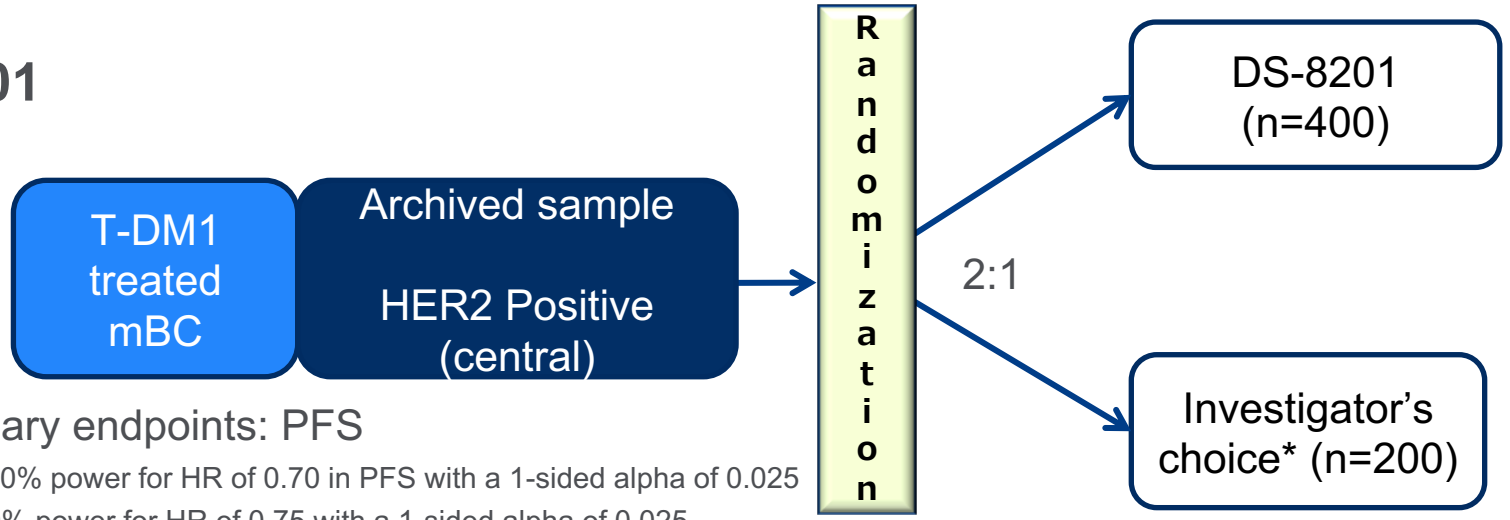
S Modi et al. N Engl J Med 2019. DOI: 10.1056/NEJMoa1914510

Courtesy of Sara Hurvitz, MD

DESTINY-Breast02 and -Breast03: U301 & U302

Ph III HER2+ mBC Trial Designs

U301



*trastuzumab + capecitabine or lapatinib + capecitabine

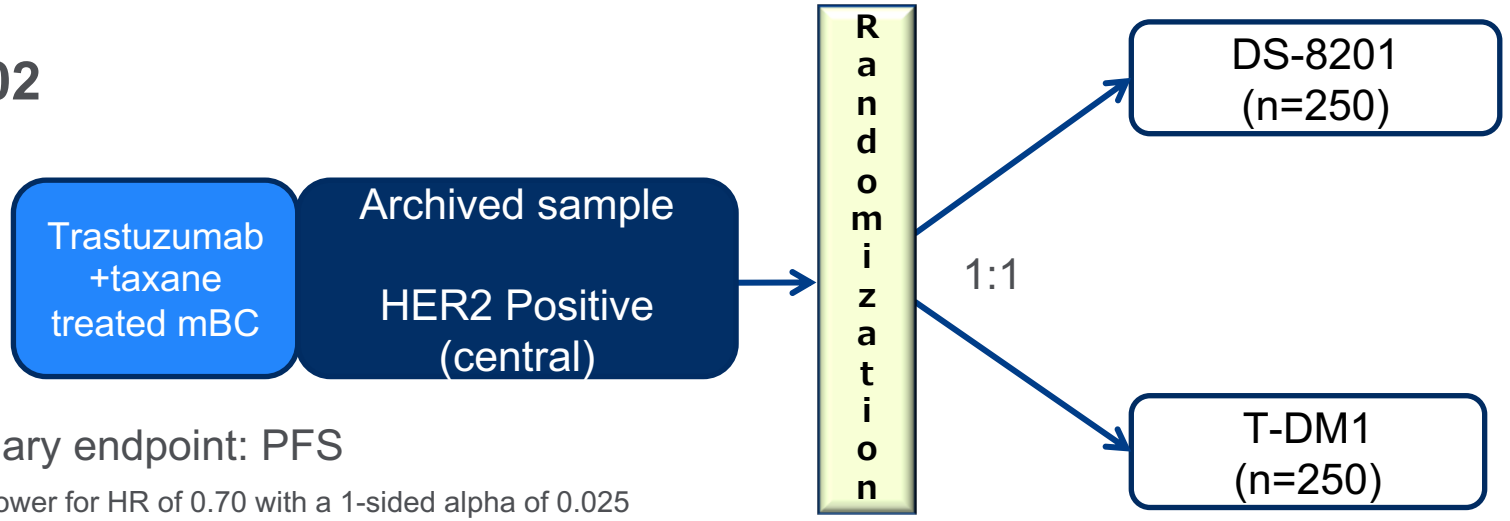
Primary endpoints: PFS

PFS: 90% power for HR of 0.70 in PFS with a 1-sided alpha of 0.025

OS: 80% power for HR of 0.75 with a 1-sided alpha of 0.025

PFS will be tested first, if positive, OS will be tested at the same alpha level. There is a planned OS interim analysis at the same time when PFS primary analysis is performed.

U302



Primary endpoint: PFS

90% power for HR of 0.70 with a 1-sided alpha of 0.025

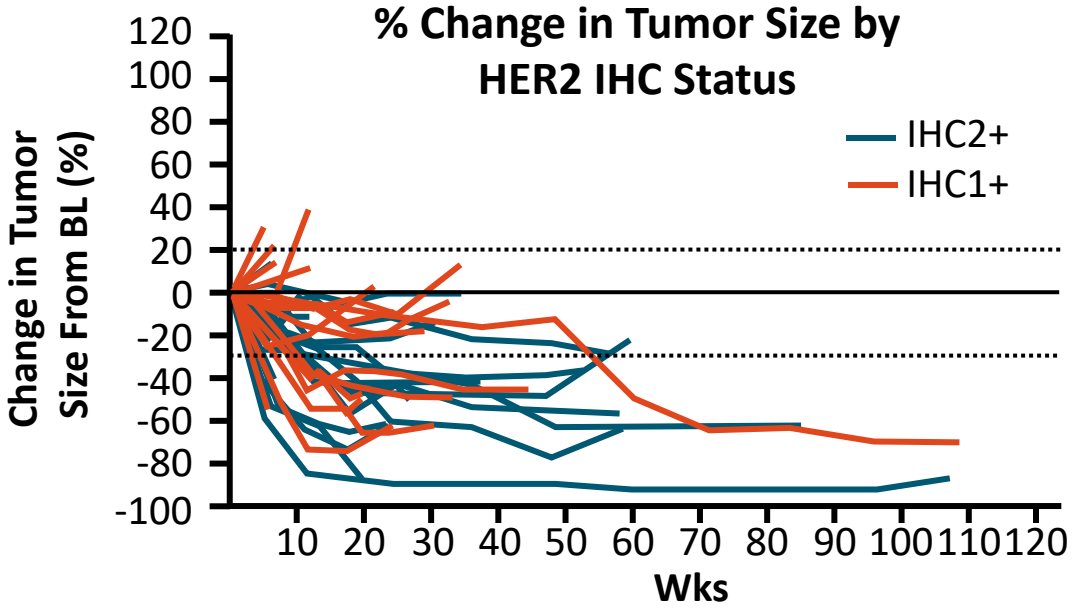
Courtesy of Sara Hurvitz, MD

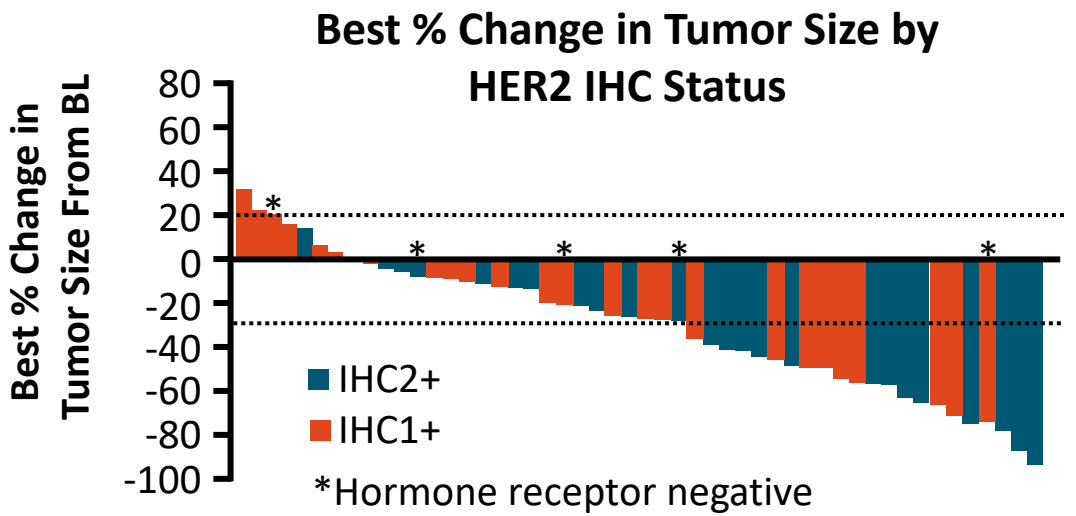
How to Best Sequence New ≥3rd-Line Agents?

	Trastuzumab Deruxtecan	**Tucatinib + Tras/Cape**	**Neratinib + Capecitabine**
PROS	Very high ORR	OS and PFS benefit	PFS benefit
	Durable benefit Long PFS	Activity in both treated and progressive brain mets	Delays time to CNS Rx
	Activity maintained in pts with treated brain mets	Manageable toxicity profile	
CONS	ILD is serious potential risk	Absolute PFS benefit modest	Serious diarrhea is common
	No data on efficacy in progressive brain mets		Benefit modest

Courtesy of Sara Hurvitz, MD

HER2-Low MBC: Use of trastuzumab deruxtecan??





Line at 20% indicates PD; line at -30% indicates PR.

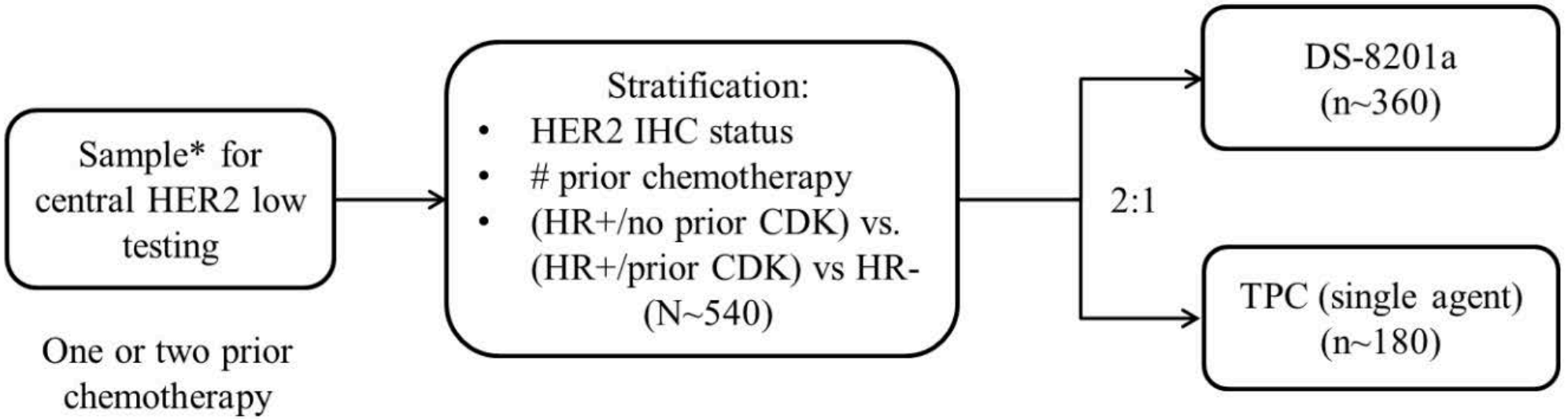
Efficacy in HER2-Low MBC	Confirmed ORR, %	Median DoR, Mos	Median PFS, Mos
All (N = 51)	44.2	9.4	7.6
IHC 2+ (n = 24)	**54.5**	11.0	**13.6**
IHC 1+ (n = 27)	**33.3**	7.9	**5.7**
HR+ (n = 45)	47.4	11.0	7.9
Prior CDK4/6 inhibitor (n = 15)	33.3	NR	7.1

Modi. SABCS 2018. Abstr P6-17-02.

Courtesy of Sara Hurvitz, MD

Slide credit: clinicaloptions.com

DESTINY-Breast04
HER2 Low (1+ or 2+ IHC)



CDK = cyclin-dependent kinase, HER2 = human epidermal growth factor receptor 2, IHC = immunohistochemistry, TPC = treatment of physician's choice.

