Key Questions and Emerging Research in the Management of HER2-Positive Breast Cancer

Wednesday, July 8, 2020
5:00 PM – 6:00 PM ET

Faculty

Lisa A Carey, MD
Ian E Krop, MD, PhD

Moderator

Neil Love, MD

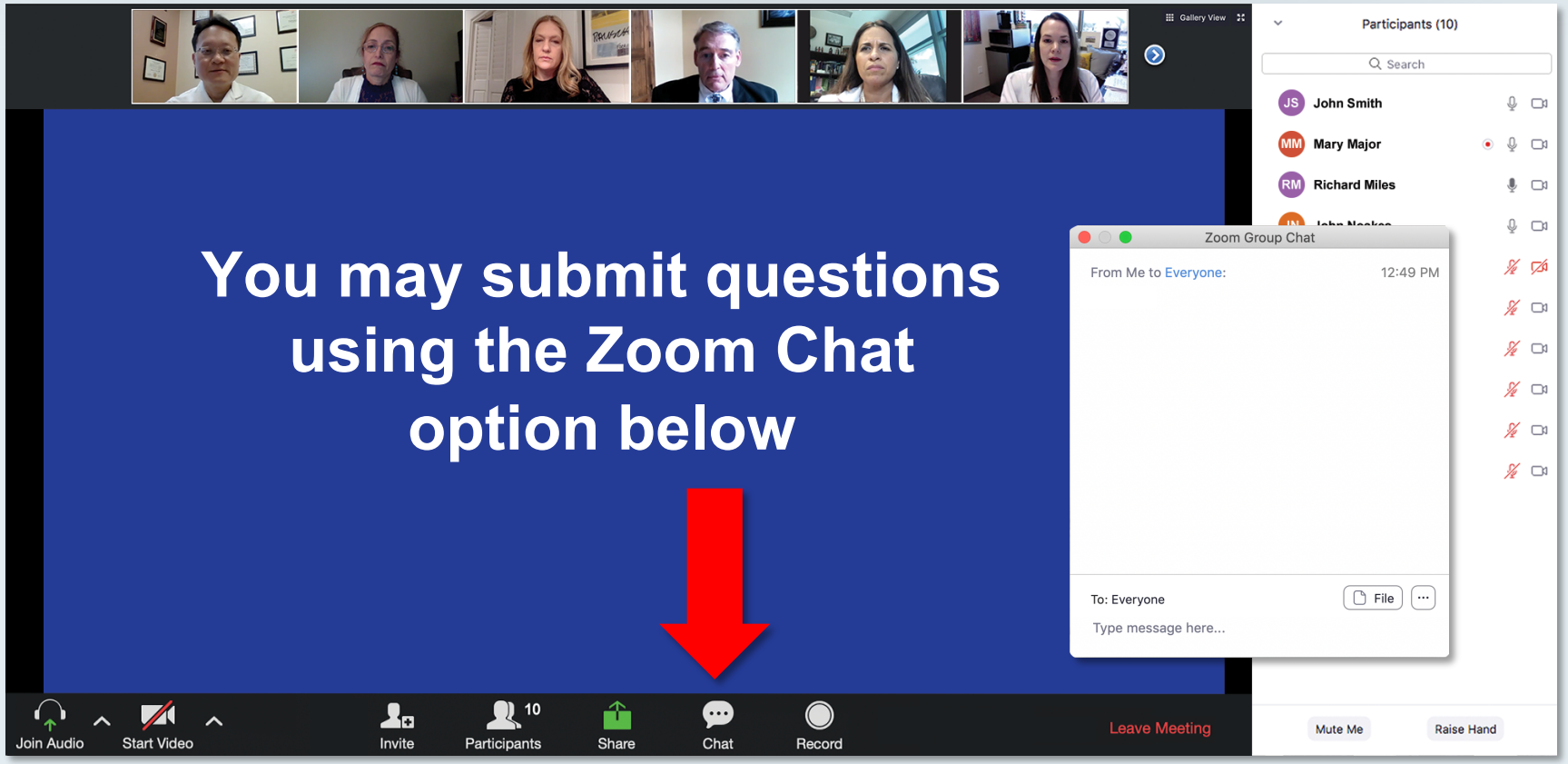
RTP
RESEARCH TO PRACTICE

Faculty

Lisa A Carey, MD
Richardson and Marilyn Jacobs Preyer
Distinguished Professor for Breast
Cancer Research
Deputy Director for Clinical Sciences
Lineberger Comprehensive Cancer Center
Chapel Hill, North Carolina

Ian E Krop, MD, PhD
Associate Chief, Division of Breast Oncology
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Dr Love and Faculty Encourage You to Ask Questions



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

ONCOLOGY TODAY

WITH DR NEIL LOVE

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The Current and Future Role of Immune Checkpoint Inhibitors and Other Novel Therapies in Urothelial Bladder Cancer

Thursday, July 9, 2020

5:00 PM – 6:00 PM ET

Faculty

Arjun Balar, MD

Siamak Daneshmand, MD

Ashish M Kamat, MD, MBBS

Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Key Questions and Emerging Research in the Management of Multiple Myeloma

Monday, July 13, 2020
5:00 PM – 6:00 PM ET

Faculty

Shaji K Kumar, MD
Noopur Raje, MD

Moderator

Neil Love, MD

RTP
RESEARCH TO PRACTICE

Meet The Professors

Clinical Investigators Discuss Existing and Emerging Treatment Strategies for Patients with Ovarian, Cervical and Endometrial Cancer

Tuesday, July 14, 2020

12:00 PM – 1:00 PM ET

Faculty

Michael J Birrer, MD, PhD
Kathleen Moore, MD

Moderator

Neil Love, MD

Research To Practice®

Recent Advances in Medical Oncology: Triple-Negative Breast Cancer

Monday, July 20, 2020

5:00 PM – 6:00 PM ET

Faculty

Joyce O'Shaughnessy, MD

Hope S Rugo, MD

Moderator

Neil Love, MD

Research To Practice®

Recent Advances in Medical Oncology: ER-Positive Breast Cancer

Monday, August 17, 2020

5:00 PM – 6:00 PM ET

Faculty

Virginia Kaklamani, MD, DSc

Sara M Tolaney, MD, MPH

Moderator

Neil Love, MD

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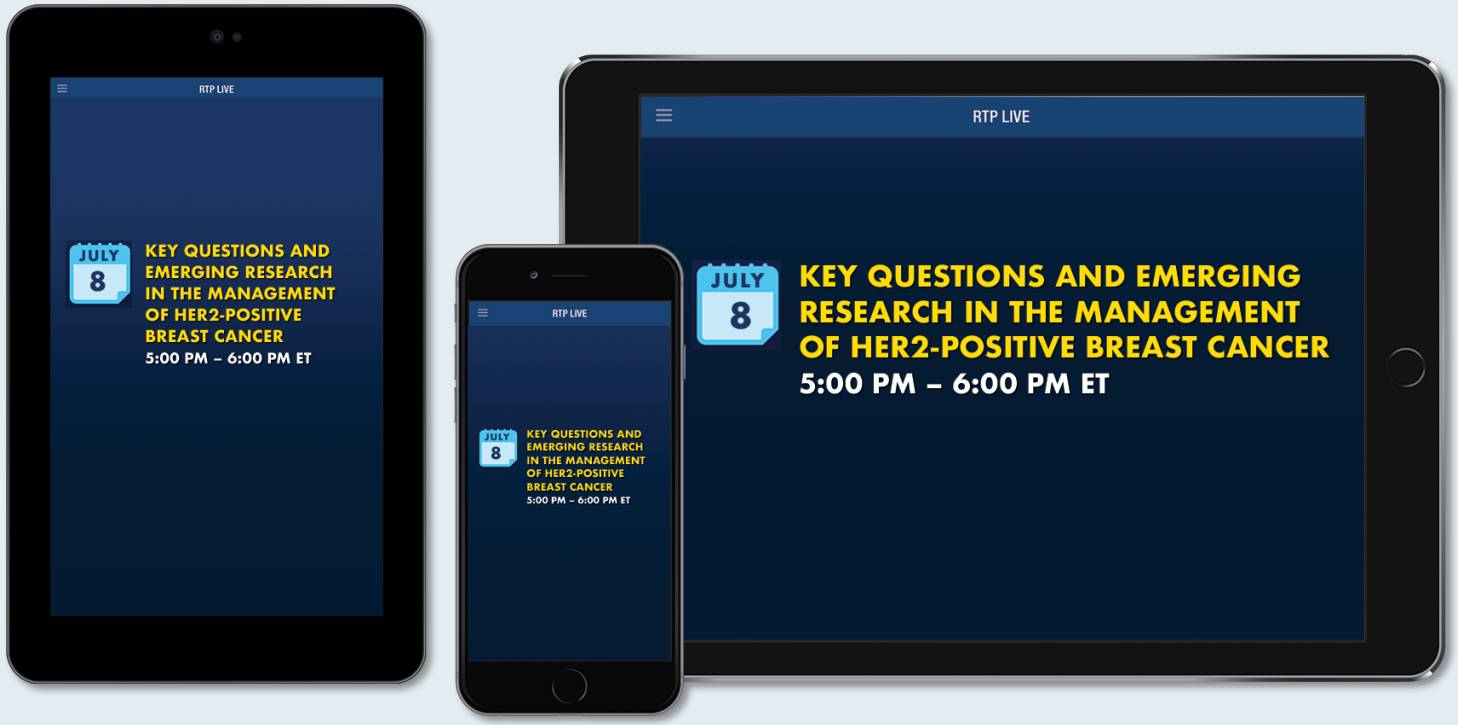

About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

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RESEARCH TO PRACTICE

Community Oncologists

Patricia A DeFusco, MD
Director, Breast Program
Hartford HealthCare Cancer Institute
Hartford Hospital
Hartford, Connecticut

Nick C Leasure, MD
Assistant Section Chief
Section of Hematology and Oncology
Tower Health Medical Group
Reading, Pennsylvania

Justin Peter Favaro, MD, PhD
Oncology Specialists of Charlotte
Charlotte, North Carolina

YanJun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Agenda

Module 1: Localized HER2-Positive Breast Cancer — Dr Carey

- **Key Recent Data Sets**
  - Adjuvant: APHINITY update (pertuzumab); ATEMPT — T-DM1 vs HP
  - Postneoadjuvant: KATHERINE — T-DM1 for residual disease
- **Cases/Questions from General Medical Oncologists**
- **Faculty Cases**