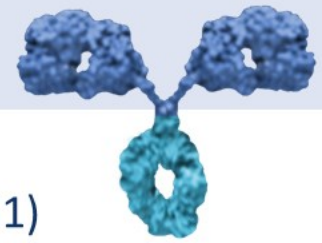
https://clinicaltrials.gov/ct2/show/NCT03734029

Courtesy of Sara Hurvitz, MD

Margetuximab: Fc-engineered to Activate Immune Responses

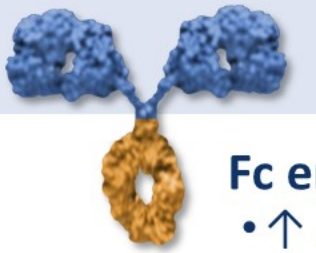
Trastuzumab

Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



Fc:
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

Margetuximab[1,2]



Fab:
- Same specificity and affinity
- Similarly disrupts signaling

Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

Receptor Type	Receptor	Allelic Variant	Relative Fc Binding	Affinity Fold-Change
Activating	**CD16A**	158F	Lower	6.6x ↑
		158V	Higher	4.7x ↑
	CD32A	131R	Lower	6.1x ↓
		131H	Higher	↔
Inhibitory	**CD32B**	232I/T	Equivalent	8.4x ↓

1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Planned* Exploratory PFS Analyses by FcγR Genotypes (CBA)

Margetuximab benefit appears to be increased in low-affinity CD16A-158F allele carriers

		Median PFS (95% CI), Months		HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
		Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy			
	All patients	5.8 (5.52–6.97)	4.9 (4.17–5.59)	0.78	(0.61–0.99)	0.044
Activating function	CD16A/F carrier (FV or FF), n=437	6.9 (5.55–8.15)	5.1 (4.14–5.59)	0.68	(0.52–0.90)	0.005
	CD16A/FF, n=192	8.2 (5.52–10.51)	5.6 (4.50–8.31)	0.69	(0.46–1.05)	0.080
	CD16A/FV, n=245	6.3 (5.52–7.23)	4.3 (4.01–5.59)	0.71	(0.50–1.01)	0.055
	CD16A/VV, n=69	4.8 (2.46–5.65)	5.6 (2.86–11.04)	1.78	(0.87–3.62)	0.110
	CD32A/RR, n=122	5.7 (4.80–10.55)	5.5 (2.76–8.21)	0.69	(0.41–1.17)	0.166
	CD32A/RH, n=247	6.9 (5.55–8.15)	5.6 (4.17–6.67)	0.74	(0.52–1.06)	0.102
	CD32A/HH, n=137	5.6 (3.29–8.28)	4.1 (2.79–5.59)	0.80	(0.49–1.30)	0.365
Inhibitory function	CD32B/II†, n=380	5.8 (5.55–7.66)	5.5 (4.17–5.65)	0.85	(0.64–1.13)	0.265
	CD32B/IT†, n=117	6.0 (4.14–NA)	5.5 (2.79–7.16)	0.63	(0.36–1.10)	0.098

*Non-alpha allocating, exploratory analysis.

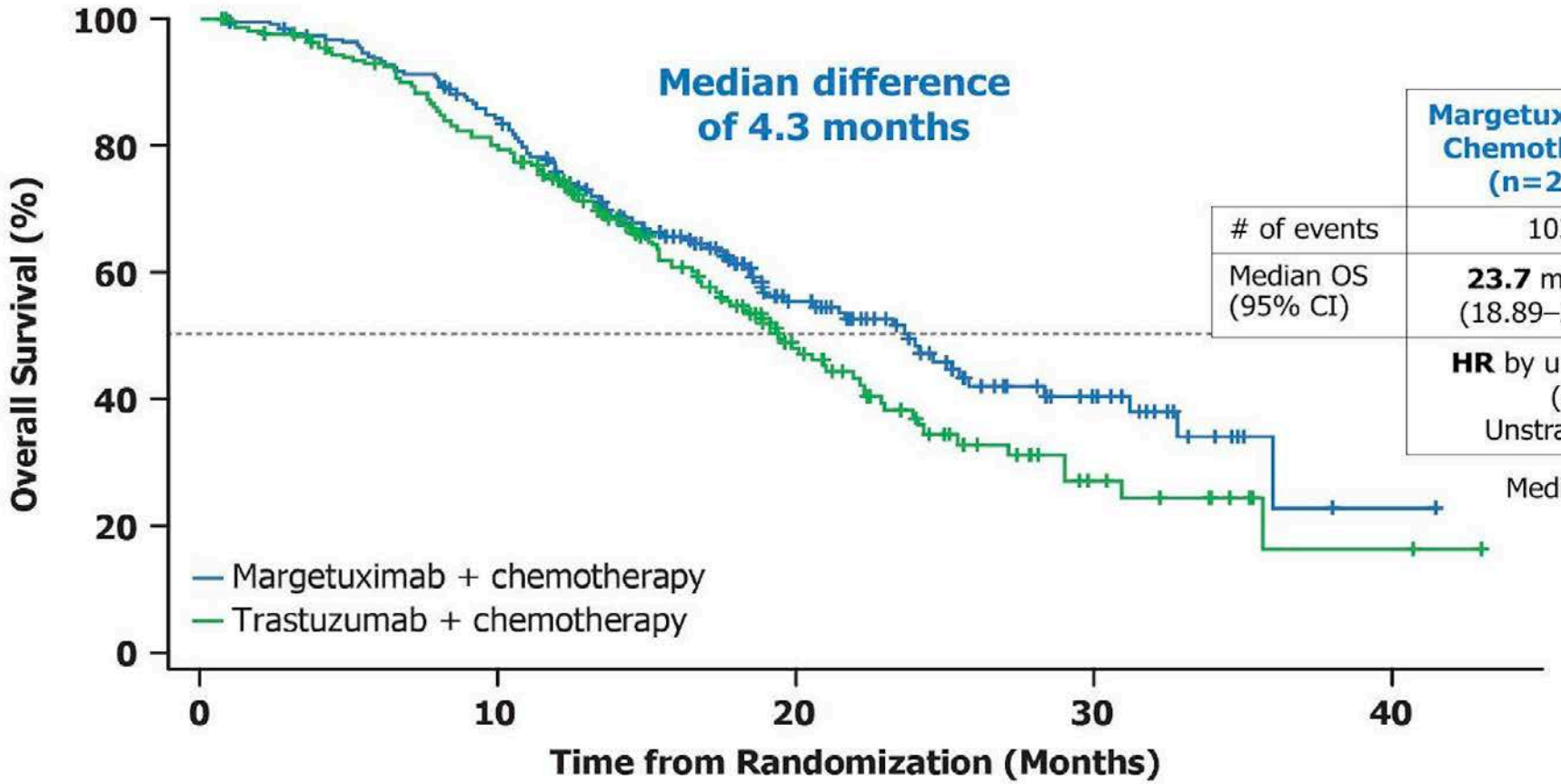
†CD32B/TT not included on forest plot because n=9 is too small (5 on margetuximab, 4 on trastuzumab) to make analysis meaningful.

Courtesy of Sara Hurvitz, MD

Prespecified OS in CD16A-158F carriers

[1]Sep-2019 Cutoff

CD16A-158F Carriers, FF or FV, n=437 of 506 (86%) genotyped



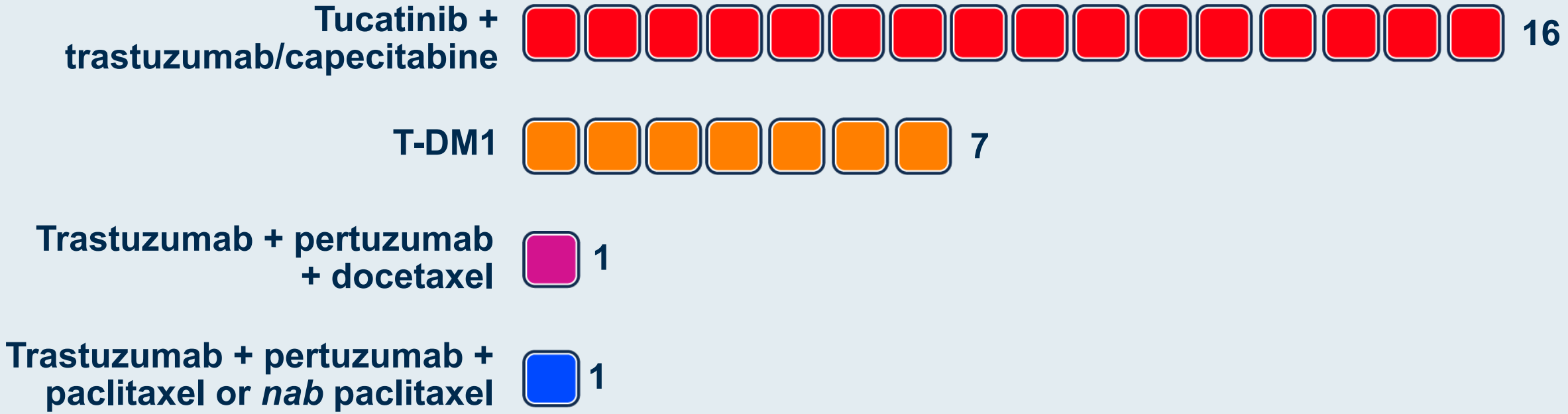
	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	114
Median OS (95% CI)	**23.7** months (18.89–28.32)	**19.4** months (16.85–22.28)
HR by unstratified Cox model, **0.79** (95% CI, 0.61–1.04) Unstratified log-rank ***P*=0.087**		

Median follow-up: 15.6 months

Margetuximab	221	219	212	204	196	181	157	135	111	91	68	55	42	31	27	19	13	8	2	1	1	0
Trastuzumab	216	210	201	192	176	165	145	123	98	81	57	43	30	21	16	11	9	6	2	2	2	1	0

Courtesy of Sara Hurvitz, MD

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



Survey of 25 Breast Cancer Clinical Investigators

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

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

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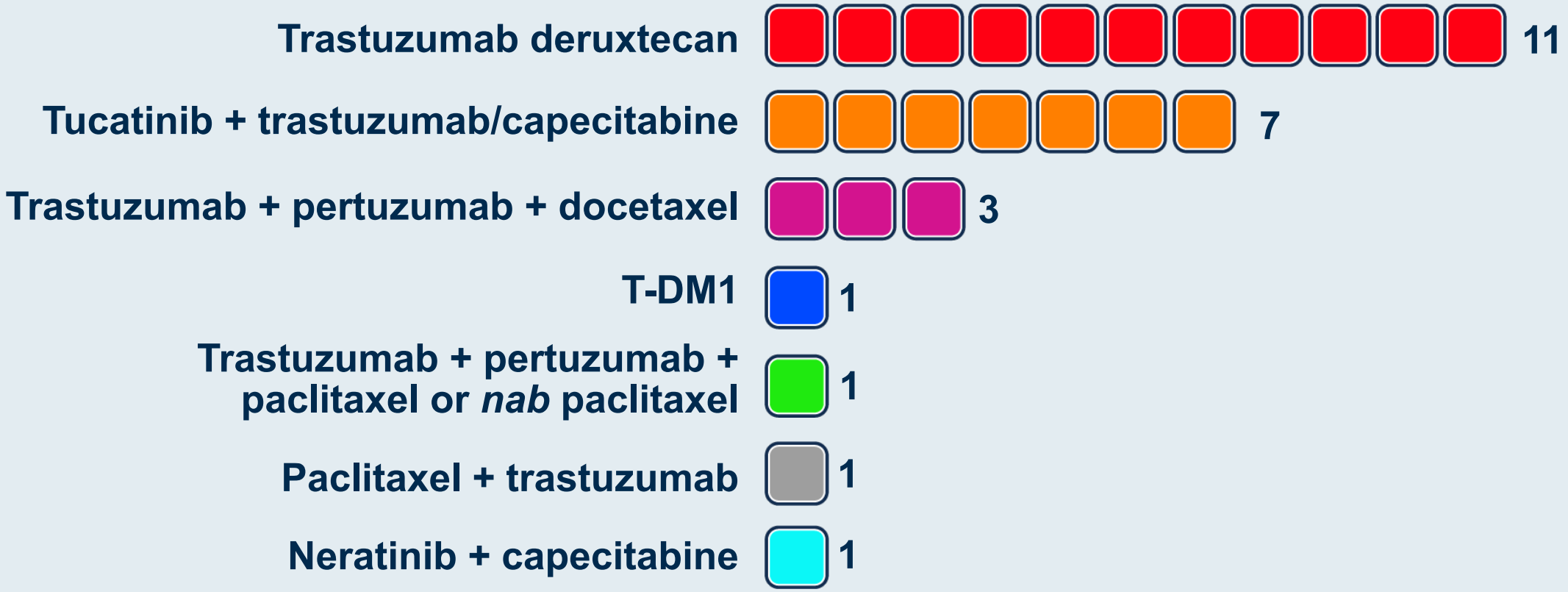

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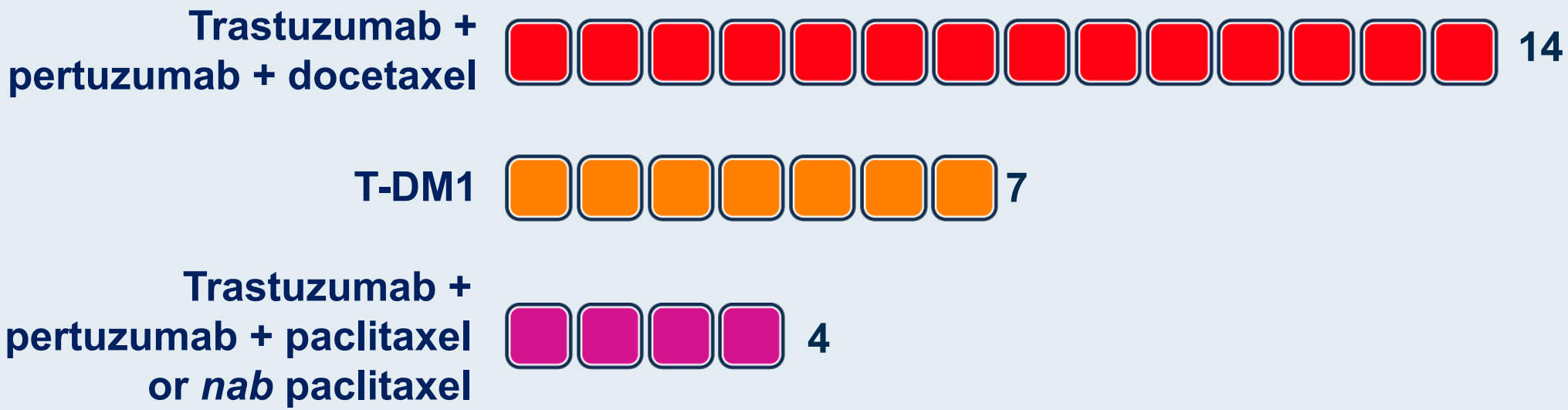