Module 2: HER2-Positive Metastatic Breast Cancer — Dr Krop

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  - HER2CLIMB: Tucatinib/trastuzumab/capecitabine
  - DESTINY-Breast01: Trastuzumab deruxtecan
  - NALA: Neratinib/capecitabine
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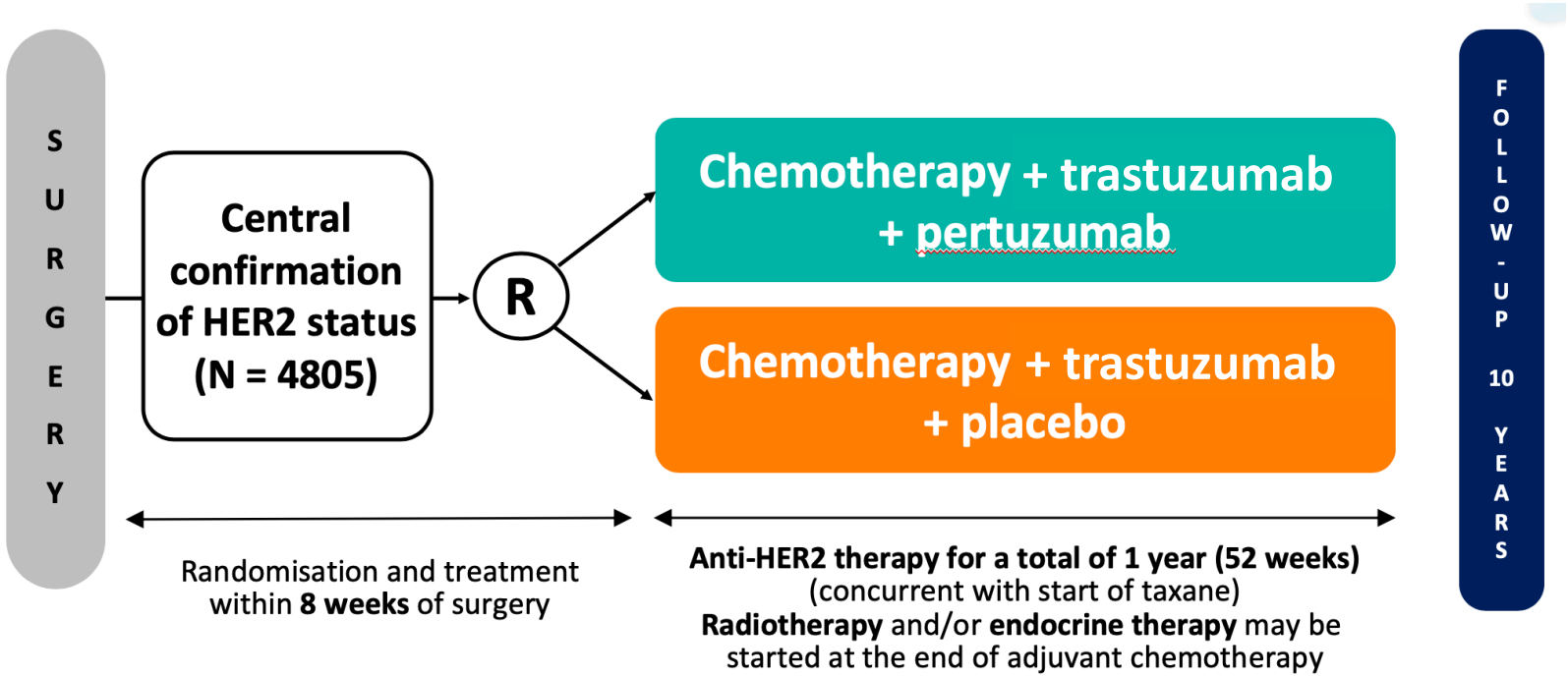
Early HER2+ Breast Cancer Treatment Timeline

	Trastuzumab (H)	Pertuzumab (added to H)	Neratinib (after H)	T-DM1 (in RD)	TH/T-DM1 in stage 1	Tailoring to risk…
	2005	2013-18	2018	2019	2017-19	2020+
Key trials	Many	APHINITY	ExteNET	KATHERINE	APT/ ATEMPT	COMPASS DECRESCENDO
△ outcome	>10% ↑ RFS/OS all	~ 2-3% ↑ RFS esp N+	~2-3% ↑ RFS esp ER+	10% ↑ RFS	RFS > 95%	?

Courtesy of Lisa A Carey, MD

APHINITY – Lessons Learned from the Update



ASCO/NEJM 2017:

- **3y iDFS HR 0.81 (△1.7%)**
- **> 3% benefit ER-, N+**
- **Diarrhea, esp with TCHP (18%)**

Von Minckwitz et al, NEJM 2017

Courtesy of Lisa A Carey, MD

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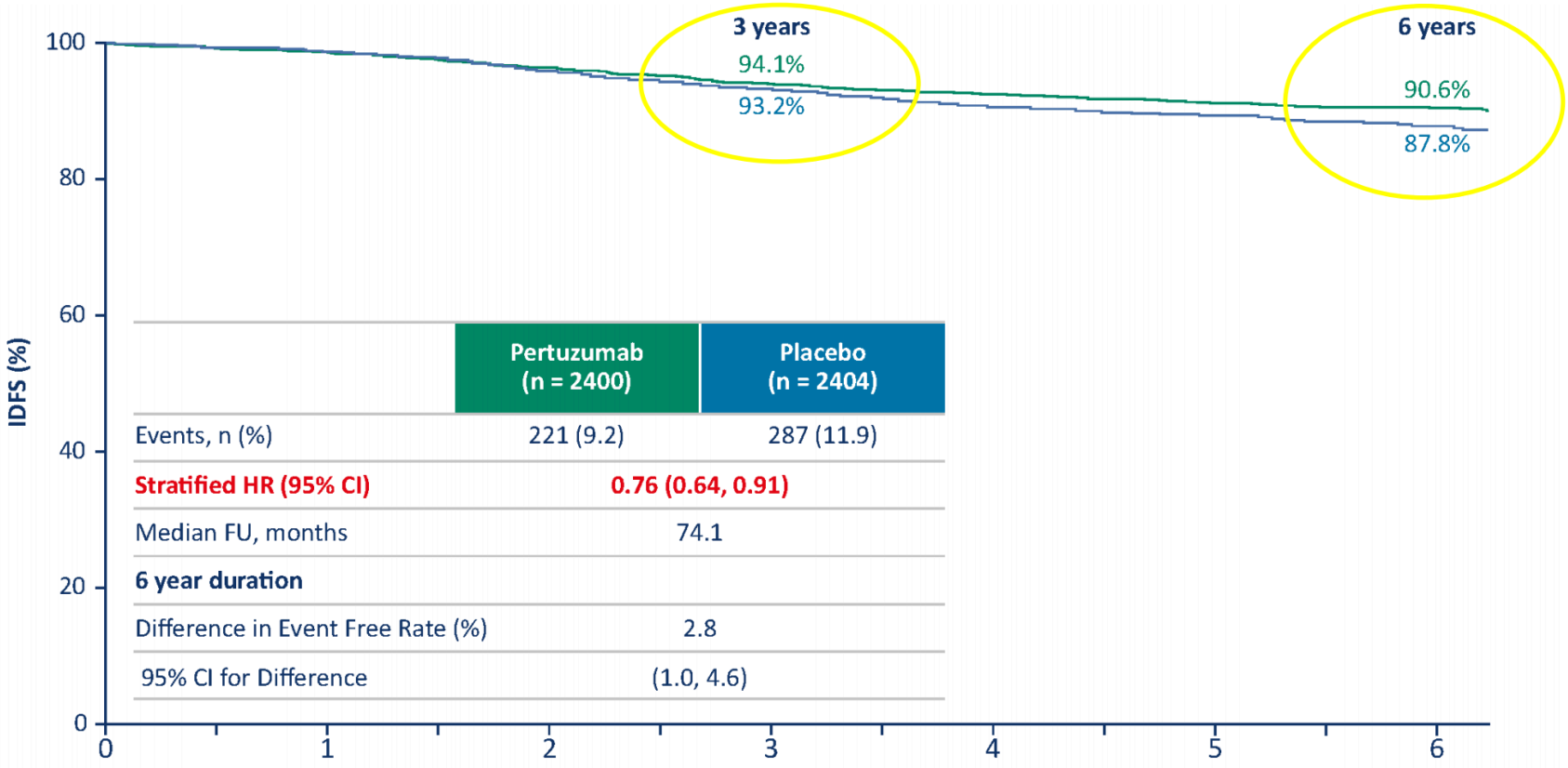
APHINITY @ SABCS 2019

2nd interim analysis, 74m follow-up
Time to first iDFS event:



	Pertuzumab (n = 2400)	Placebo (n = 2404)
Events, n (%)	221 (9.2)	287 (11.9)
Stratified HR (95% CI)	**0.76 (0.64, 0.91)**	
Median FU, months	74.1	
6 year duration		
Difference in Event Free Rate (%)	2.8	
95% CI for Difference	(1.0, 4.6)	

Little effect in N- 4.5% absolute △ in N+

Unlike 2017 benefit seen in both ER+ and ER-

No new cardiac safety signals

Piccart M et al, AACR-SABCS 2019

Courtesy of Lisa A Carey, MD

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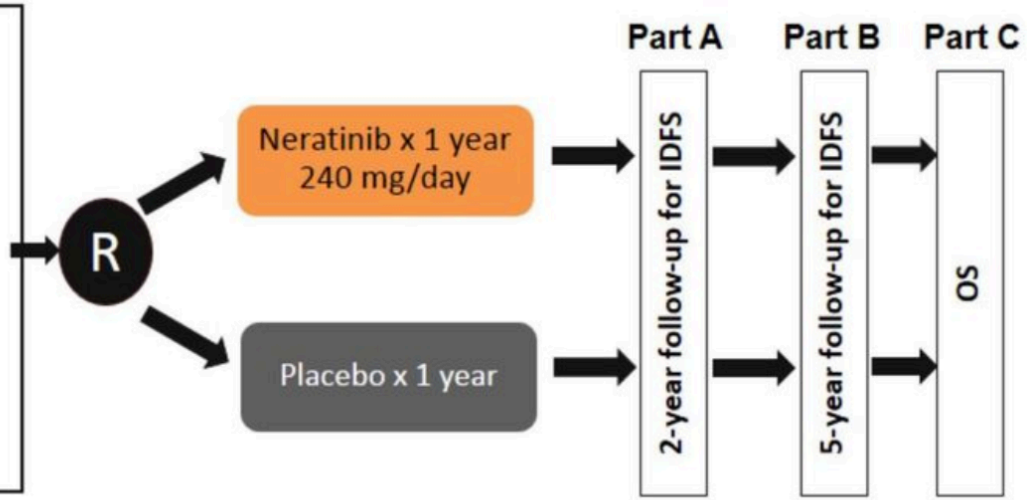
Neratinib: Extended Adjuvant Anti-HER2 Therapy

ExteNET

- HER2+ breast cancer (local)
- Prior adjuvant trastuzumab and chemotherapy
- Completed trastuzumab ≤ 1 year prior to study entry
- Lymph node positive or non-pCR after adjuvant therapy
- ER/PR status unknown



iDFS @ 5y:
87.7% vs 90.2% (△2.5%)
Esp in Asia, HR+, 4+ LN

Study population received chemo+H.

Behavior post HP or T-DM1?

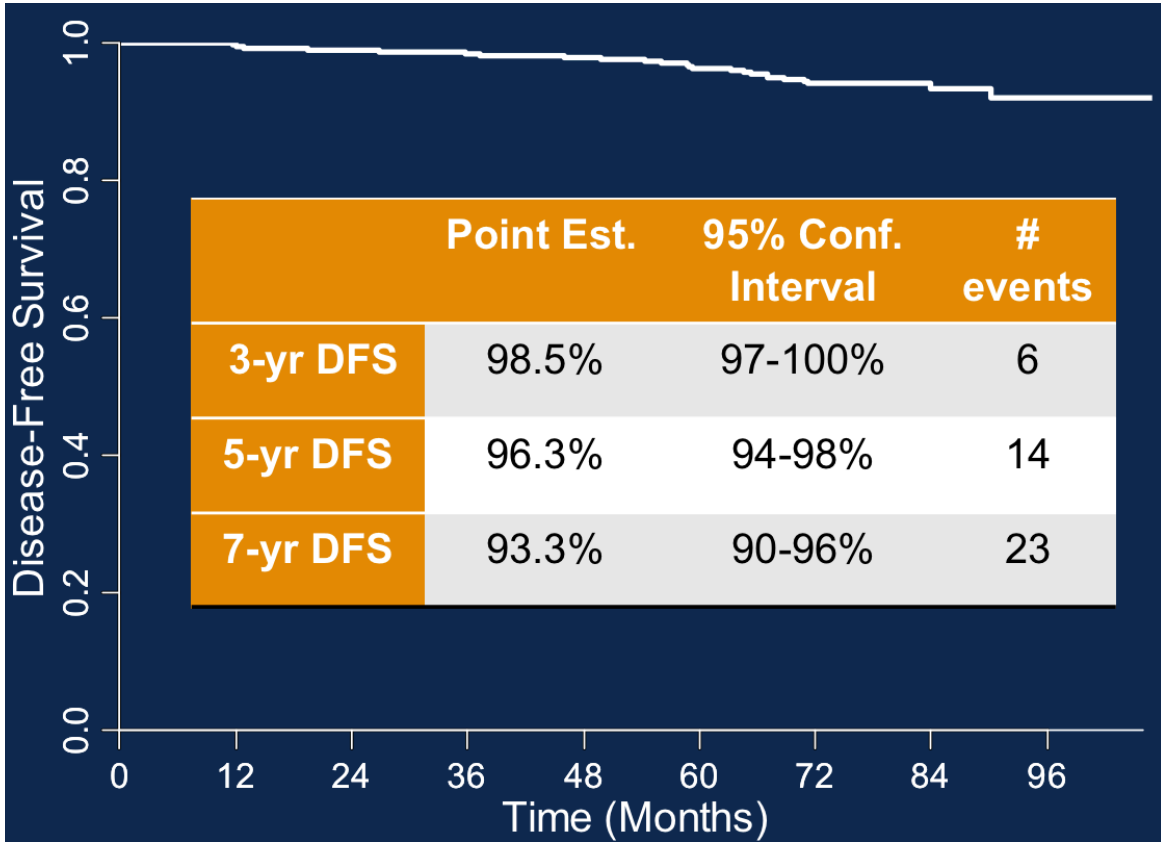
Gr3+ Diarrhea 40%
→ structured intensive prophylaxis with loperamide x 1-2m

CONTROL Trial: additional maneuvers may help (budesonide, colestipol,) dose escalation

Martin M et al, Lancet Oncol 2017; Barcenas CH et al, Ann Oncol 2020

APT and ATEMPT: Optimizing Rx of Stage I HER2+

APT: 12 weeks TH, trastuzumab to 1y
Single arm beat-the-threshold trial



	Point Est.	95% Conf. Interval	# events
3-yr DFS	98.5%	97-100%	6
5-yr DFS	96.3%	94-98%	14
7-yr DFS	93.3%	90-96%	23

Practice-changing for low anatomic risk HER2+ BC.

Tolaney S et al, JCO 2019

Courtesy of Lisa A Carey, MD

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ATEMPT (TBCRC 033): T-DM1 in Stage I

Stage 1 HER2+
N0 or N1mic allowed

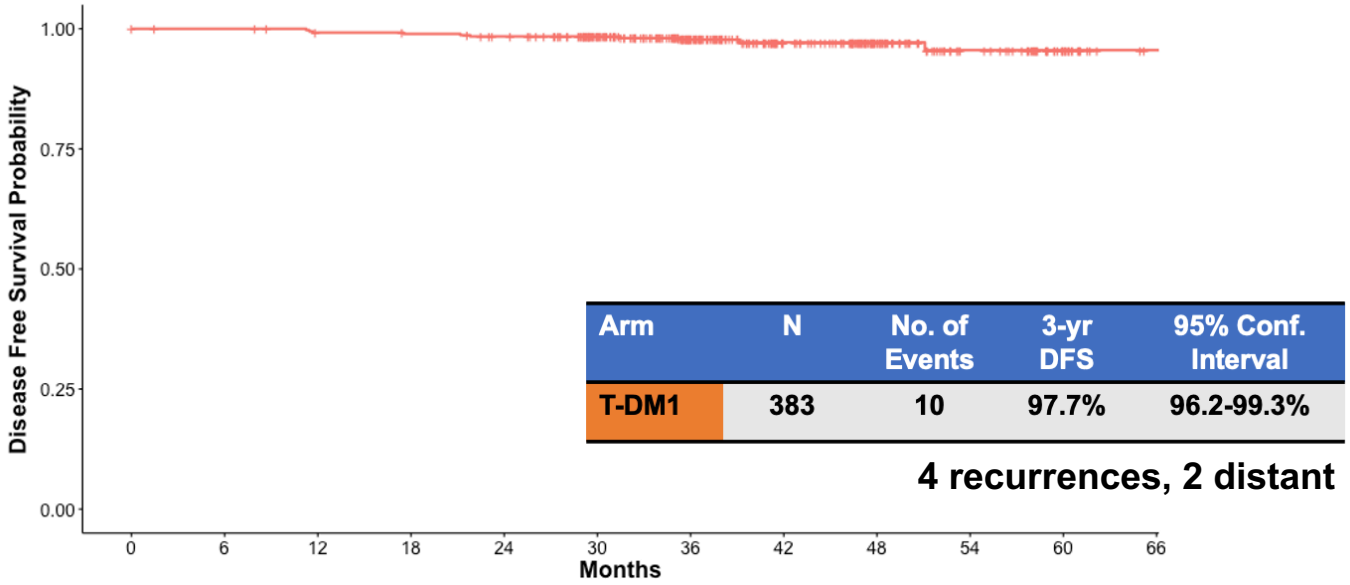
N = 497

3 : **N = 383** — **T-DM1** 3.6 mg/kg IV q3 wks x 17

1 : **N = 114** — **TH**

1º endpoint
iDFS T-DM1 arm

43% T1a-b, 57% T1c
75% ER+



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

4 recurrences, 2 distant

Side effects T-DM1 vs TH:

	T-DM1	TH
Gr 2+ PN	11%	23%
Plt ↓	11%	1%
LFT abnl	10%	5%
Asx EF ↓*	1%	6%
D/C from tox	17%	6%

* < 1% CHF either arm

Courtesy of Lisa A Carey, MD

Tolaney S et al, AACR-SABCS 2019

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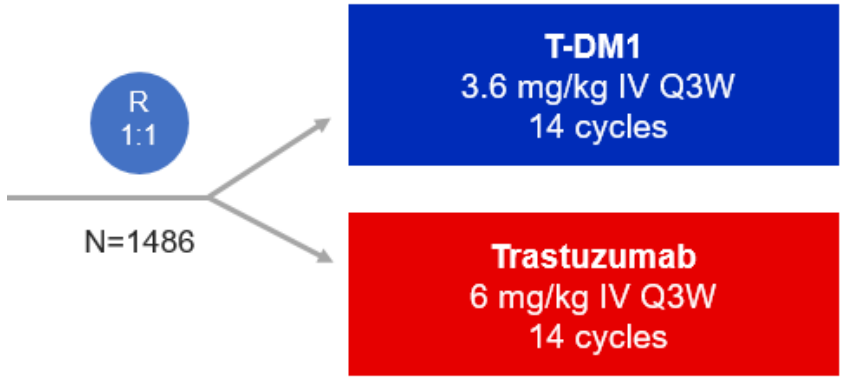
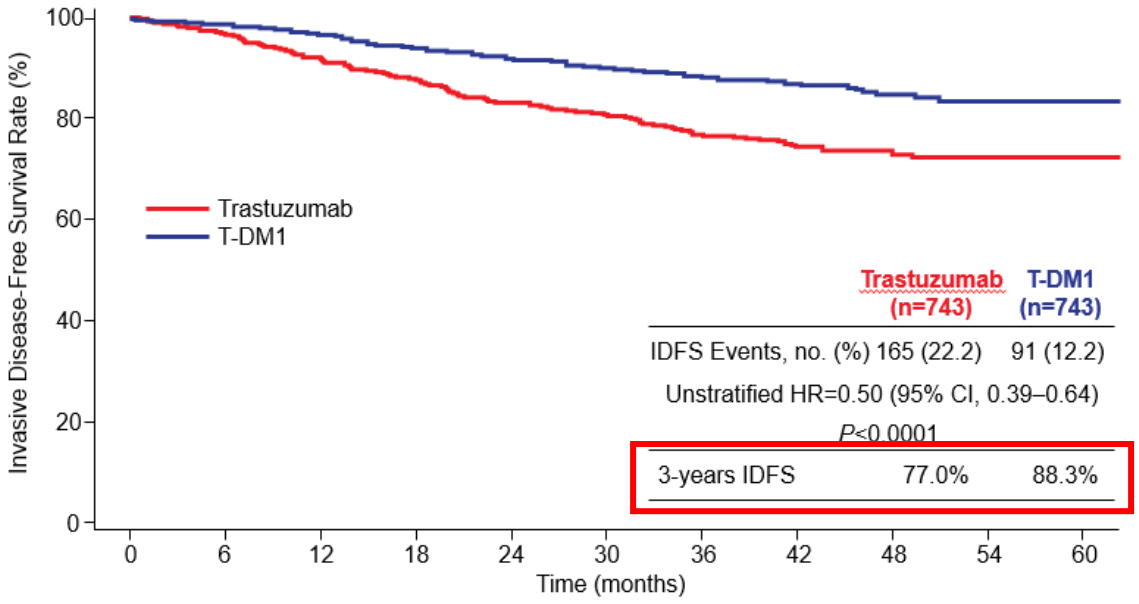
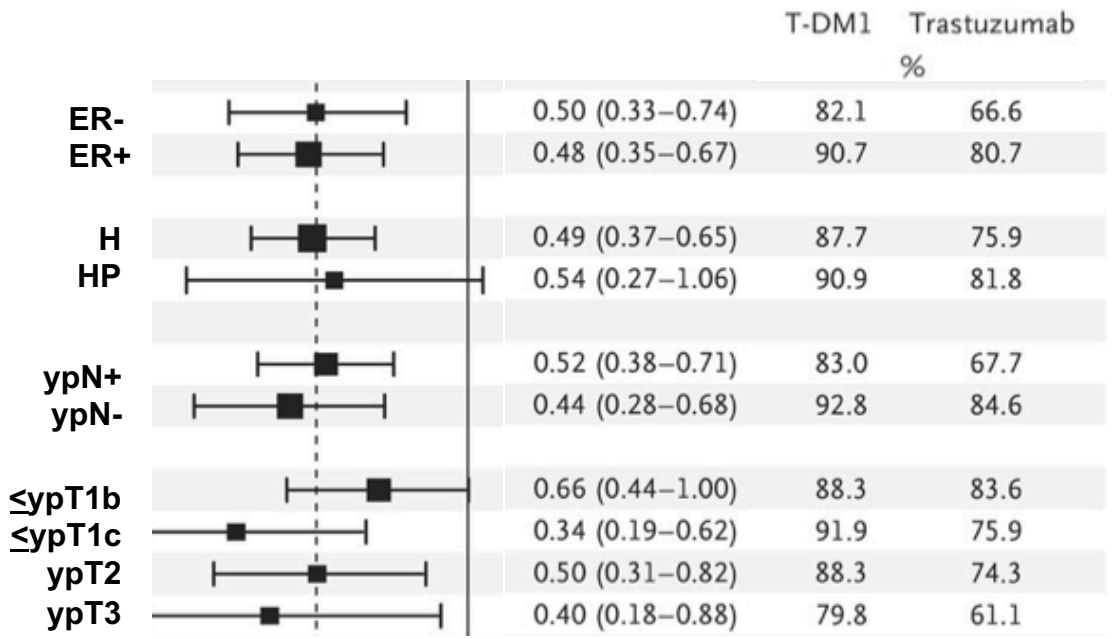
KATHERINE

KATHERINE: HER2+ Residual disease after chemo + H







- **EFS ER-, LN+ still 82-83%**
- **Very few received pertuzumab**

Von Minckwitz et al, NEJM 2018

Courtesy of Lisa A Carey, MD

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Strategies for Treatment of Early HER2+ Breast Cancer

Clinical stage	Initial Rx	Path stage	Adjuvant phase*
Stage I cT1N0	**Surgery**	pT1aN0	No systemic therapy (ET prn)
		pT1b-c,N0	TH x 12 wk, H to 6-12m
Stage II cT2-3N0 cT0-2N1	**Neoadjuvant Rx** Chemo + H (HP if LN+)	pCR	H or HP to 1y
		Residual disease	T-DM1 x 14 cycles
Stage III cT3N1 cT4N(any) cT(any)N2-3	**Neoadjuvant Rx** Chemo + HP	pCR	H or HP to 1y
		Residual disease	T-DM1 x 14 cycles Consider neratinib x 1y if ER+
Surgery first Stage II-III	*Neoadjuvant recommended!*	Stage II-III	Chemo + H (HP if LN+) Consider neratinib x 1y if ER+ and 4+ LN

*ET recommended if HR+

Courtesy of Lisa A Carey, MD

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Agenda

Module 1: Localized HER2-Positive Breast Cancer — Dr Carey

- **Key Recent Data Sets**
  - Adjuvant: APHINITY update (pertuzumab); ATEMPT — T-DM1 vs HP
  - Postneoadjuvant: KATHERINE — T-DM1 for residual disease
- **Cases/Questions from General Medical Oncologists**
  - 35-year-old woman with locally recurrent ER/PR+, HER2+ IDC
  - 38-year-old woman with 3-cm, node-positive ER/PR+, HER2+ IDC
- **Faculty Cases**

A 35-year-old woman with a 6-cm, ER-positive, HER2-positive IDC achieves a pathologic complete response to neoadjuvant TCHP. She receives 1 year of adjuvant trastuzumab, undergoes oophorectomy and begins an adjuvant aromatase inhibitor. Four years later she presents with a 5-cm, ER-positive, HER2-positive in-breast recurrence and again receives neoadjuvant TCHP with a pathologic complete response. Regulatory and reimbursement issues aside, what adjuvant anti-HER2 therapy would you recommend?

a. Trastuzumab
b. Trastuzumab/pertuzumab
c. T-DM1
d. Trastuzumab → neratinib
e. Trastuzumab/pertuzumab → neratinib
f. T-DM1 → neratinib
g. Other

Nick C Leasure, MD

What is the size of the smallest tumor for which you would recommend neoadjuvant systemic therapy for a patient with ER-negative, HER2-positive, node-negative infiltrating ductal carcinoma (IDC)?