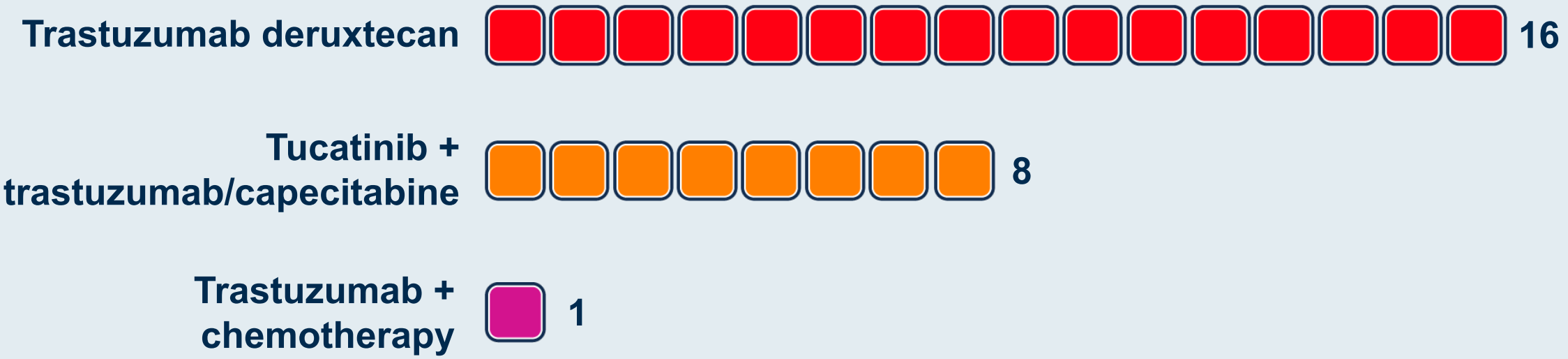
Survey of 25 Breast Cancer Clinical Investigators

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

1. Trastuzumab + chemotherapy
2. Trastuzumab + lapatinib
3. Neratinib + paclitaxel
4. Neratinib + capecitabine
5. Tucatinib + trastuzumab/capecitabine
6. Trastuzumab deruxtecan
7. Lapatinib + capecitabine
8. Other

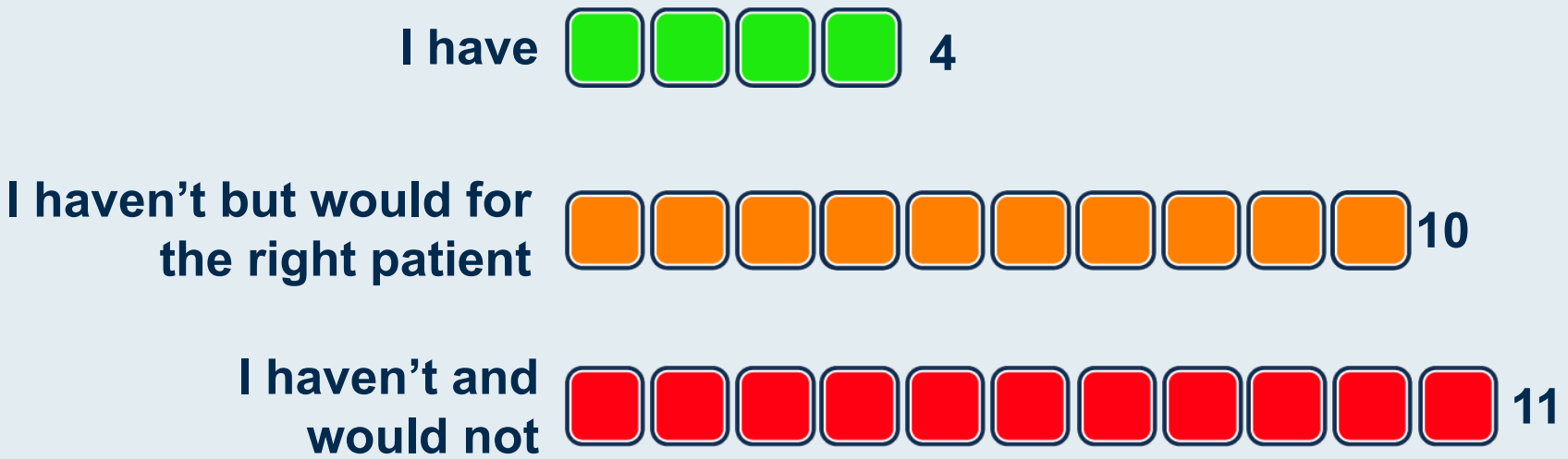
RTP RESEARCH TO PRACTICE

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



Survey of 25 Breast Cancer Clinical Investigators

Regulatory and reimbursement issues aside, have you administered or would you administer trastuzumab deruxtecan to a patient with HER2-low metastatic breast cancer outside of a clinical trial setting?



Survey of 25 Breast Cancer Clinical Investigators

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

50 y.o. female diagnosed 2002 with stage III ER+ HER2+ BC, s/p TCH, lumpectomy with residual disease, tamoxifen. 2 years later metastases to spine. Treated with trastuzumab/endocrine therapy, lapatinib/trastuzumab/endocrine therapy; vinorelbine/trastuzumab/pertuzumab; T-DM1, went on HER2CLIMB trial of trastuzumab/capecitabine +/- tucatinib; I thought she was getting tucatinib because she had rash, SBO, colitis, dose reduced tucatinib (or placebo), ultimately taken off study for PD 14 mos after enrolling (Later found out she was on placebo arm!). Placed on study of trastuzumab deruxtecan 9/2018. Still on study with disease control (cycle 37 now). Tolerating well but significant hair thinning. Nausea much better than at beginning of study.

Agenda

Module 1: Considerations in the Care of Patients with Localized HER2-Positive Breast Cancer (BC) Receiving Neoadjuvant Systemic Therapy — Dr Pegram

Module 2: Adjuvant and Extended-Adjuvant Therapy for Patients with Localized HER2-Positive BC — Dr Tolaney

Module 3: Optimizing the Management of HER2-Positive Metastatic BC (mBC) — Dr Hurvitz

Module 4: Treatment of HER2-Positive Brain Metastases — Dr Anders

Module 5: Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hamilton

Treatment of HER2-Positive Breast Cancer Brain Metastases

Carey K. Anders, MD
Medical Director of the Duke Center for Brain and Spine Metastases
Duke Cancer Institute
December 2020

Case Presentation – Dr Anders: 46-year-old woman with HER2-positive breast cancer and metastases to the brain

46 yr old female presents to your clinic for systemic therapy recommendations for metastatic hormone receptor negative, HER2-positive breast cancer metastatic to brain. She was initially diagnosed with *de novo* metastatic breast cancer to the liver 2.5 years prior and initially received paclitaxel/trastuzumab pertuzumab. At her visit, she had been on T-DM1 for 8 months, and had radiosurgery to 3 brain metastases 4 months prior; T-DM1 was continued post-SRS as her liver lesions were stable. She now has intracranial progression with 5 new lesions that are all sub-cm. Her performance status remains excellent and she is hopeful to avoid additional radiation to the brain. Based on the available literature, you advise her that the next best step is:

A. Vinorelbine/trastuzumab

B. Tucatinib/trastuzumab/capecitabine

C. Trastuzumab deruxtecan

D. Abemaciclib/trastuzumab

Case Presentation – Dr Anders: 47-year-old woman with HER2-positive breast cancer and metastases to the brain

47 yr old female with a known ER/PR negative, HER2-positive breast cancer to the liver who has previously progressed on taxane/trastuzumab/pertuzumab, and was on T-DM1 when she developed 3 supratentorial brain metastases that were treated with SRS. She continued on T-DM1 for 6 months following SRS when her LFT's started to rise and she developed RUQ pain. Her brain lesions remain stable. You recommend which of the following in hopes to achieving highest response in her liver metastases?

A. Vinorelbine/trastuzumab

B. Tucatinib/trastuzumab/capecitabine

C. Trastuzumab deruxtecan

D. Neratinib/capecitabine

Courtesy of Carey K Anders, MD

A 47-year-old woman with HER2-positive, ER/PR-negative mBC who received paclitaxel/trastuzumab/pertuzumab, then T-DM1 and stereotactic radiation therapy to 3 supratentorial brain metastases develops extensive lymphangitic lung disease causing mild dyspnea. What is your most likely treatment?

1. Tucatinib + trastuzumab/capecitabine
2. Trastuzumab deruxtecan
3. Neratinib
4. Neratinib + capecitabine
5. Neratinib + paclitaxel
6. Trastuzumab + chemotherapy
7. Trastuzumab + lapatinib
8. Other

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Brain metastases are a common consequence of advanced cancer

Primary site	Incidence Rates
Lung (overall)	16.3–19.9%
SCLC*	29.7% (at 5 years)
NSCLC*	12.6% (at 5 years)
Breast	10–15%
HER2 positive	25–50%
Triple negative	20%
Melanoma	6.9–7.4% → 40 – 50%
Renal	6.5–9.8%
Colorectal	3.0%

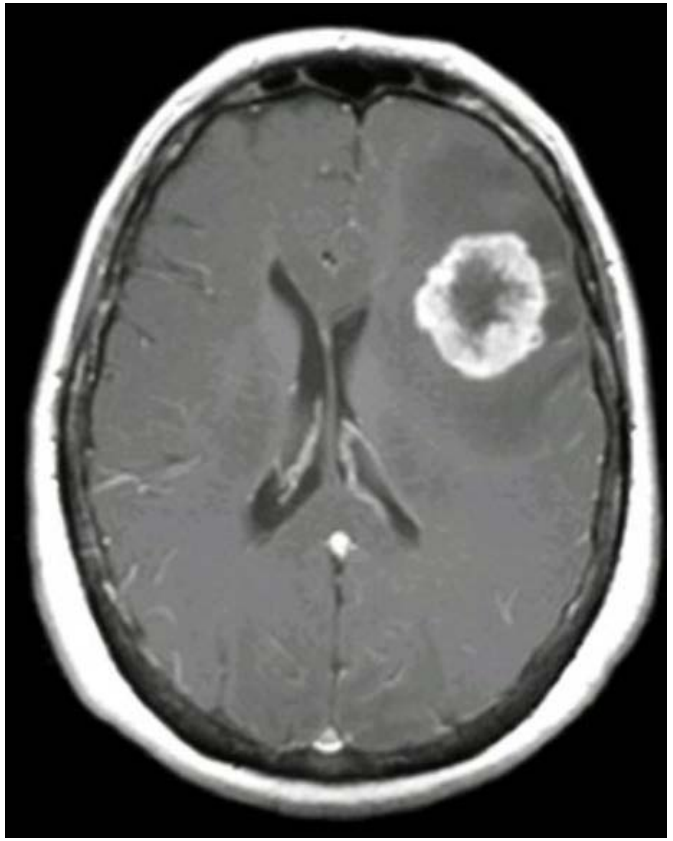
*can be up to 50–60% depending on study and disease duration

Courtesy of Carey K Anders, MD

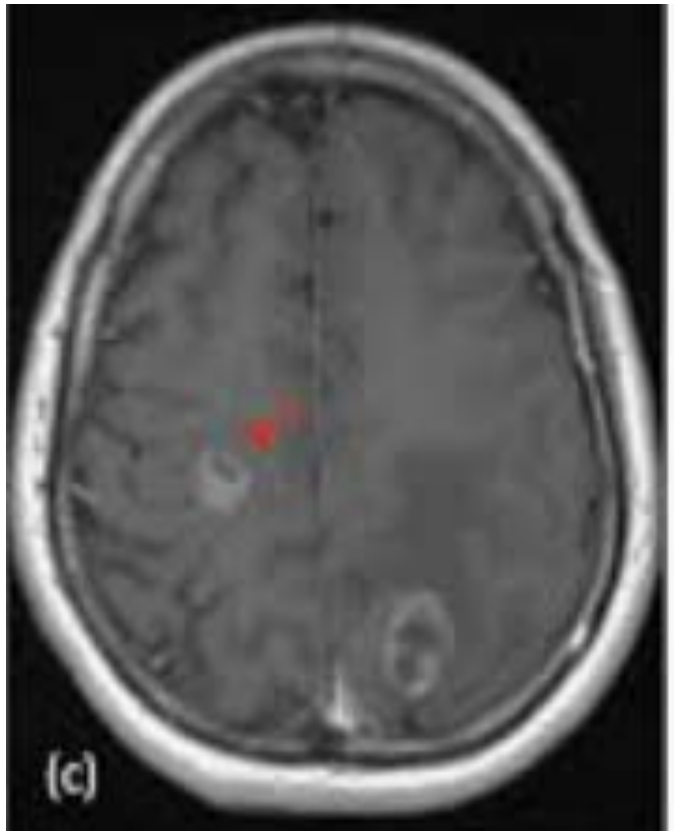
Glitza Oliva et al. Ann Oncol 2018;29: 1509–1520
Barnholtz-Sloan et al. J. Clin Oncol. 2004;22(14):2865–72
Schouten et al. Cancer. 2002;94(10):2698–705
Chamberalin et al. Neuro-Oncology. 2017;19(1):i1–i24