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 77-year-old woman with a 2-cm, ER-positive, HER2-positive, node-negative IDC? (Dr Favaro)

	Smallest tumor size	Neoadjuvant systemic therapy
 LISA A CAREY, MD	2 cm	None
 VIRGINIA KAKLAMANI, MD, DSC	2 cm	None
 IAN E KROP, MD, PHD	2 cm	None
 JOYCE O'SHAUGHNESSY, MD	1 cm	TCH
 HOPE S RUGO, MD	0.2 cm	Paclitaxel/trastuzumab
 SARA M TOLANEY, MD, MPH	1.5 cm	THP

THP = paclitaxel/trastuzumab/pertuzumab; TCH = docetaxel/carboplatin/trastuzumab

An 80-year-old woman presents with a 0.5-cm, ER-negative, HER2-positive, node-negative IDC. Regulatory and reimbursement issues aside, what adjuvant systemic therapy would you recommend?

 LISA A CAREY, MD	None
 VIRGINIA KAKLAMANI, MD, DSC	Paclitaxel/trastuzumab
 IAN E KROP, MD, PHD	T-DM1
 JOYCE O'SHAUGHNESSY, MD	TCH
 HOPE S RUGO, MD	T-DM1 (for 6 months or less)
 SARA M TOLANEY, MD, MPH	T-DM1

A 60-year-old woman presents with a 1.3-cm, ER-negative, HER2-positive IDC with 1 positive sentinel node. Would you incorporate adjuvant pertuzumab and/or postadjuvant neratinib into this patient's treatment?

What would be your approach if the patient had ER-positive IDC?

	ER-negative	ER-positive
 LISA A CAREY, MD	Pertuzumab	Pertuzumab
 VIRGINIA KAKLAMANI, MD, DSC	Pertuzumab	Pertuzumab and neratinib
 IAN E KROP, MD, PHD	Pertuzumab	Pertuzumab
 JOYCE O'SHAUGHNESSY, MD	Pertuzumab	Pertuzumab and neratinib
 HOPE S RUGO, MD	Pertuzumab	Pertuzumab (discuss neratinib)
 SARA M TOLANEY, MD, MPH	Pertuzumab	Pertuzumab

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?

 LISA A CAREY, MD	Yes, for all patients
 VIRGINIA KAKLAMANI, MD, DSC	Yes, for all patients
 IAN E KROP, MD, PHD	Yes, for all patients
 JOYCE O'SHAUGHNESSY, MD	Yes, for all patients
 HOPE S RUGO, MD	Yes, for select patients
 SARA M TOLANEY, MD, MPH	Yes, for all patients

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 38-year-old woman with a 3-cm, ER-positive, HER2-positive IDC with 1 positive axillary node on biopsy?

a. None
b. Paclitaxel/trastuzumab
c. Paclitaxel/trastuzumab/pertuzumab
d. ACTH
e. ACTHP
f. TCH
g. TCHP
h. Other

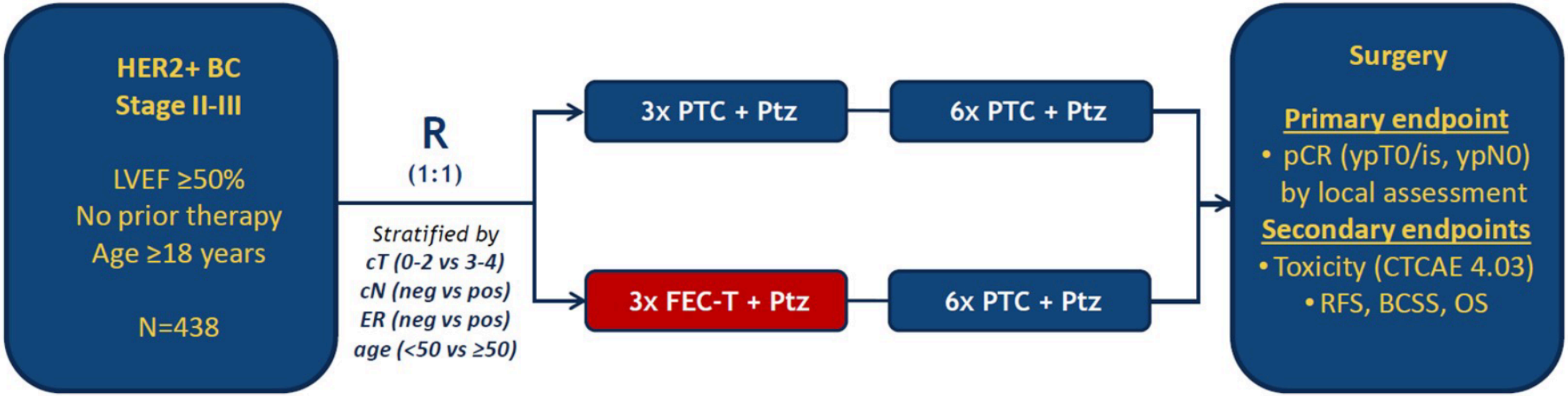
Patricia A DeFusco, MD

Which neoadjuvant systemic therapy, if any, would you generally recommend for a 38-year-old woman with a 3-cm, ER-positive, HER2-positive IDC with 1 positive axillary node on biopsy?

 LISA A CAREY, MD	TCHP
 VIRGINIA KAKLAMANI, MD, DSC	TCHP
 IAN E KROP, MD, PHD	TCHP
 JOYCE O'SHAUGHNESSY, MD	TCHP
 HOPE S RUGO, MD	TCHP
 SARA M TOLANEY, MD, MPH	TCHP

TCHP = docetaxel/carboplatin/trastuzumab/pertuzumab

TRAIN-2: Phase III Trial of Neoadjuvant Chemotherapy with or without Anthracyclines in the Presence of Dual HER2 Blockade



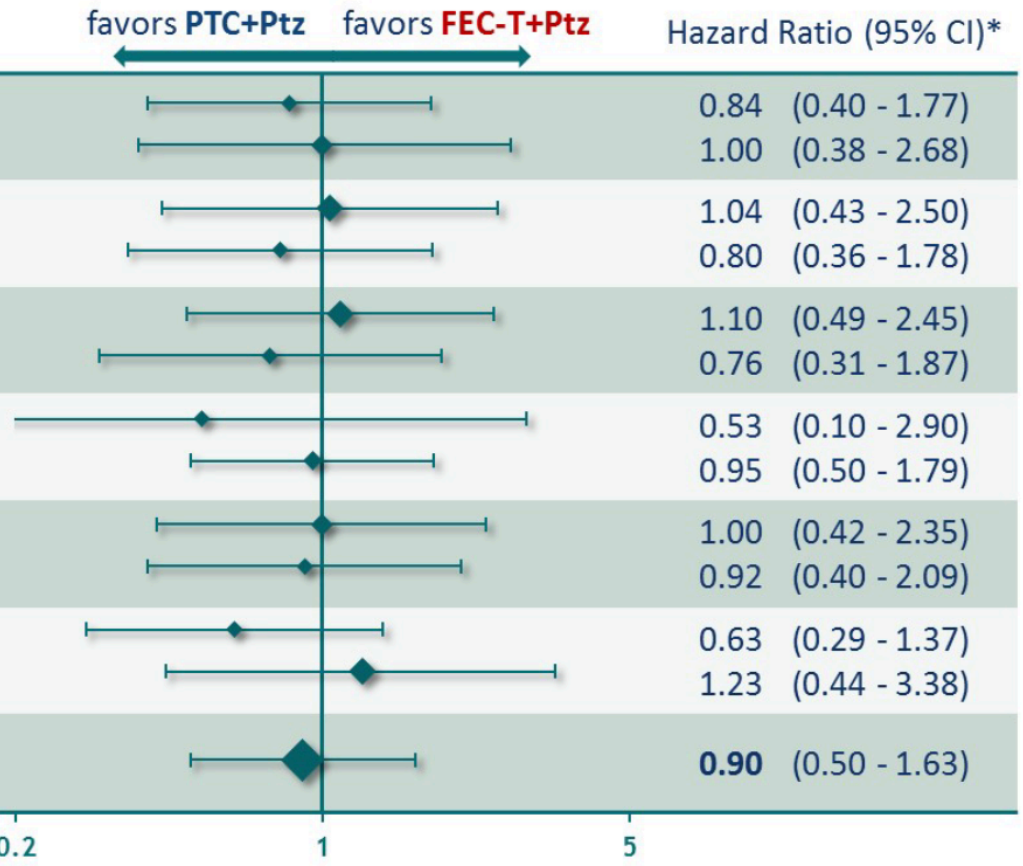
PTC + Ptz = paclitaxel/trastuzumab/carboplatin + pertuzumab
FEC-T + Ptz = FEC + traszutumab + pertuzumab

- Primary endpoint pCR (PTC + Ptz vs FEC-T = Ptz): 68% vs 67% (p=0.95)
- Outcome was consistent across prespecified subgroups (cT, cN, HR status, age)

van Ramhorst MS et al. *Lancet Oncol* 2018;19(12):1630-40; van der Voort A et al. ASCO 2020;Abstract 501.

TRAIN-2 Event-Free Survival: 3-Year Follow-Up

	PTC+Ptz		FEC-T+Ptz		Hazard Ratio (95% CI)*
	Events	total	events	Total	
HR-positive	13	126	15	129	0.84 (0.40 - 1.77)
HR-negative	8	93	8	90	1.00 (0.38 - 2.68)
Age <50 years	10	118	10	119	1.04 (0.43 - 2.50)
Age ≥50 years	11	101	13	100	0.80 (0.36 - 1.78)
cT0-2	13	154	11	147	1.10 (0.49 - 2.45)
cT3-4	8	65	12	72	0.76 (0.31 - 1.87)
cN negative	2	76	4	82	0.53 (0.10 - 2.90)
cN positive	19	143	19	137	0.95 (0.50 - 1.79)
Disease stage II#	11	151	10	139	1.00 (0.42 - 2.35)
Disease stage III	10	68	13	80	0.92 (0.40 - 2.09)
Tumor grade 1-2	11	113	16	107	0.63 (0.29 - 1.37)
Tumor grade 3	8	95	7	101	1.23 (0.44 - 3.38)
All patients	21	219	23	219	**0.90** (0.50 - 1.63)



disease stage II includes one patient with stage I disease (PTC+Ptz) & disease stage III includes one patient with stage IV disease (FEC-T+Ptz)

*HR <1 favors PTC+Ptz

van der Voort A et al. ASCO 2020;Abstract 501.

TRAIN-2 Safety: 3-Year Follow-Up

Most common Grade ≥3 hematologic AEs	PTC + Ptz (n = 218)	FEC-T + Ptz (n = 220)
Neutropenia	54%	60%
Anemia	21%	20%
Thrombocytopenia	19%	18%
Febrile neutropenia	1%	10%

Cardiotoxicity	PTC + Ptz (n = 218)	FEC-T + Ptz (n = 220)	*p*-value
LVEF decrease ≥10% or LVEF <50%	22%	36%	0.0016
LVEF decrease ≥10% and LVEF <50%	3%	8%	0.044

- 2 patients (1%) in the FEC-T + Ptz arm developed chemotherapy-associated acute leukemia

van der Voort A et al. ASCO 2020;Abstract 501.

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  - 38-year-old woman with 3-cm, node-positive ER/PR+, HER2+ IDC
- **Faculty Cases**
  - 46-year-old woman with a 6-mm, node-negative ER/PR-, HER2+ IDC
  - 33-year-old woman with ER-, HER2+ IDC and postneoadjuvant residual disease

A 46-year-old woman presents with extensive DCIS, undergoes right mastectomy and sentinel lymph node biopsy and is found to have 6 mm of ER/PR-negative, HER2-positive invasive disease with negative sentinel nodes. Regulatory and reimbursement issues aside, what adjuvant systemic therapy would you recommend?

a. None
b. Paclitaxel/trastuzumab
c. Paclitaxel/trastuzumab/pertuzumab
d. ACTH
e. ACTHP
f. TCH
g. TCHP
h. T-DM1
i. Other

Case Presentation – Dr Carey: 46-Year-Old Woman with ER-negative/HER2-Positive, Node-Negative IDC

- 46 yo woman with extensive DCIS + breast mass
- Right mastectomy/SN: 6mm ER-, PR-, HER2 3+ IDC, SN negative
- Randomized to T-DM1 arm of ATEMPT
  - Grade 1 peripheral neuropathy, fatigue, rash, and nausea likely from T-DM1
  - Ran Boston Marathon while on T-DM1
- NED @ 5+y, no residual toxicities, still a runner!

*ET recommended if HR+

Case Presentation – Dr Carey: 33-Year-Old Woman with ER-negative/HER2-Positive, Node-Positive IDC

- 33 yo woman with right nipple changes and mass, clinical 8mm, 3 abnormal LN. Biopsy + grade 3 IDC, ER-, PR-, HER2 3+
- TCHP x 6 cycles
  - clinical CR
  - Nausea / vomiting despite Rx, grade 1 PN
- Partial mastectomy w/ AND + ypT0N1 (1/26 LN with RD), RT
- Adjuvant T-DM1 tolerated well – grade 1 nausea only first few days post infusion.
- NED <2y from dx.

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  - NALA: Neratinib/capecitabine
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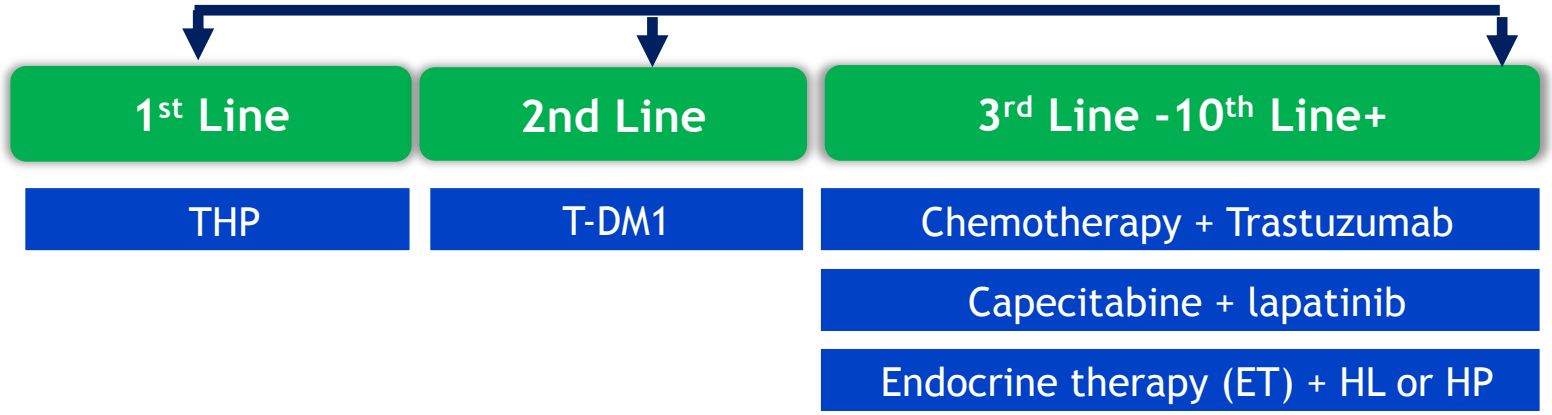
Treatment Paradigm for Metastatic HER2+ Breast Cancer (Circa 2019)

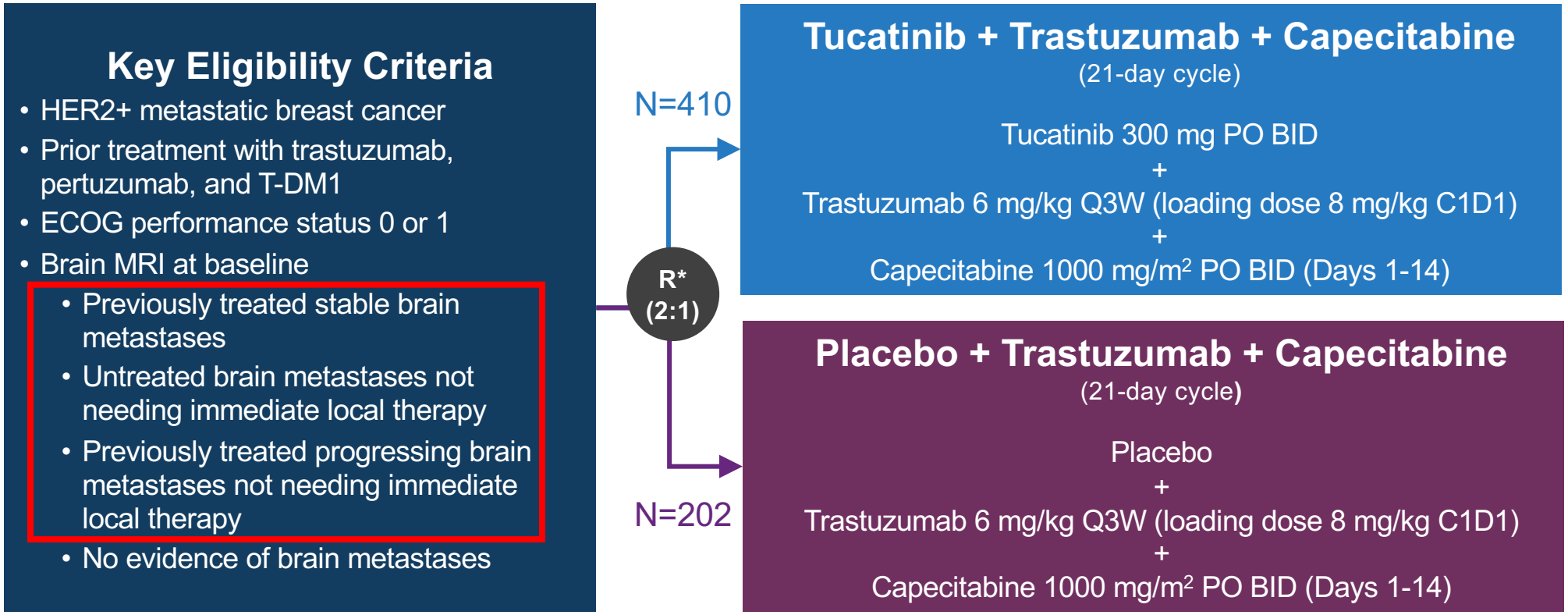


- Efficacy of chemotherapy + trastuzumab is limited in ≥3rd line
  - PFS ≈ 5 months
  - ORR ≈ 20%

*e.g. control arms of SOPHIA and HER2CLIMB trials

Slide adapted from S Tolaney ASCO 2018. Courtesy of Ian E Krop, MD, PhD

HER2CLIMB Trial Design



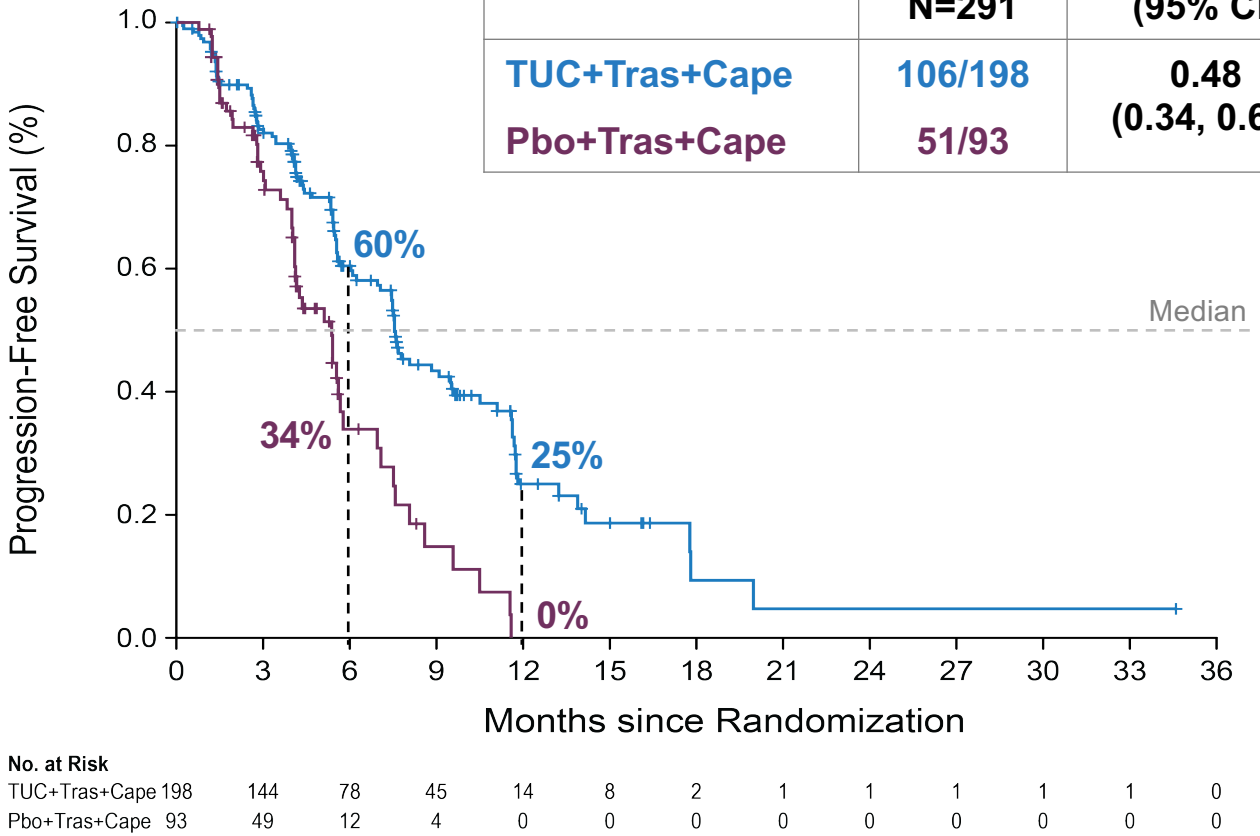
*Stratification factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region (US or Canada or rest of world)

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

Murthy RK et al. SABCS 2019;Abstract GS1-01. Courtesy of Ian E Krop, MD, PhD

Progression-Free Survival for Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	106/198	0.48 (0.34, 0.69)	<0.00001
Pbo+Tras+Cape	51/93		



Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

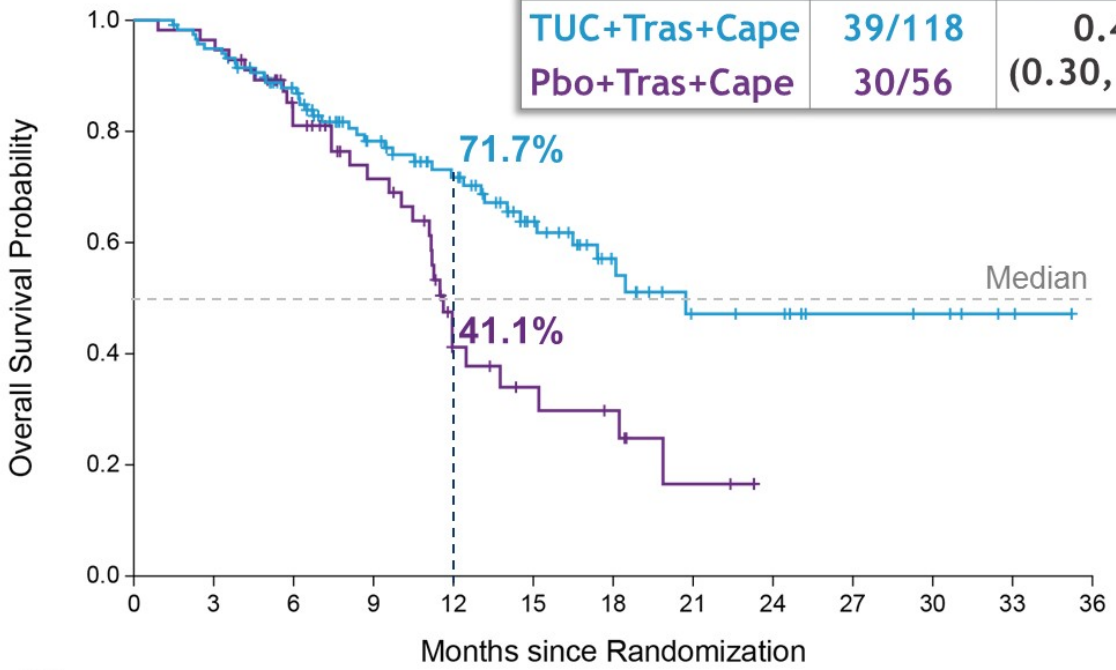
One-year PFS (95% CI):	
TUC+Tras+Cape 25% (17, 34)	Pbo+Tras+Cape 0%
Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