Radiographic Images of Brain Metastases

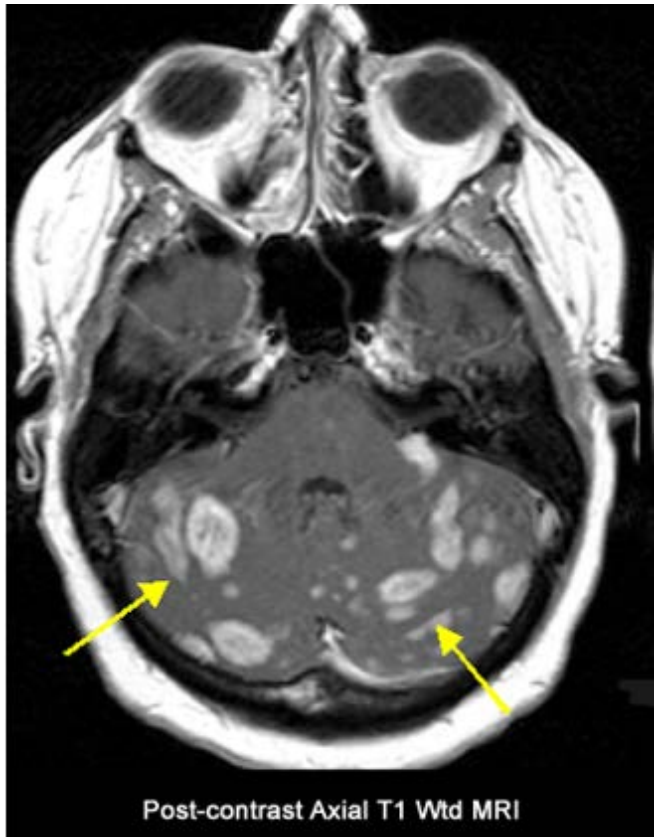
- Solitary lesion



Limited lesions

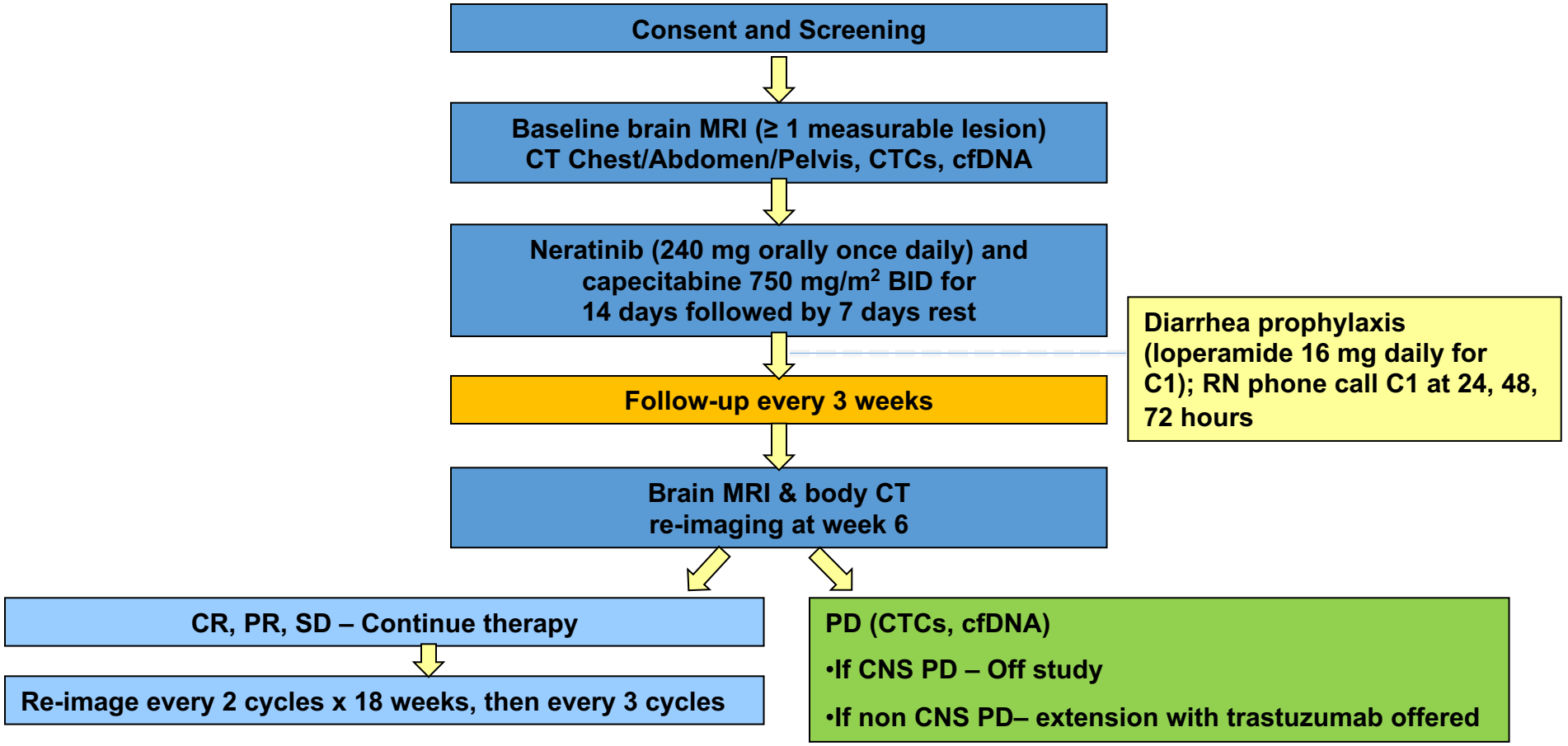


Multiple lesions



Courtesy of Carey K Anders, MD

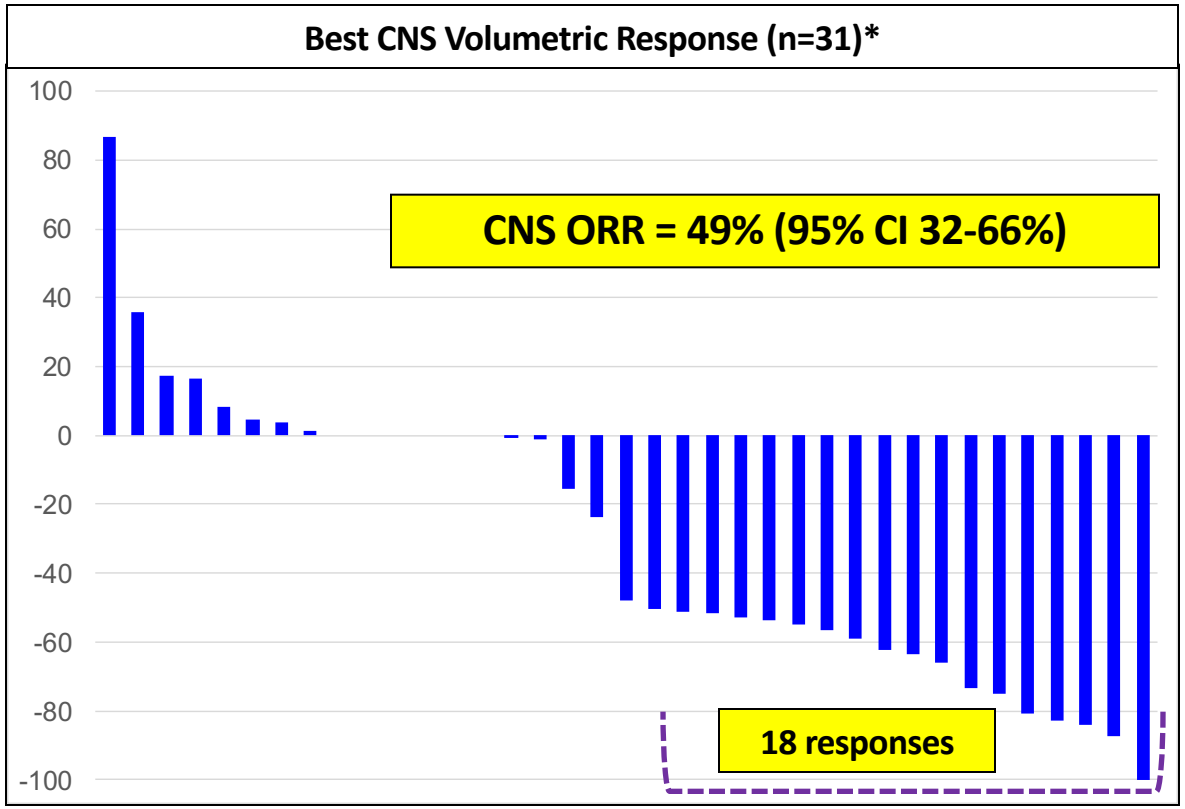
TBCRC 022 (Ph II neratinib/capecitabine): Study Design



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

Courtesy of Carey K Anders, MD

Primary Endpoint – Neratinib/Capecitabine:
CNS Volumetric Response



*** 6 patients did not reach first re-staging evaluation and are categorized as '0'**
┼ No patient had clear increase in steroid use, non-target lesions, non-CNS lesions, or worsening neurological symptoms at time of radiographic response

Courtesy of Carey K Anders, MD

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

HER2CLIMB Primary Analysis Results – SABCS 2019

- The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis.
- Importantly, the secondary endpoint of PFS in patients with brain metastases was met.

PFS by BICR N=480*	Overall Survival N=612	PFS by BICR in patients with brain metastases N=291
Risk of progression or death was reduced by **46%**	Risk of death was reduced by **34%**	Risk of progression or death was reduced by **52%**
95% CI: 0.42 to 0.71, P<0.001	95% CI, 0.50 to 0.88, P=0.005	95% CI, 0.34 to 0.69, P<0.001

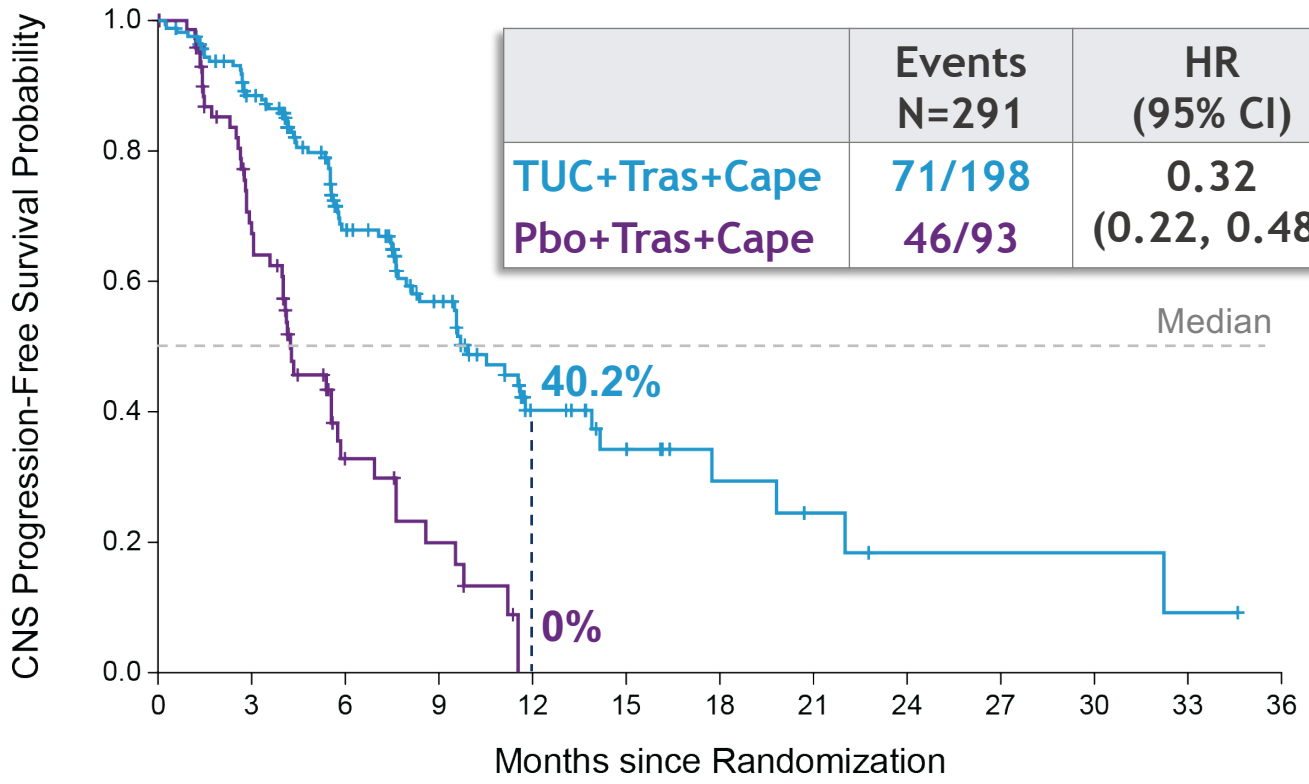
PFS: progression-free survival; BICR: blinded independent central review
*The primary endpoint of PFS was assessed in the first 480 patients enrolled.

Murthy RK, et al. *N Engl J Med* 2020;382:597-609.