Prespecified efficacy boundary for $PFS_{BrainMets}$ (P=0.0080) was met at the first interim analysis.
Data cut off: Sep 4, 2019

Murthy RK et al. SABCS 2019;Abstract GS1-01. Courtesy of Ian E Krop, MD, PhD

OS Benefit in Patients with Active Brain Metastases

	Events N=174	HR (95% CI)	P Value
TUC+Tras+Cape	39/118	0.49 (0.30, 0.80)	0.004
Pbo+Tras+Cape	30/56		



No. at Risk

TUC+Tras+Cape	118	111	89	66	51	33	19	11	10	6	5	2	0
Pbo+Tras+Cape	56	54	39	29	12	8	6	2	0	0	0	0	0

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

One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
71.7% (61.4, 79.7)	41.1% (25.5, 56.1)
Median OS (95% CI):	
20.7 months (15.1, NE)	11.6 months (10.5, 13.8)

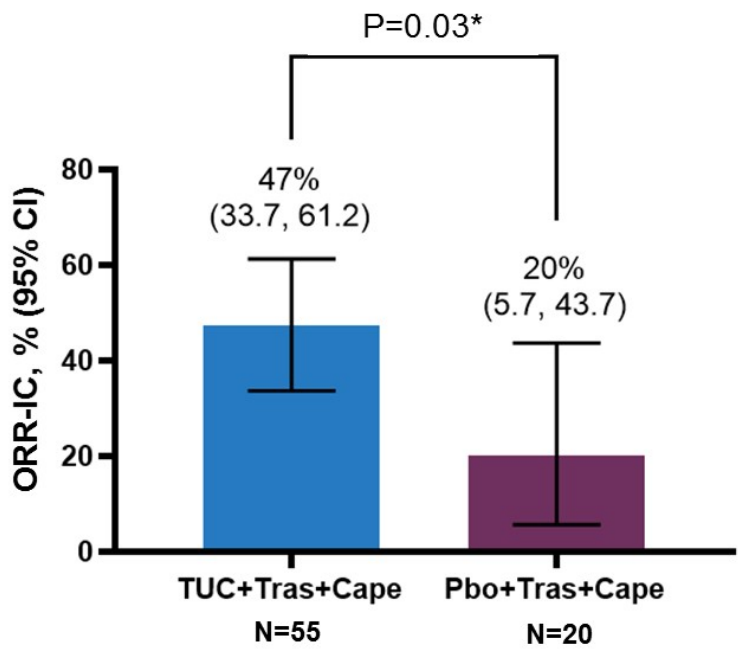
NE: not estimable

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. Courtesy of Ian E Krop, MD, PhD

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

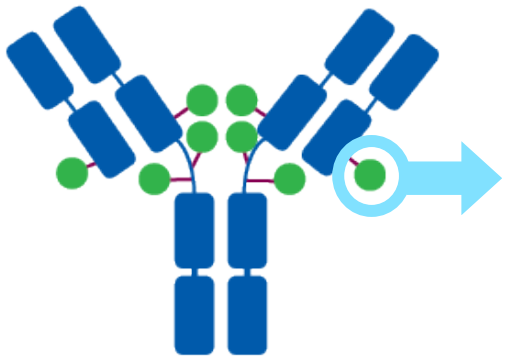
Presented by Nancy Lin. Courtesy of Ian E Krop, MD, PhD

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

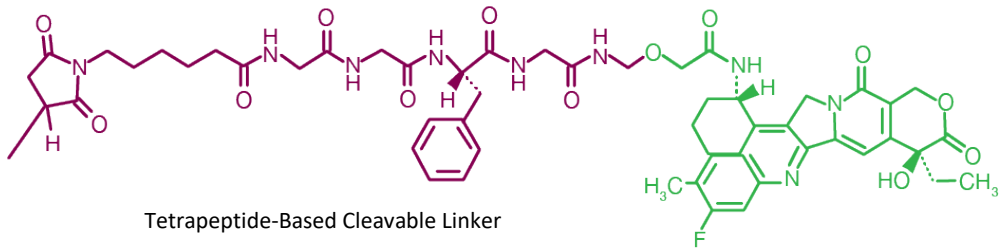
Trastuzumab deruxtecan is an ADC composed of 3 components:

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

Humanized anti-HER2 IgG1 mAb[1-3]



Deruxtecan[1,2]



Tetrapeptide-Based Cleavable Linker

Topoisomerase I Inhibitor payload (DXd)

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

The clinical relevance of these features is under investigation.

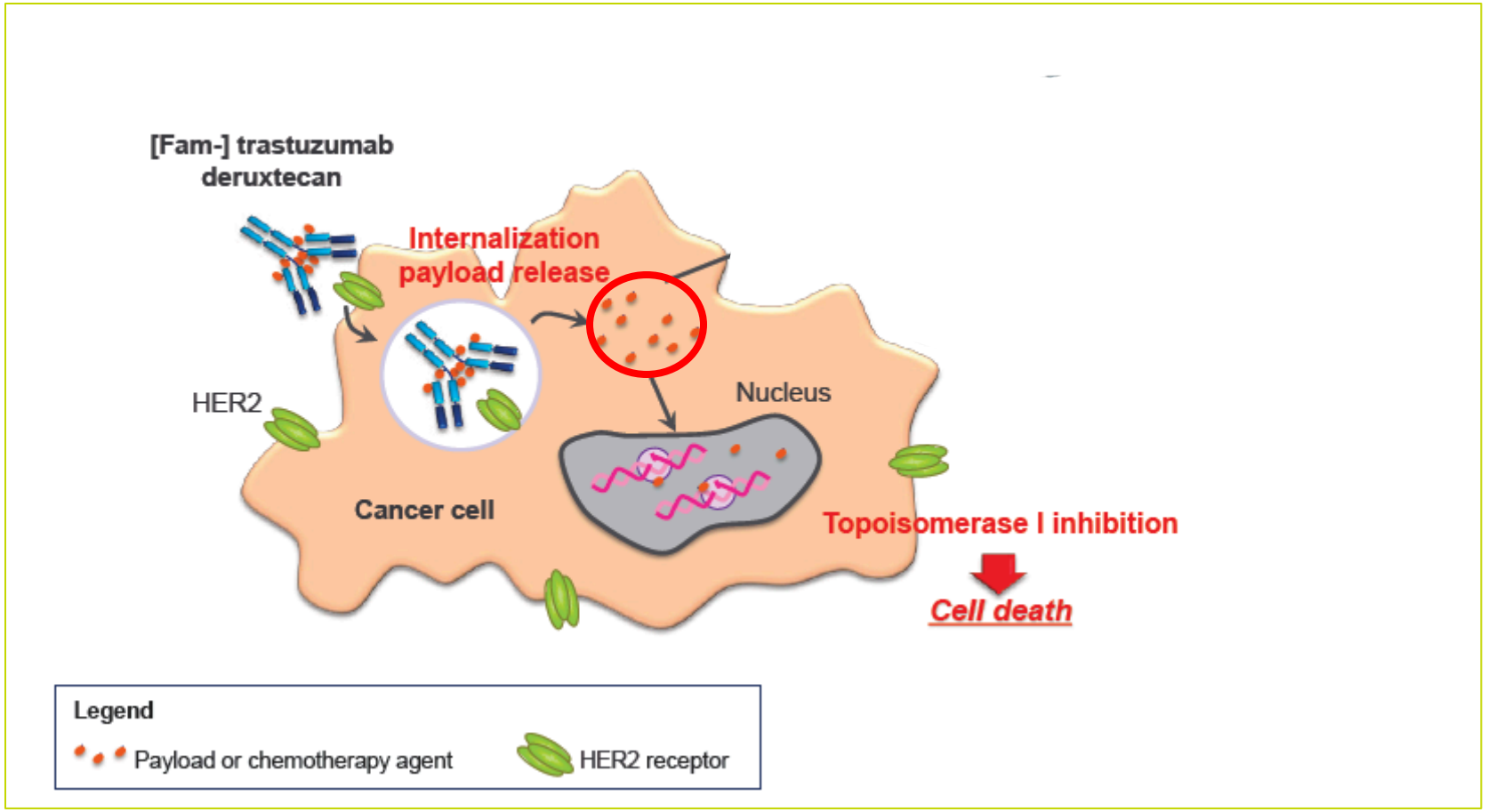
ADC, antibody-drug conjugate; MOA, mechanism of action.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.

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

Courtesy of Ian E Krop, MD, PhD

DS-8201's membrane-permeable payload can attack neighbouring cancer cells (i.e. a bystander effect)



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

1. Ogitani Y et al. *Cancer Sci*. 2016;107:1039–1046 . 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097–5108. Courtesy of Ian E Krop, MD, PhD

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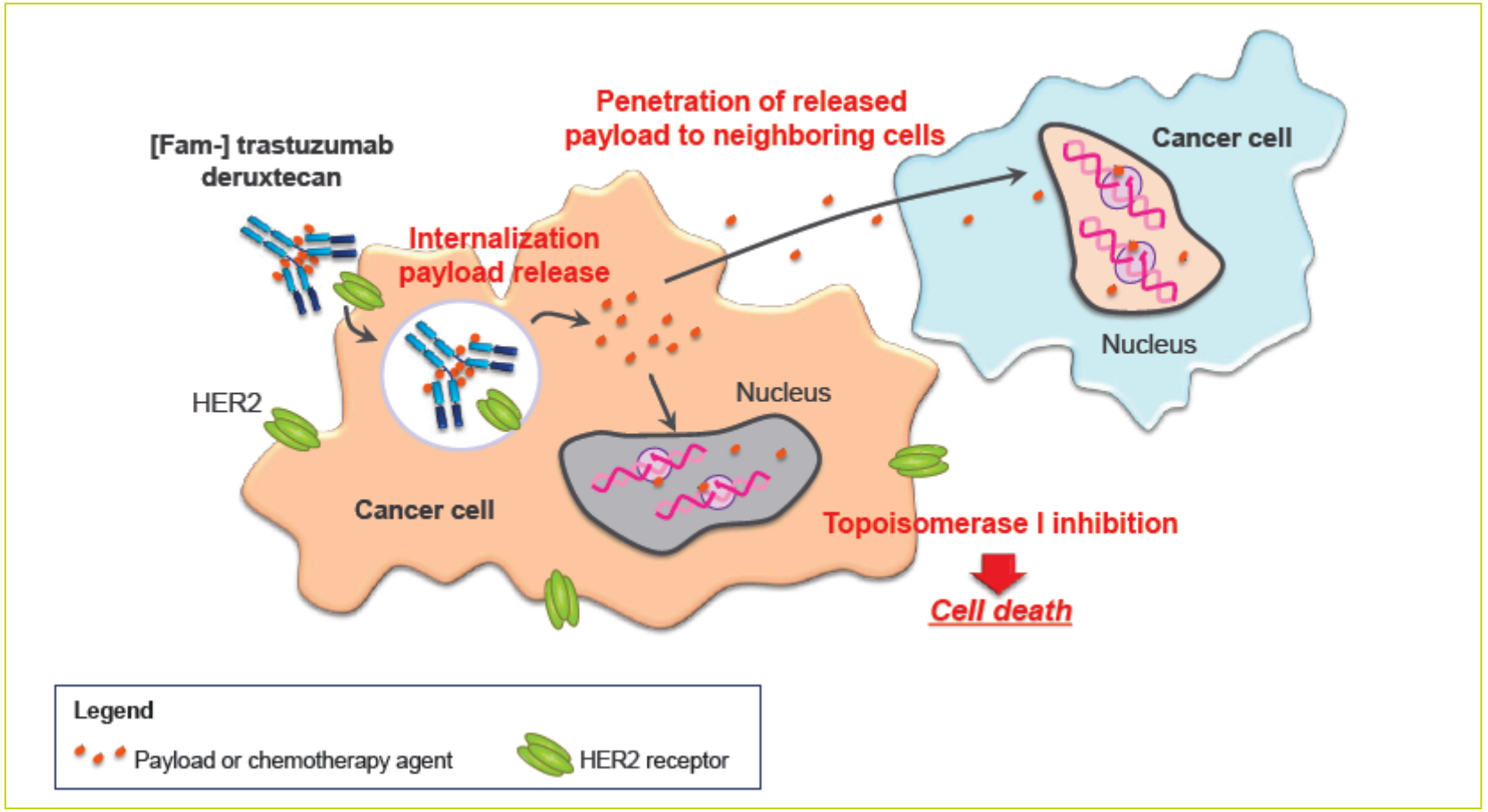