PRESENTED BY: Nancy Lin, nlin@partners.org

Courtesy of Carey K Anders, MD

HER2CLIMB: CNS-PFS Benefit in Patients with Brain Metastases



	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	71/198	0.32 (0.22, 0.48)	<0.00001
Pbo+Tras+Cape	46/93		

No. at Risk													
TUC+Tras+Cape	198	132	74	45	18	11	6	4	2	2	2	1	0
Pbo+Tras+Cape	93	41	11	6	0	0	0	0	0	0	0	0	0

Risk of CNS progression or death was reduced by 68% in patients with brain metastases

One-year CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
40.2% (29.5, 50.6)	0%

Median CNS-PFS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
9.9 months (8.0, 13.9)	4.2 months (3.6, 5.7)

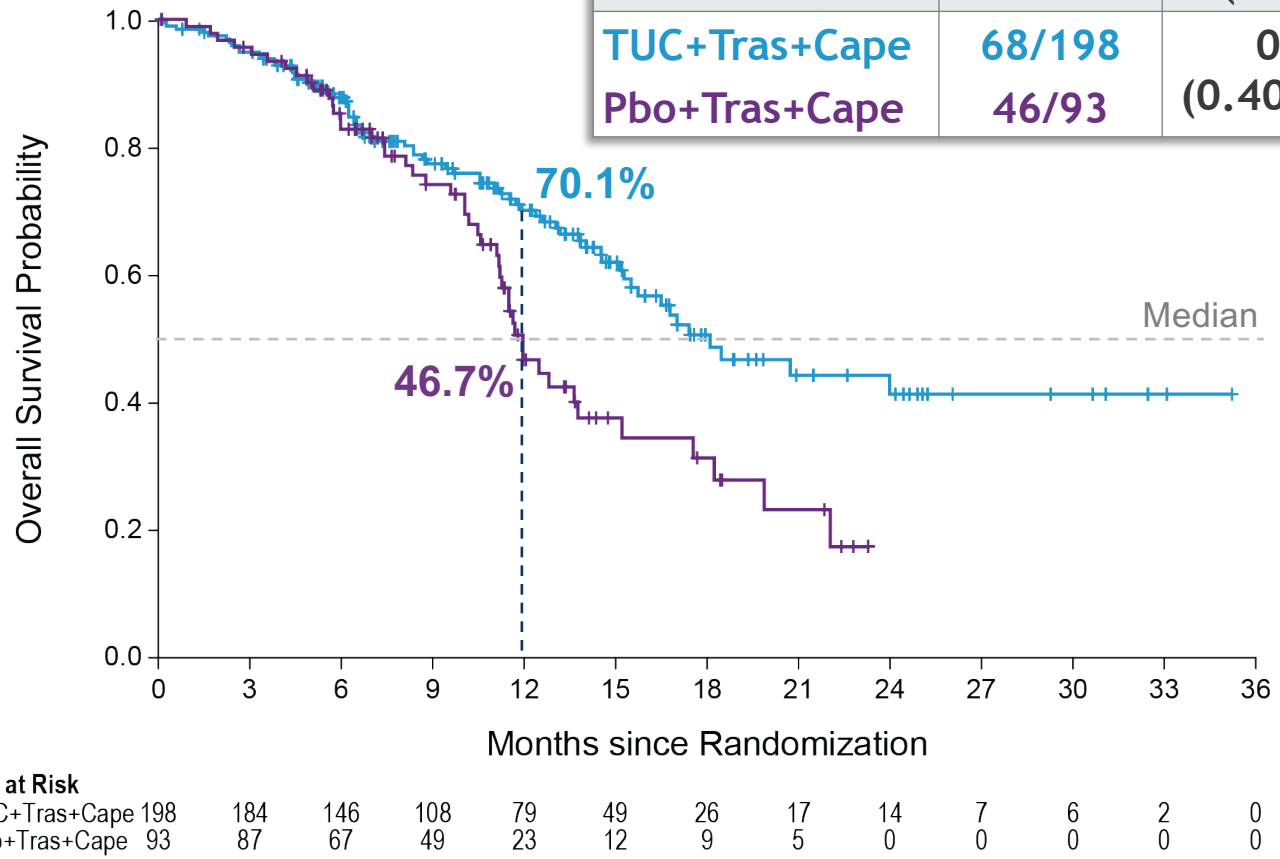
Stable BrMets:	13.9 mos	5.6 mos
Active BrMets:	9.5 mos	4.1 mos

CNS-PFS: time from randomization to disease progression in the brain or death by investigator assessment.
HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

PRESENTED BY: Nancy Lin, nlin@partners.org
Courtesy of Carey K Anders, MD

HER2CLIMB: OS Benefit in Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



Risk of death was reduced by 42% in patients with brain metastases

One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
70.1% (62.1, 76.7)	46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

NE: not estimable

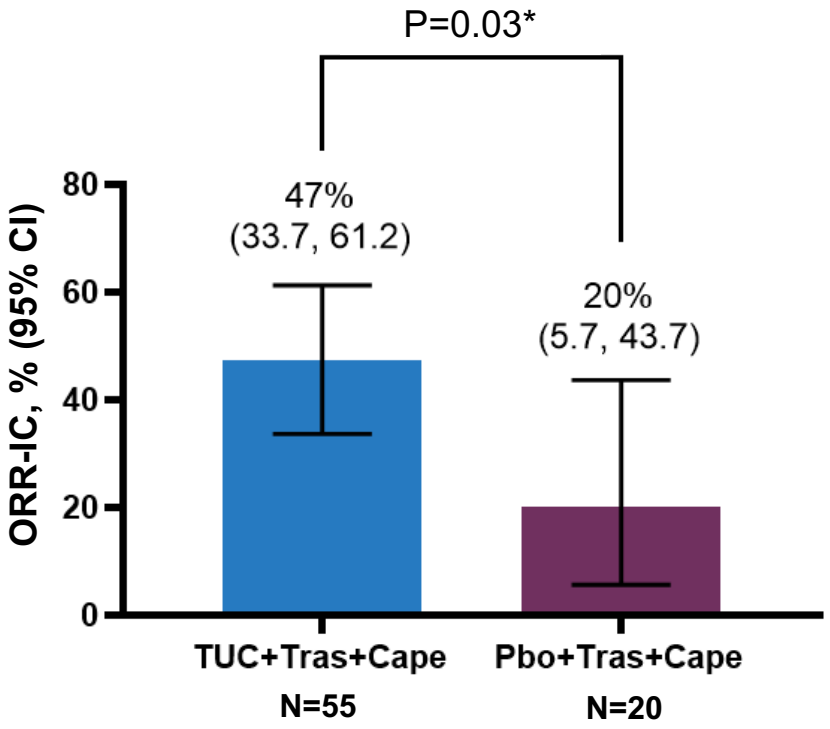
Stable BrMets:	15.7 mos	13.6 mos
Active BrMets:	20.7 mos	11.6 mos

HR: hazard ratio computed from Cox proportional hazards model using stratification factors (ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization. All P values are nominal.

PRESENTED BY: Nancy Lin, nlin@partners.org

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)



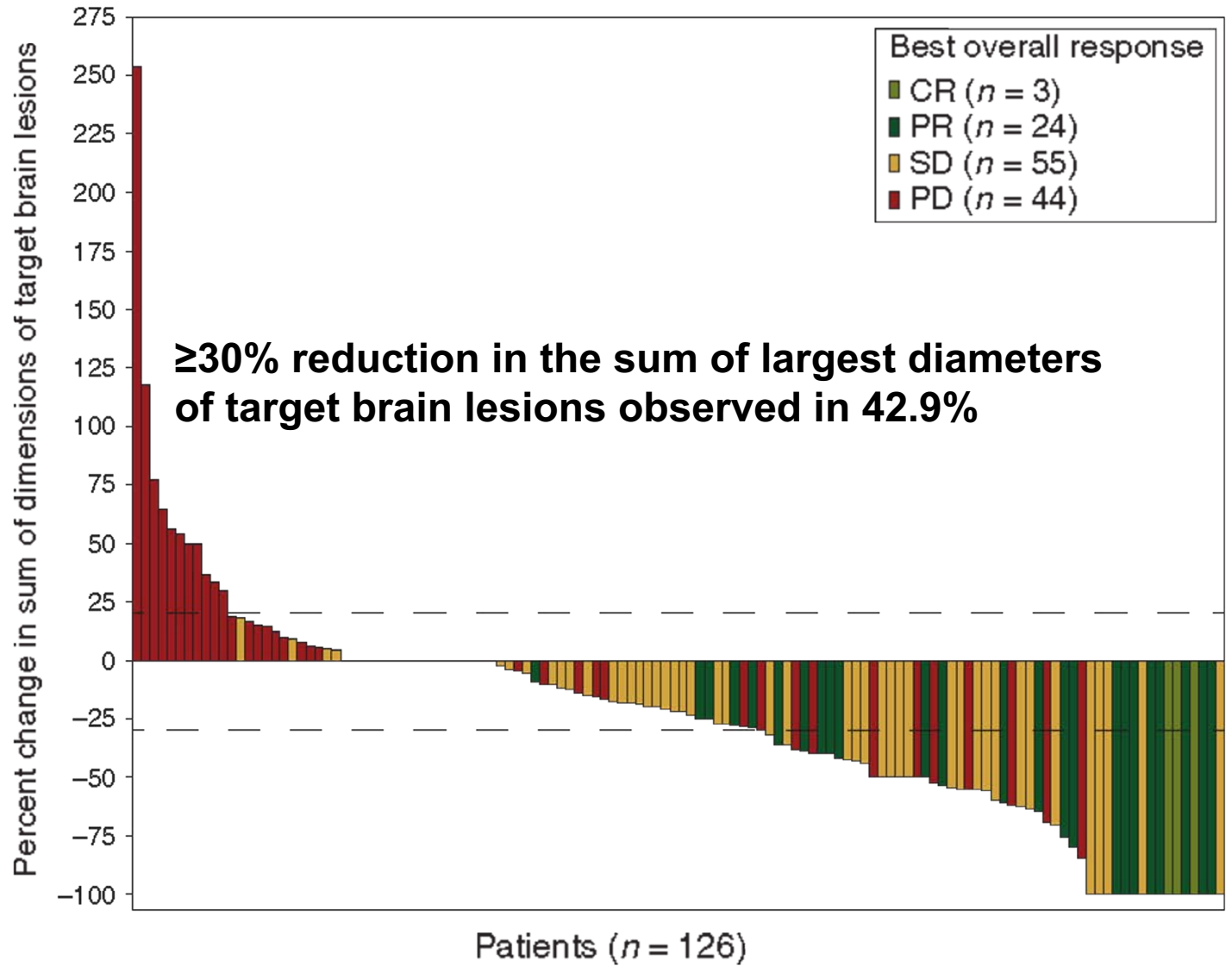
*Stratified Cochran-Mantel-Haenszel P value

	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).

PRESENTED BY: Nancy Lin, nlin@partners.org

KAMILLA Trial (Cohort 1): Response to T-DM1 in Brain



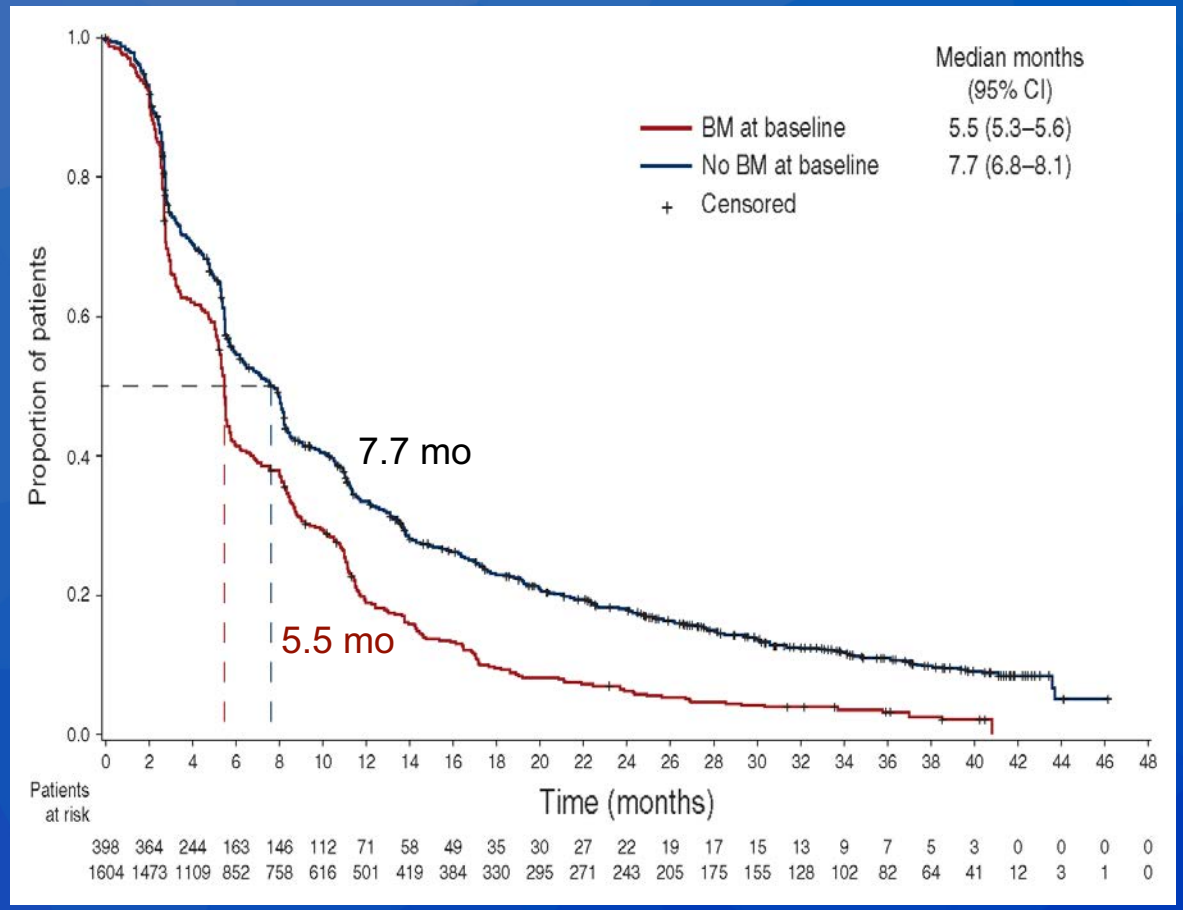
Of the 126 patients with measurable brain metastases at baseline:

- Complete response = 3 (2.4%)
- Partial response = 24 (19%)
- Best overall response rate across all organs = 21.4%
- Stable disease ≥6 mo = 27 (21.4%)
- Clinical benefit rate = 42.9%

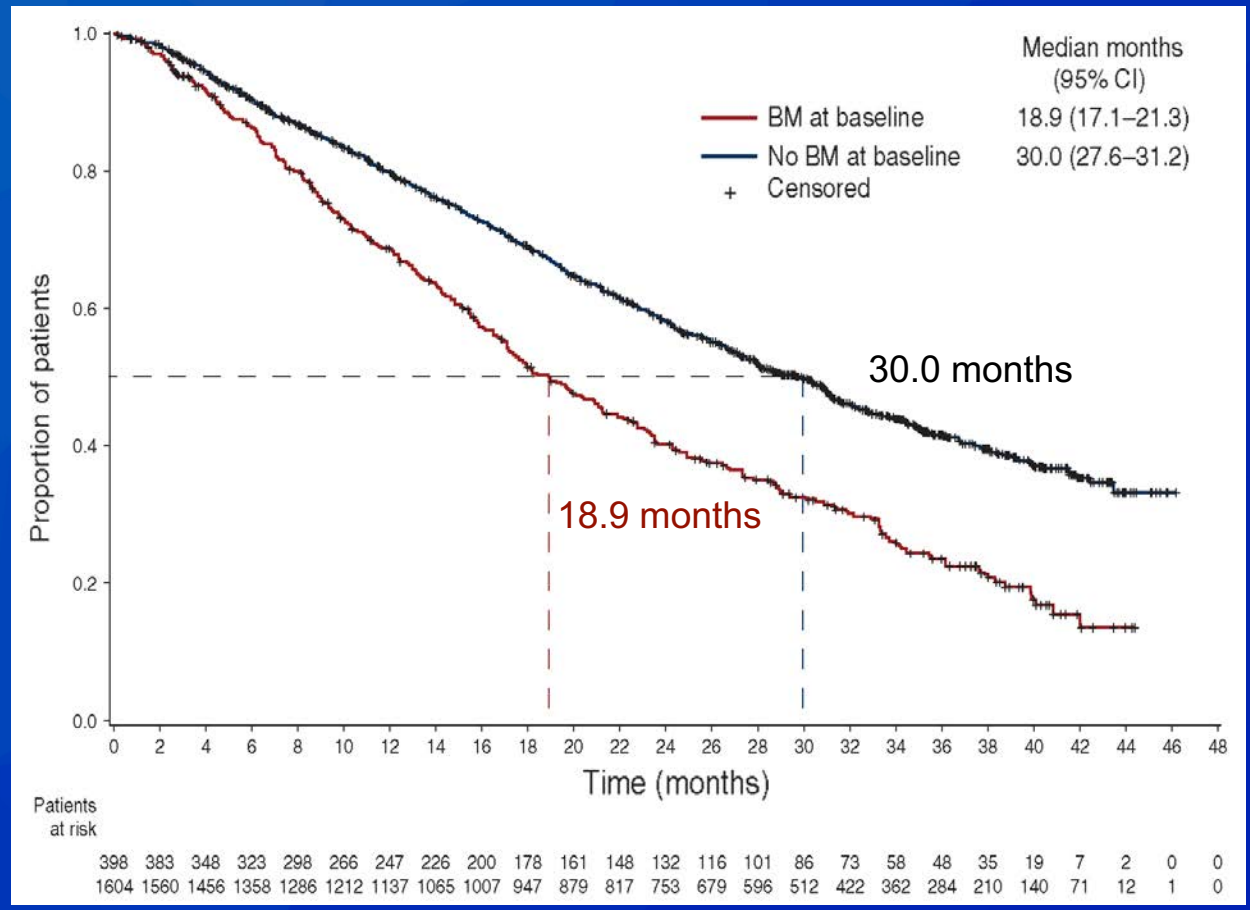
Montemurro F et al. *Ann Oncol* 2020;31(10):1350-8.

KAMILLA Trial (Cohort 1): Survival for Patients with BM vs No BM at Baseline

PFS



OS

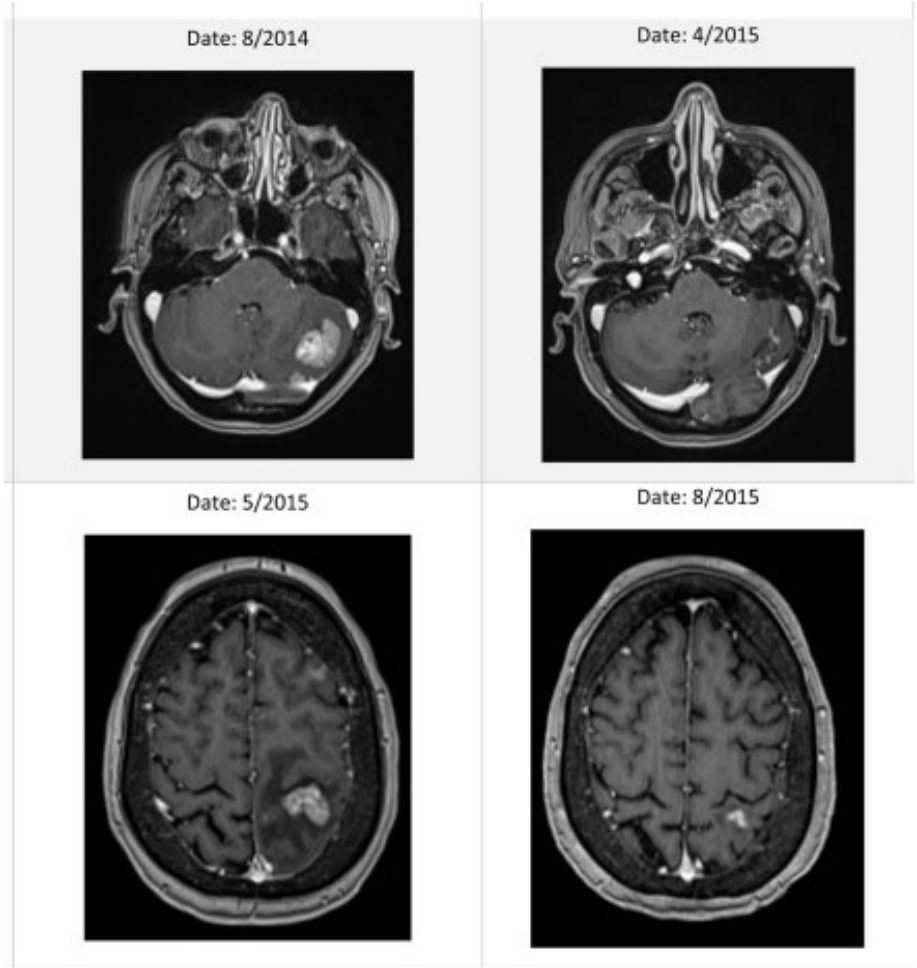


BM = brain metastases

- This exploratory analysis of patients with HER2-positive mBC and BM enrolled in a prospective clinical trial shows that T-DM1 is active and well tolerated.

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

T-DM1 activity in HER2+ brain metastases: UNC experience and case reports



Case report of n = 10 pts illustrated
PFS of 5.5 mos; OS 8.5 mos

Four patients treated at UNC with durable responses, one over 16 mos.

Ph II study of T-DM1 plus neratinib in HER2+ BCBM activated through TBCRC 022

(PI R. Freedman)

R. Bartsch,et al, Clin.Exp.Metastasis 2015.

Keith, K et al. Cancer Treat Comm 2016.

Courtesy of Carey K Anders, MD

DESTINY-Breast01: PFS for patients with stable brain metastases treated with trastuzumab deruxtecan

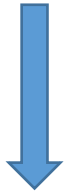
The median response duration was 14.8 months (95% CI, 13.8 to 16.9) (Figure 3A). The median duration of progression-free survival was 16.4 months (95% CI, 12.7 to not reached) among all patients and 18.1 months (95% CI, 6.7 to 18.1) among the 24 patients who were enrolled with treated and asymptomatic brain metastases. Estimated overall survival was 93.9% (95% CI, 89.3 to 96.6) at 6 months and 86.2% (95% CI, 79.8 to 90.7) at 12 months; the median overall survival was not reached at the time of this report (Fig. S2).

Courtesy of Carey K Anders, MD

Modi et al. NEJM 2020;382(7):610-21

How do we synthesize this data into a practical clinical algorithm?

Post-CNS radiation systemic therapy considerations



HER2-targeted therapy algorithms for HER2+ metastatic breast cancer

- **1st line: THP**
- **2nd line: T-DM1**
- **3rd line: Current options:**
  - **Trastuzumab-deruxtecan (Stable BrM)**
  - **(Progressive BrM)**
    - **Tucatinib/Trastuzumab/Capecitabine**
    - **Neratinib/Capecitabine**
    - **Lapatinib/Capecitabine**

Many outstanding questions:

1. **Would incorporating tucatinib earlier in the treatment for patients with brain metastases be of benefit?**

2. **Would combining tucatinib with H/P or T-DM1 be of benefit to patients with brain metastases?**

3. **Would combining tucatinib with trastuzumab deruxtecan be of benefit to patients with brain metastases?**

4. **Would switching therapy to tucatinib regimen post-CNS XRT be of benefit to patients with brain metastases?**

5. **Many more…..?**

Courtesy of Carey K Anders, MD

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

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

RTP
RESEARCH
TO PRACTICE

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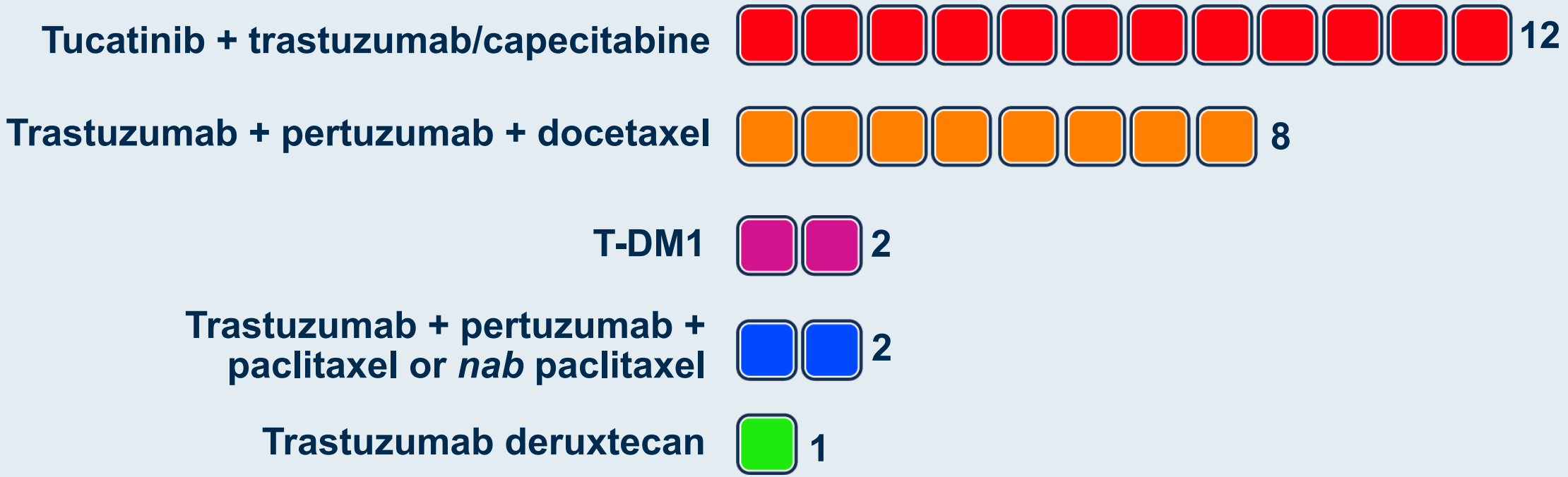
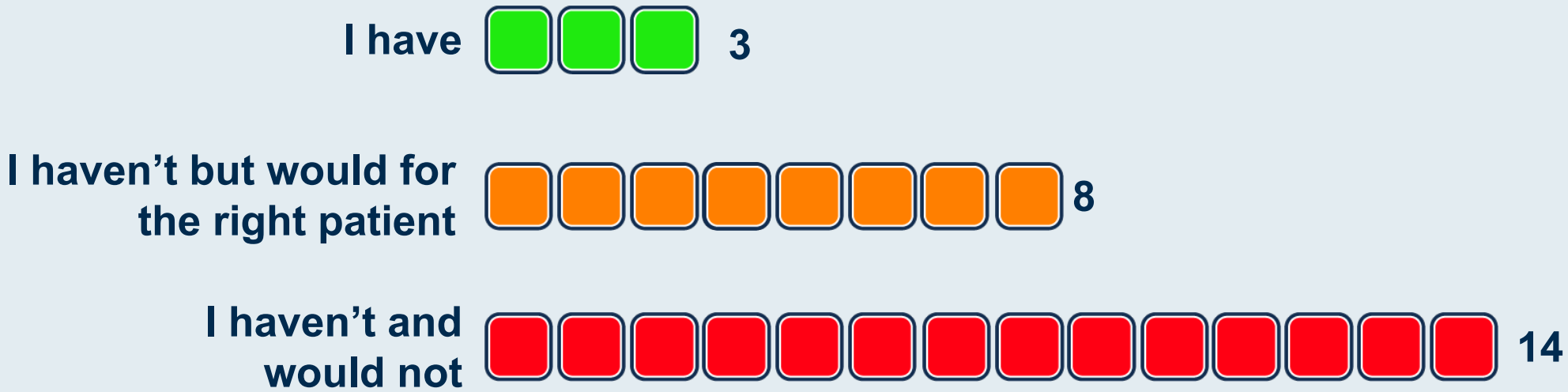


Survey of 25 Breast Cancer Clinical Investigators

Have you administered or would you administer tucatinib combined with something other than trastuzumab/capecitabine outside of a clinical trial setting?