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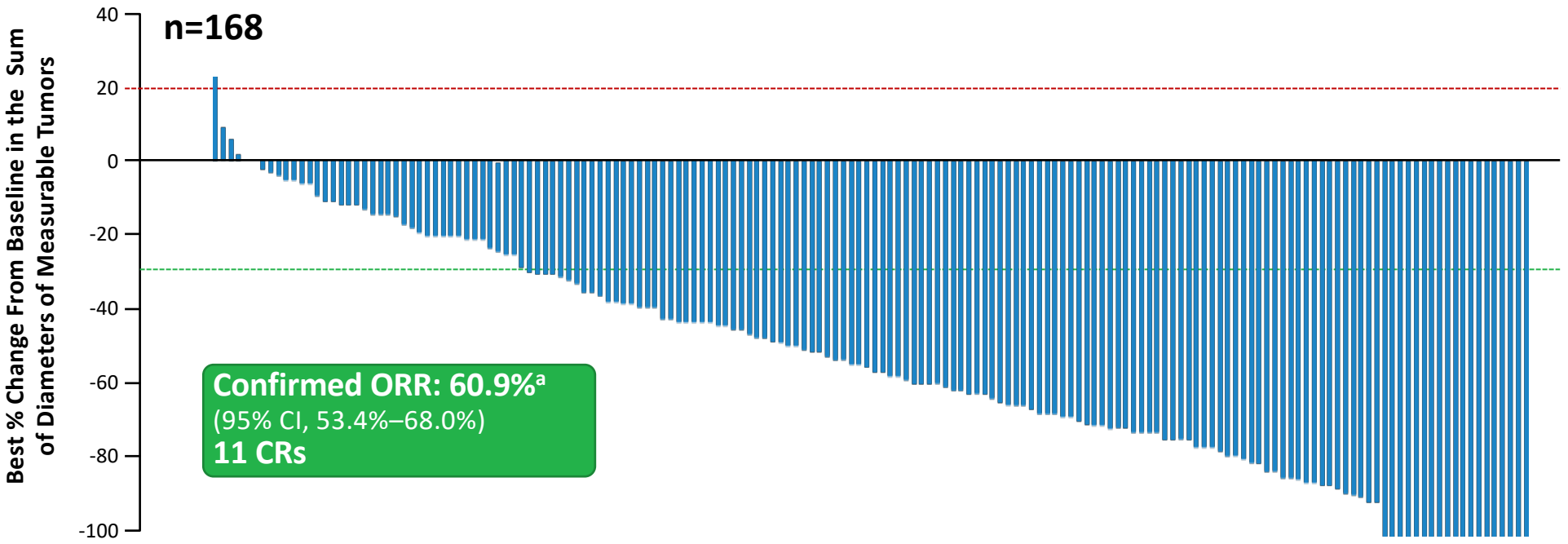
1. Ogitani Y et al. *Cancer Sci*. 2016;107:1039–1046 . 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097–5108. Courtesy of Ian E Krop, MD, PhD

DESTINY-Breast01: Best Change in Tumor Size



By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a] Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

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

Courtesy of Ian E Krop, MD, PhD

DESTINY-Breast01: Adverse Events of Special Interest: Interstitial Lung Disease

	Patients who received T-DXd 5.4 mg/kg (N=184)					
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)**

Drug related; ILD was determined by the Independent ILD Adjudication Committee based on 44 preferred terms.

Among the 25 total events:

- Median time to investigator-reported onset was 193 days (range, 42-535 days)
- 17 of 20 patients with grade ≥2 ILD received corticosteroids
- 7 patients recovered, 2 were recovering, 12 were either outcome unknown or not followed until resolution, and 4 died
- Of the 4 fatal cases, onset was from 63-148 days, 3 received steroids as part of treatment, and death occurred 9-60 days after diagnosis

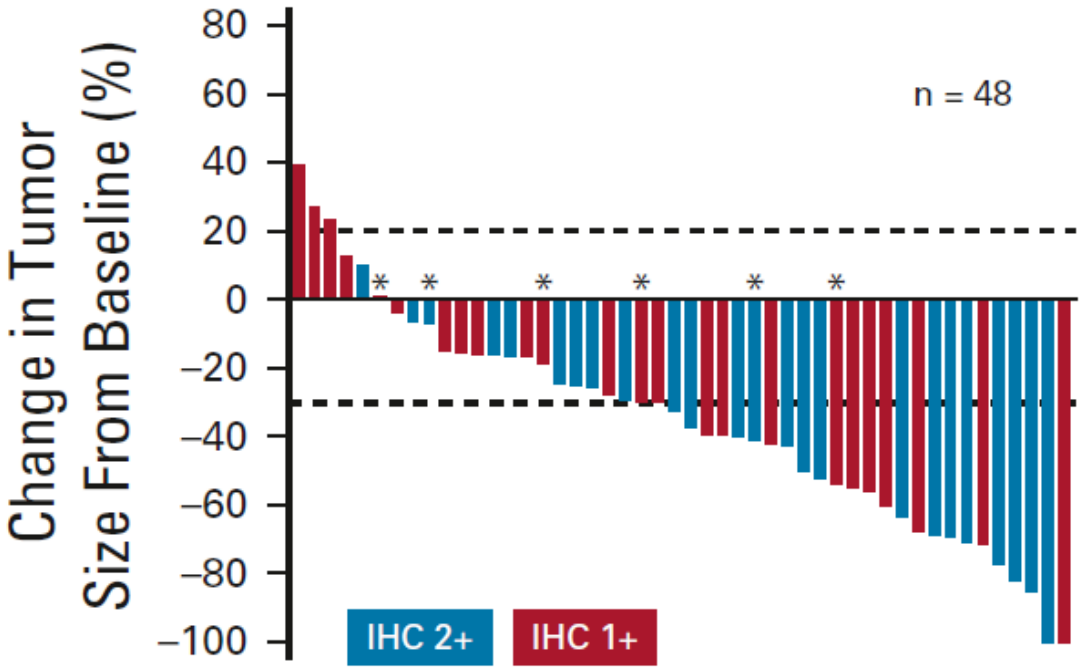
Recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

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

ILD, interstitial lung disease.

Courtesy of Ian E Krop, MD, PhD

Effect of trastuzumab deruxtecan in heavily pretreated* HER2-low metastatic breast cancer



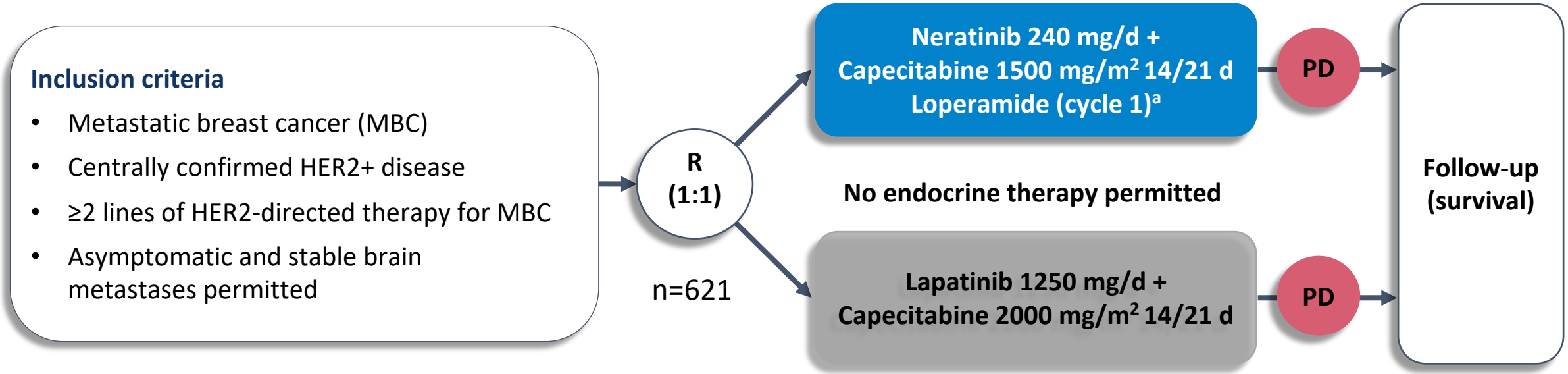
Clinical activity (by independent review)

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

*median of 7.5 prior regimens

Modi et al, JCO 2020 38:1888. Courtesy of Ian E Krop, MD, PhD

NALA study design



Stratification variables

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

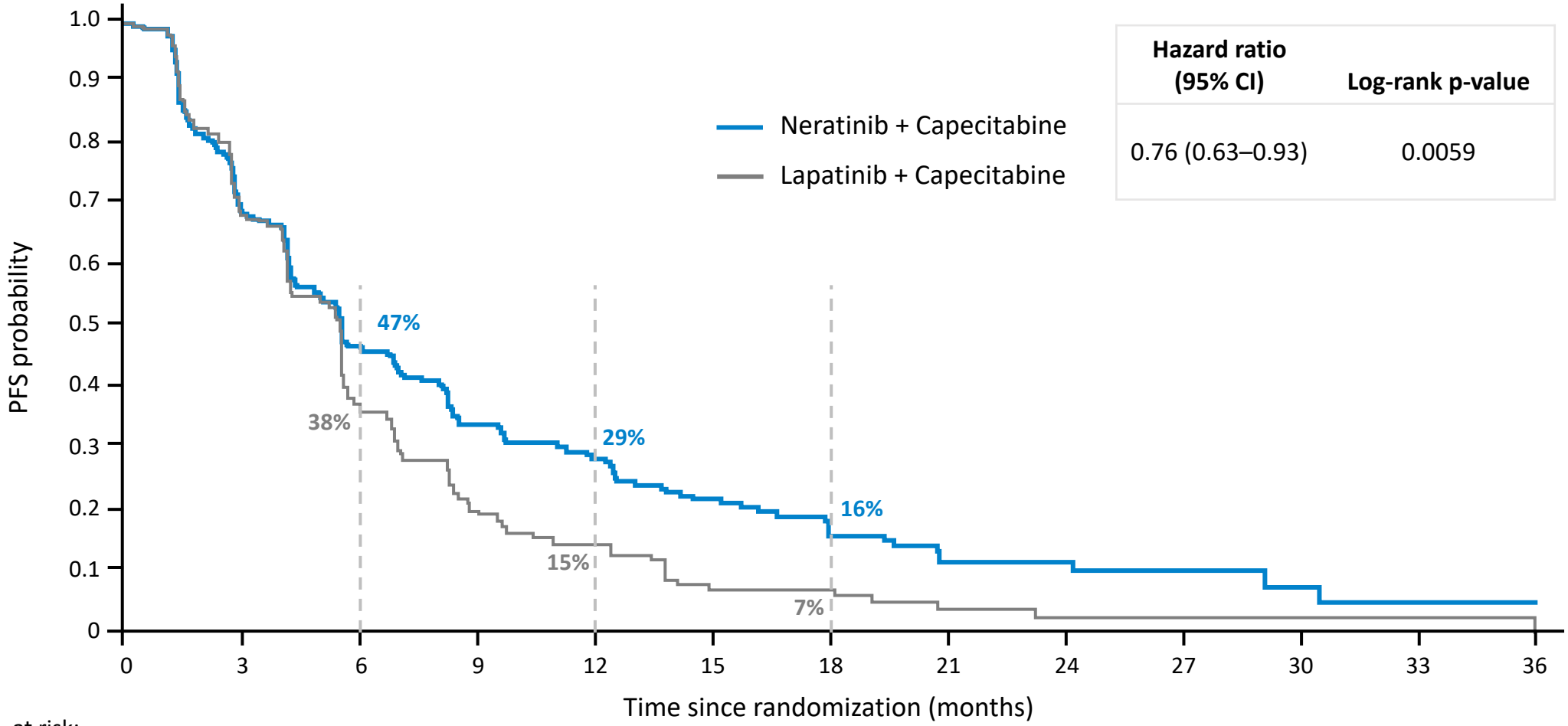
Endpoints

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

Saura C et al. ASCO 2019;Abstract 1002. Courtesy of Ian E Krop, MD, PhD

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

Centrally confirmed PFS (co-primary endpoint)