Survey of 25 Breast Cancer Clinical Investigators

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Module 5: Incidence and Management of Adverse Events Associated with HER2-Targeted Therapy — Dr Hamilton

RTP
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TO PRACTICE

Adverse Events (AEs) associated with HER2 targeted therapies

Erika Hamilton, MD

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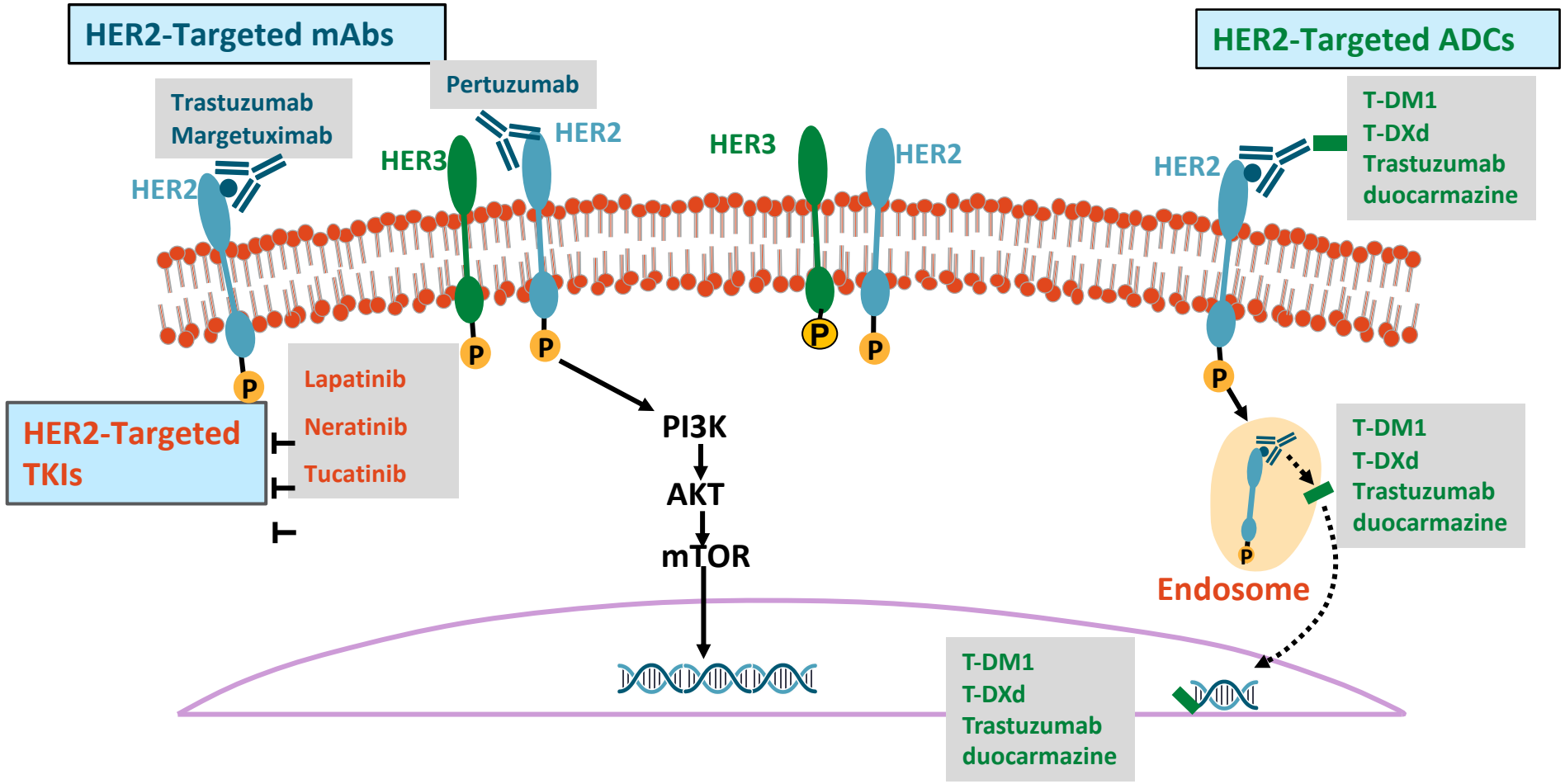
Targeted therapies for HER2+ breast cancer



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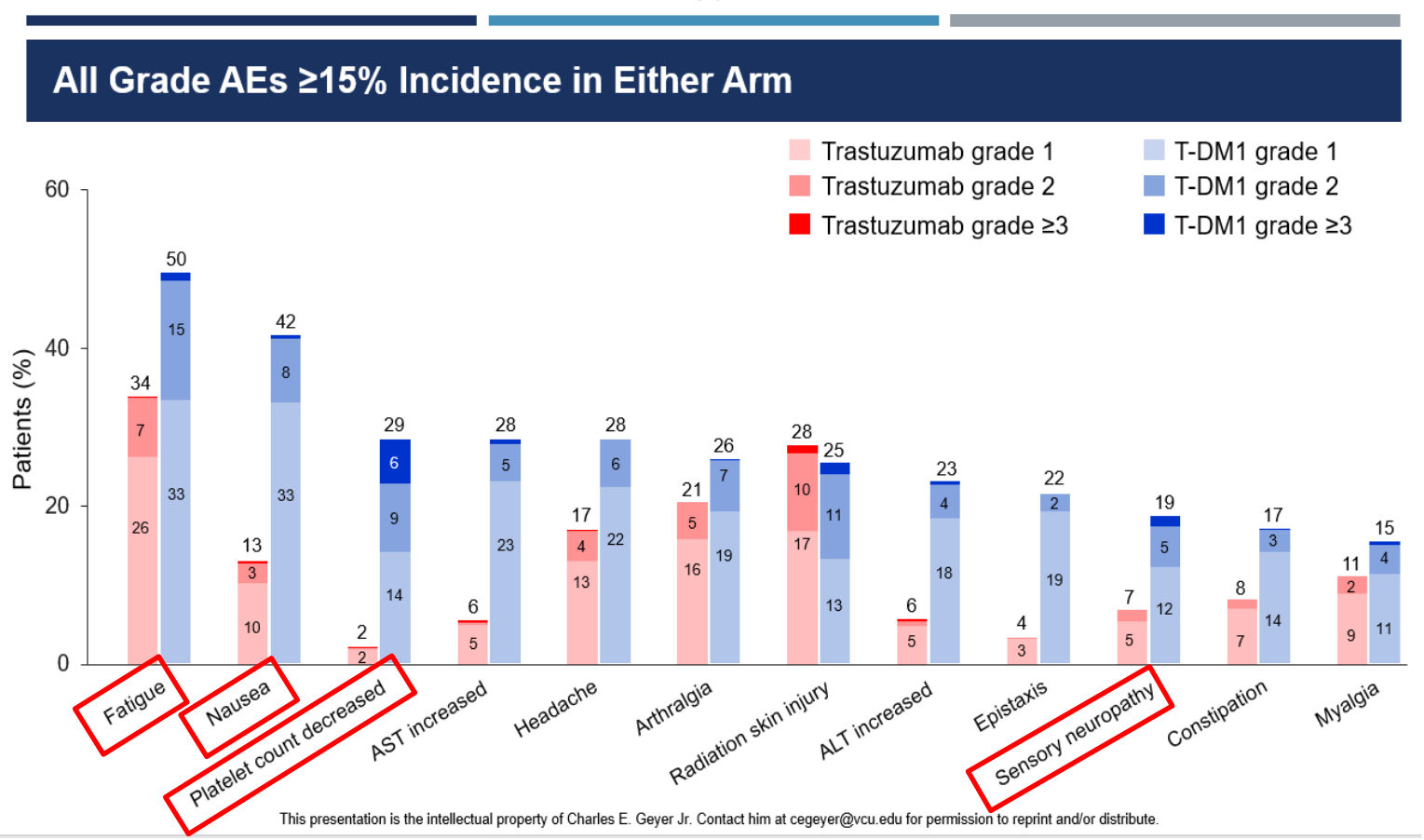
Gajria. Expert Rev Anticancer Ther. 2011; Pernas. Ther Adv Med Oncol. 2019

KATHERINE Trial (Trastuzumab vs T-DM1): Adverse event profile



Number of patients	Trastuzumab n=720	T-DM1 n=740
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serious AEs	58 (8.1)	94 (12.7)
AEs leading to tx discontinuation	15 (2.1)	133 (18.0)
AE with fatal outcome*	0	1 (0.1)

*Fatal AE was intracranial hemorrhage after a fall associated with T-DM1–induced thrombocytopenia

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Geyer C et al SABCS 2018

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KATHERINE: Dose reductions and Treatment discontinuations

Dose reductions

	Trastuzumab (n=720)	T-DM1 (n=740)
Cycles of trastuzumab/T-DM1 completed, n (%)		
7 cycles	664 (92.2)	637 (86.1)
14 cycles	583 (81.0)	528 (71.4)
Patients with a dose reduction, n (%)		
No dose reduction	N/A	634 (85.7)
One dose level reduction (3.0 mg/kg)	N/A	77 (10.4)
Two dose level reductions (2.4 mg/kg)	N/A	29 (3.9)

Treatment discontinuations

	Trastuzumab n=720	T-DM1 n=740
Patients discontinuing due to adverse events	15 (2.1%)	133 (18.0%)
Platelet count decreased	0	31 (4.2%) ✓
Blood bilirubin increased	0	19 (2.6%)
Aspartate aminotransferase (AST) increased	0	12 (1.6%)
Alanine aminotransferase (ALT) increased	0	11 (1.5%)
Peripheral sensory neuropathy	0	11 (1.5%) ✓
Ejection fraction decreased	10 (1.4%)	9 (1.2%)

Geyer C et al SABCS 2018

Courtesy of Erika Hamilton, MD

ATEMPT Trial (T-DM1 vs. TH): Adverse event profile

Treatment related AEs Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

Tolaney S et al SABCS 2019

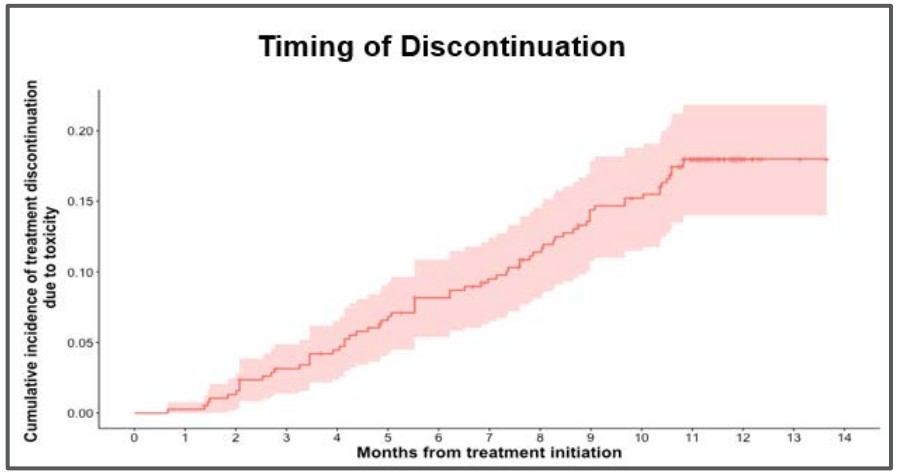
Courtesy of Erika Hamilton, MD

ATEMPT: Toxicities and treatment discontinuations

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic 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

T-DM1



Probability of discontinuing T-DM1 within 6 months: 8.2%
Probability of discontinuing T-DM1 within 6-12 months:10.7%

Discontinuations for toxicity that were protocol mandated: 9%

- Common toxicities leading to T-DM1 discontinuation include elevation of liver enzymes or bilirubin, neuropathy and thrombocytopenia

Tolaney S et al SABCS 2019

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Diarrhea seen with neratinib across trials

Trial	EXTENET				NALA				TBCRC 022	
Patient population	HER2+ EBC after adjuvant trastuzumab therapy				HER2+ MBC after ≥2L of anti HER2 therapy				HER2+ MBC with brain mets	
Treatment	Neratinib (N=1408)		Placebo (N=1408)		Neratinib+Cape (N=303)		Lapatinib+Cape (n=311)		Neratinib+Cape (N=49)	
Grade	G1-2	G3	G1-2	G3	All grade	G3-4	All grade	G3-4	G2	G3
Treatment related diarrhea, % of pts	55	40	34	2	83	24	66	13	33	29

Δ38%

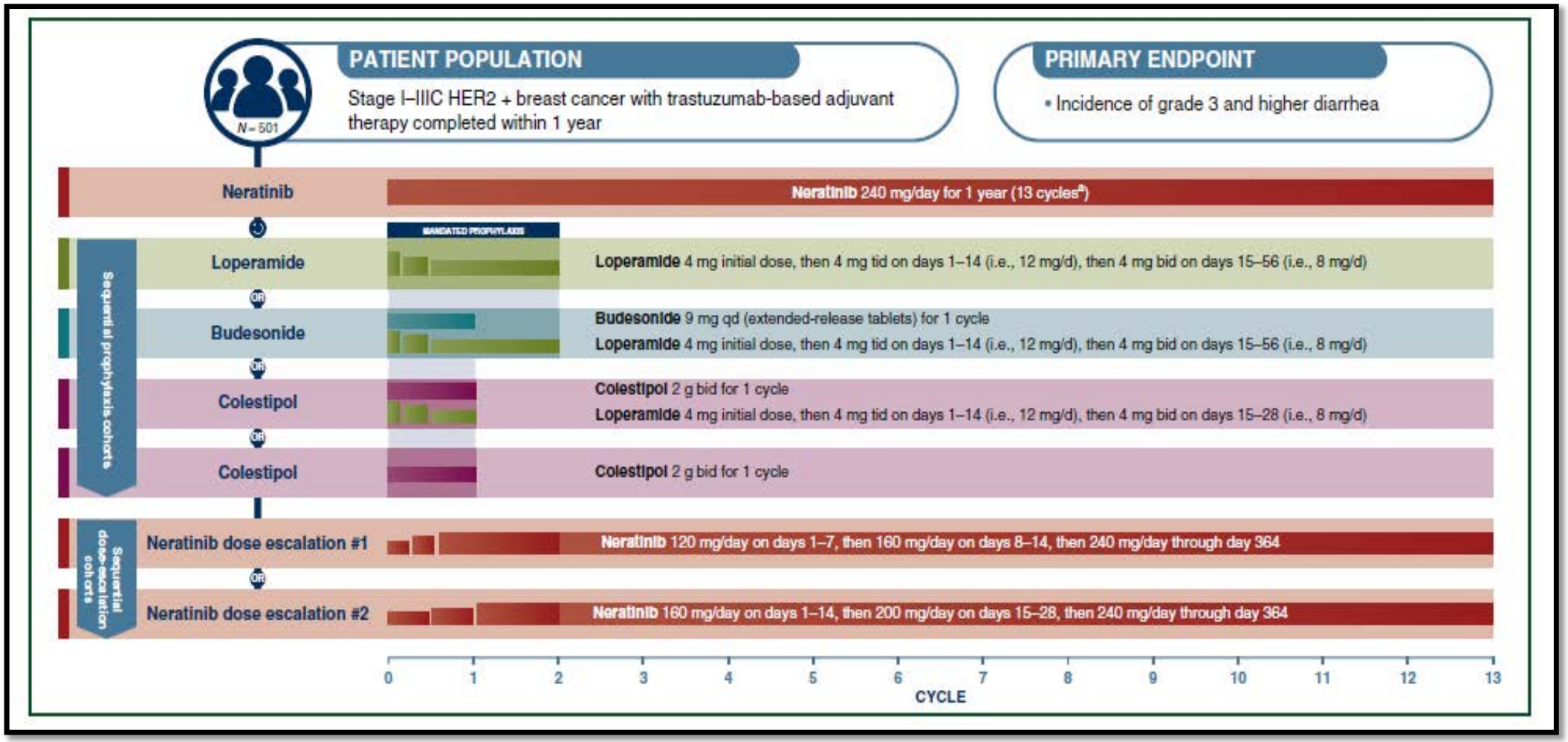
Δ11%

Martin Met al. NEJM 2017
Saura C et al ASCO 2019
Freedman RA et al JCO 2019

Courtesy of Erika Hamilton, MD

CONTROL Trial: Improving tolerability of Neratinib in EBC

Treatment schedules by CONTROL cohort



Barcenas CH et al 2020

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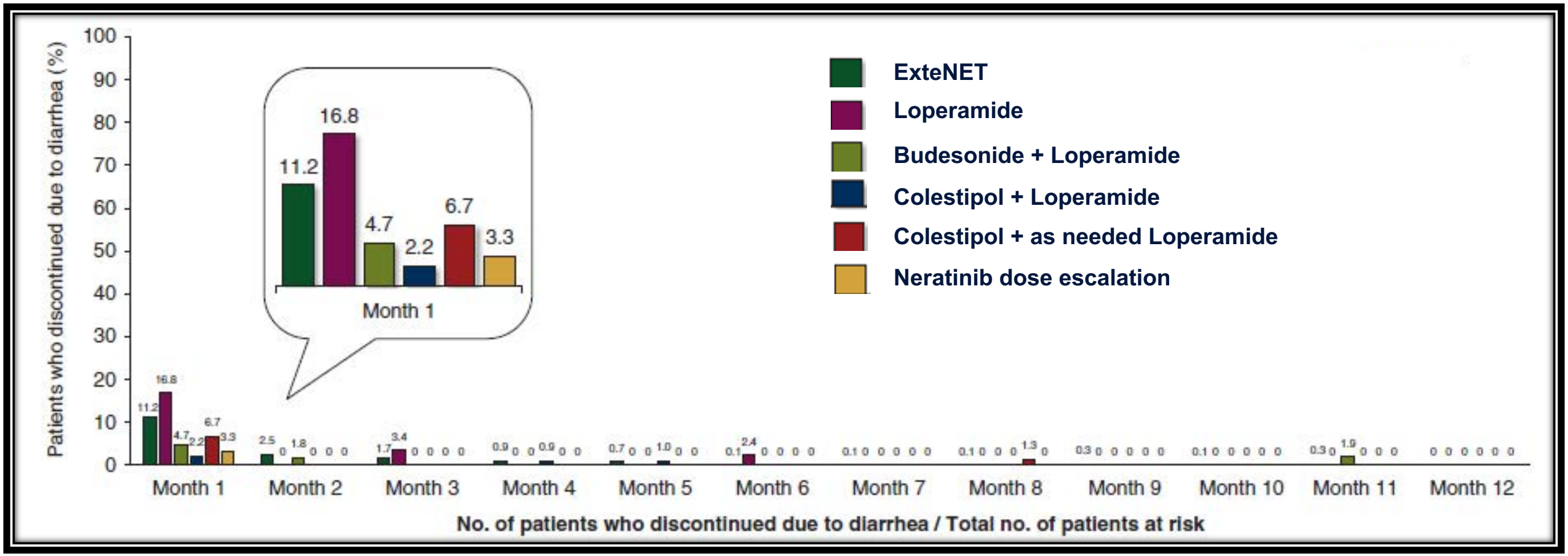
CONTROL: Treatment discontinuations d/t diarrhea



FDA label for Neratinib includes data on the use of prophylactic loperamide plus budesonide

Barcenas CH et al 2020

Courtesy of Erika Hamilton, MD

Prophylaxis for diarrhea with Neratinib

Dose management for EBC

Dose management for MBC

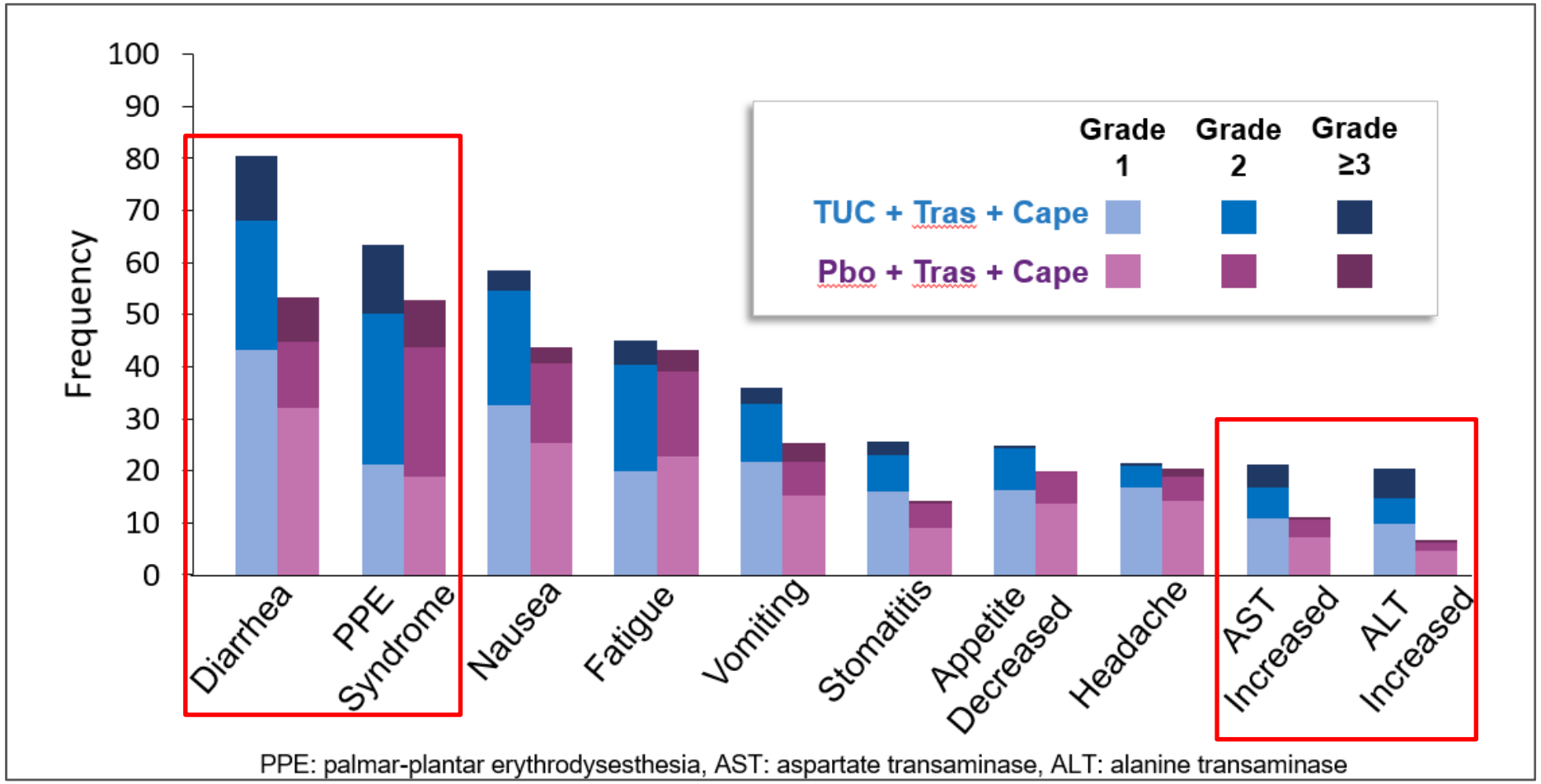
Neratinib 240mg once a day daily

Capecitabine twice a day for 14days and 7days off

An antidiarrheal should be taken with Neratinib for the first 2 months (EBC & MBC)

Courtesy of Erika Hamilton, MD

HER2CLIMB Trial (Tucatinib or Placebo + Capecitabine/Trastuzumab) - Most common AEs (≥20% in the Tucatinib arm)



PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

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Courtesy of Erika Hamilton, MD

Murthy R et al. SABCS 2019

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Murthy R et al. SABS 2019

Management of toxicities with Tucatinib

Diarrhea

- Antidiarrheal prophylaxis not required
- Administer antidiarrheal treatment as clinically indicated
- Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea
- Based on the severity of the diarrhea, consider dose reductions of capecitabine and possibly tucatinib

Hepatotoxicity

- Monitor ALT, AST and bilirubin prior to starting Tucatinib, q 3weeks during treatment and as clinically indicated
- Based on the severity of the hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue tucatinib and/or capecitabine

PPE syndrome

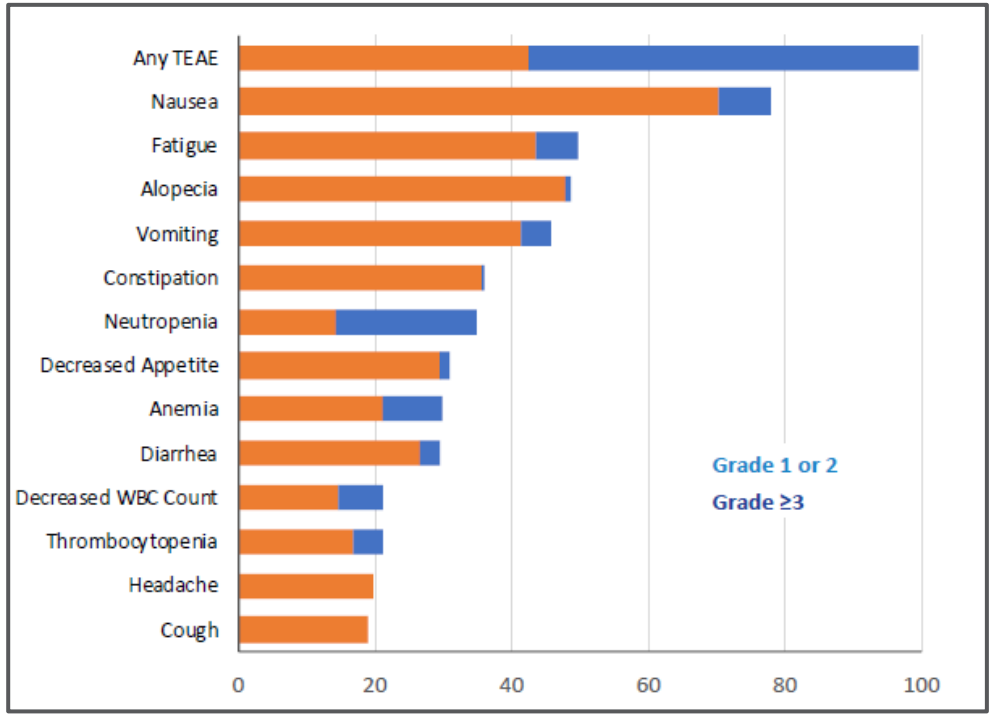
- Side effect of capecitabine
- Support care per standard capecitabine (emollients, topical creams, altered schedule, dose reductions)

Courtesy of Erika Hamilton, MD

PPE: Palmar plantar erythrodysesthesia

DESTINY Breast-01 Trial: Adverse events with TDxd

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%)**

Krop I et al SABCS 2019

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Courtesy of Erika Hamilton, 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

Pneumonitis-associated with DS-8201a

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**

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

Courtesy of Sara Hurvitz, 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

Case Presentation – Dr Hamilton: 69-year-old woman with HER2-positive breast cancer

- 69 yo F with HER2-amplified breast cancer
  - Oct 2008 L breast biopsy, ER-, PR -, HER2 3+ L4 biopsy + metastatic carcinoma c/w breast
  - Kyphoplasty and XRT L4
  - For roughly 10 years received 13 lines of HER2-directed therapy including T-DM1, pertuzumab, margetuximab, lapatinib, etc and most chemo backbones with trastuzumab
  - Metastatic disease to liver, bone and even epidural tumor in spine
  - Received trastuzumab deruxtecan
    - C3D1 -26.8% SD
    - C5D1 -55% PR
    - C7D1 -68% PR

Case Presentation – Dr Hamilton: 69-year-old woman with HER2-positive breast cancer (cont)

- At C16D1 presents to clinic feeling unwell, 99% RA, on questioning has subtle SOB on stairs and some cough when lying flat at night
  - Scans ordered and show pneumonitis
  - Steroids started at 1mg/kg and symptoms improve, wean off steroids over 4 weeks
  - Several weeks later symptoms return and she goes back on steroids with hospitalization with prolonged taper over 2 months
  - Remained off therapy for 10 months with no progression

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Triple-Negative Breast Cancer

Friday, December 11, 2020
8:30 PM – 10:00 PM ET

Faculty

P Kelly Marcom, MD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, MD, PhD

Moderator

Neil Love, MD

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