Hazard ratio (95% CI)	Log-rank p-value
0.76 (0.63–0.93)	0.0059

No. at risk:

N+C	307	183	113	69	54	35	20	13	9	7	3	2	2
L+C	314	183	82	39	24	9	8	3	2	2	2	2	1

Saura C et al. ASCO 2019;Abstract 1002. Courtesy of Ian E Krop, MD, PhD

Neratinib and Capecitabine for CNS disease (TBCRC 022)

- Phase 2 trial of patients with progressive HER2+ brain metastases (N=49)
- Patients received neratinib (240 mg po QD) and capecitabine (750 mg/m^2 BID 14d on/7d off)
- Efficacy in cohort without previous lapatinib (N=37):
  - 49% CNS objective response rate*
  - 5.5 mo median PFS

*≥50% reduction in sum of target CNS lesion volumes without progression of nontarget lesions, new lesions, escalating steroids, progressive neurologic signs or symptoms, or non-CNS progression

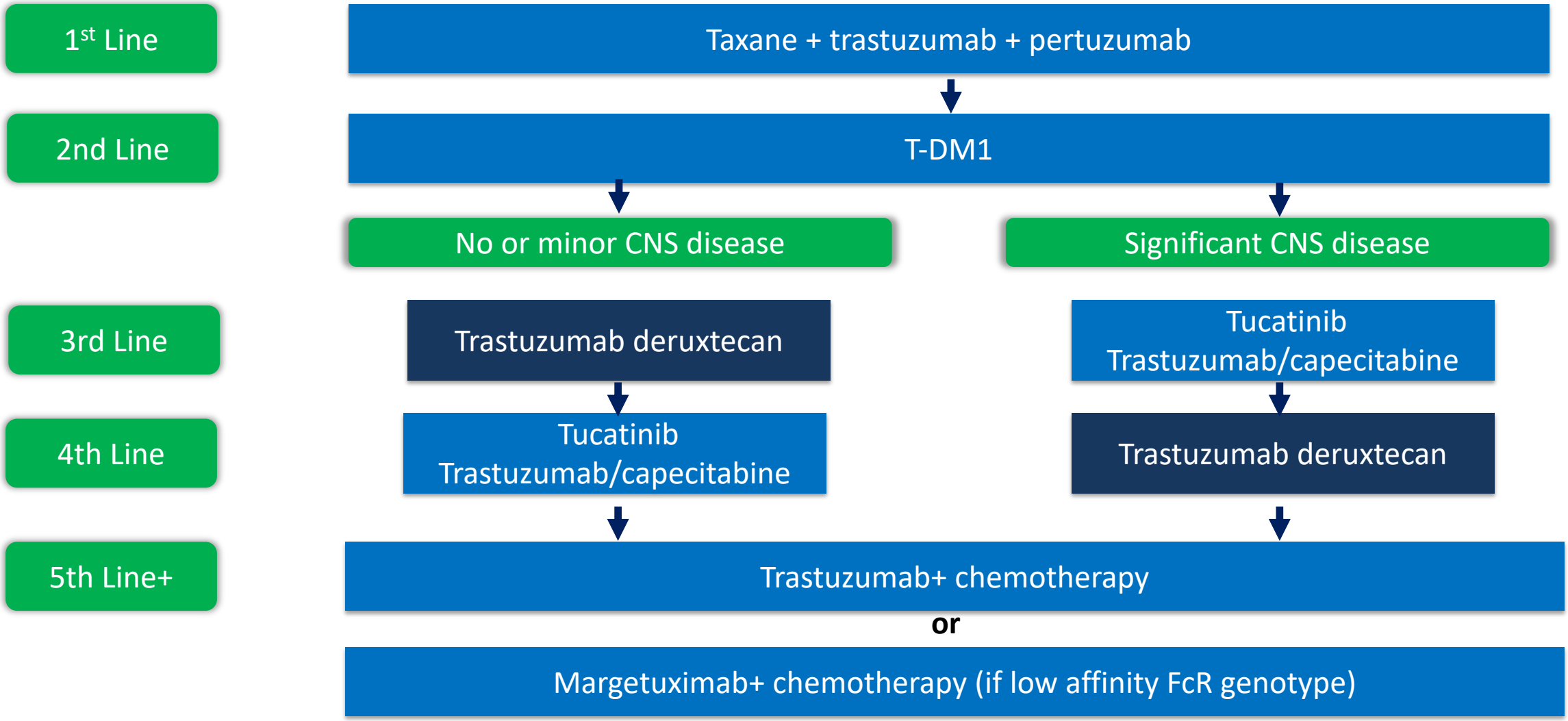
Freedman R et al. JCO 2019 37:1081. Courtesy of Ian E Krop, MD, PhD

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

	Trastuzumab Deruxtecan	Tucatinib + Tras/Cape	Neratinib + Capecitabine	Margetuximab + Chemo
PROS	Very high ORR	OS and PFS benefit	PFS benefit	Well tolerated
	Durable benefit Long PFS	Activity in both treated and progressive brain mets	Delays time to CNS Rx	Benefit may be larger in pts with low affinity FcR (FF/FV)
	Activity maintained in pts with treated brain mets	Manageable toxicity profile		Can be combined with multiple chemotherapy partners
CONS	ILD is serious potential risk	Absolute PFS benefit modest	Serious diarrhea is common	Benefit modest
	No data on efficacy in progressive brain mets		Benefit modest	

Courtesy of Ian E Krop, MD, PhD

Approach to Therapy for Metastatic HER2+ disease: Move to Personalization



Courtesy of Ian E Krop, MD, PhD

Agenda

Module 2: HER2-Positive Metastatic Breast Cancer (mBC) — Dr Krop

- **Key Recent Data Sets**
  - HER2CLIMB: Tucatinib/trastuzumab/capecitabine
  - DESTINY-Breast01: Trastuzumab deruxtecan
  - NALA: Neratinib/capecitabine
- **Cases/Questions from General Medical Oncologists**
  - 38-year-old woman with HER2+ mBC; progression on THP including new brain mets
  - 75-year-old woman with HER2+ mBC; progression on THP → T-DM1 including leptomeningeal mets
- **Faculty Cases**

A 38-year-old woman with ER-negative, HER2-positive metastatic breast cancer receives THP but after 1 year experiences disease progression, including multiple brain metastases. Regulatory and reimbursement issues aside, what systemic treatment would you recommend next?

a. Trastuzumab + chemotherapy
b. Trastuzumab + lapatinib
c. T-DM1
d. Neratinib
e. Neratinib + capecitabine
f. Neratinib + paclitaxel
g. Lapatinib + capecitabine
h. Tucatinib + trastuzumab/capecitabine
i. Trastuzumab deruxtecan
j. Other

Justin P Favaro, MD, PhD

A 38-year-old woman with ER-negative, HER2-positive metastatic breast cancer receives THP but after 1 year experiences disease progression, including multiple brain metastases. Regulatory and reimbursement issues aside, what systemic treatment would you recommend next?

 LISA A CAREY, MD	T-DM1
 VIRGINIA KAKLAMANI, MD, DSC	Tucatinib + trastuzumab/capecitabine
 IAN E KROP, MD, PHD	T-DM1
 JOYCE O'SHAUGHNESSY, MD	Tucatinib + trastuzumab/capecitabine
 HOPE S RUGO, MD	T-DM1
 SARA M TOLANEY, MD, MPH	Tucatinib + trastuzumab/capecitabine

A woman in her 70s 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?

 LISA A CAREY, MD	Tucatinib + trastuzumab/capecitabine
 VIRGINIA KAKLAMANI, MD, DSC	Trastuzumab deruxtecan
 IAN E KROP, MD, PHD	Depends on disease burden, symptomatic vs asymptomatic progression
 JOYCE O'SHAUGHNESSY, MD	Tucatinib + trastuzumab/capecitabine
 HOPE S RUGO, MD	Trastuzumab deruxtecan
 SARA M TOLANEY, MD, MPH	Trastuzumab deruxtecan

A 75-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, including significant leptomeningeal metastases. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

a. Trastuzumab + chemotherapy
b. Trastuzumab + lapatinib
c. Neratinib
d. Neratinib + capecitabine
e. Neratinib + paclitaxel
f. Lapatinib + capecitabine
g. Tucatinib + trastuzumab/capecitabine
h. Trastuzumab deruxtecan
i. Other

Yanjun Ma, MD, PhD

A woman in her 70s with ER-negative, HER2-positive metastatic breast cancer receives THP followed by T-DM1 on progression. She now presents with further disease progression, including significant leptomeningeal metastases. Regulatory and reimbursement issues aside, what systemic treatment would you recommend?

 LISA A CAREY, MD	Tucatinib + trastuzumab/capecitabine
 VIRGINIA KAKLAMANI, MD, DSC	Tucatinib + trastuzumab/capecitabine
 IAN E KROP, MD, PHD	Tucatinib + trastuzumab/capecitabine
 JOYCE O'SHAUGHNESSY, MD	Tucatinib + trastuzumab/capecitabine
 HOPE S RUGO, MD	Tucatinib + trastuzumab/capecitabine
 SARA M TOLANEY, MD, MPH	Tucatinib + trastuzumab/capecitabine

A woman with ER-negative, HER2-positive metastatic breast cancer receives THP followed by T-DM1 on progression. She presents with further disease progression, including new brain metastases, and is started on tucatinib/trastuzumab/capecitabine with sustained response followed by limited disease progression in the brain only. Regulatory and reimbursement issues aside, in addition to local therapy, what systemic treatment would you recommend?

 LISA A CAREY, MD	Continue tucatinib + trastuzumab/capecitabine
 VIRGINIA KAKLAMANI, MD, DSC	Trastuzumab deruxtecan
 IAN E KROP, MD, PHD	Continue tucatinib + trastuzumab/capecitabine
 JOYCE O'SHAUGHNESSY, MD	Continue tucatinib + trastuzumab/capecitabine
 HOPE S RUGO, MD	Trastuzumab deruxtecan
 SARA M TOLANEY, MD, MPH	Continue tucatinib + trastuzumab/capecitabine

Have you or would you administer tucatinib/trastuzumab without capecitabine to a patient with HER2-positive metastatic breast cancer who has been unable to tolerate capecitabine in the past? (Dr Ma)

 LISA A CAREY, MD	I have not but would for the right patient
 VIRGINIA KAKLAMANI, MD, DSC	I have not but would for the right patient
 IAN E KROP, MD, PHD	I have not but would for the right patient
 JOYCE O'SHAUGHNESSY, MD	I have not but would for the right patient
 HOPE S RUGO, MD	I have not but would for the right patient
 SARA M TOLANEY, MD, MPH	Only on clinical trial and for a rare patient

Have you or would you administer trastuzumab deruxtecan to a patient with HER2-low metastatic breast cancer outside of a clinical trial setting?

 LISA A CAREY, MD	I have not but would for the right patient
 VIRGINIA KAKLAMANI, MD, DSC	I have not and would not
 IAN E KROP, MD, PHD	I have not but would for the right patient
 JOYCE O'SHAUGHNESSY, MD	I have
 HOPE S RUGO, MD	I have not and would not
 SARA M TOLANEY, MD, MPH	I have not but would for the right patient

Agenda

Module 2: HER2-Positive Metastatic Breast Cancer (mBC) — Dr Krop

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  - 75-year-old woman with HER2+ mBC; progression on THP → T-DM1 including leptomeningeal mets
- **Faculty Cases**
  - 40-year-old woman with HER2+ mBC; progression on THP → T-DM1 including new brain mets
  - 54-year-old woman with HER2+ mBC (liver, adrenal); progression on trastuzumab/pertuzumab-based chemotherapy → T-DM1

A 40-year-old woman with metastatic HER2-positive disease receives THP followed by T-DM1 on progression. She presents with further disease progression including multiple new brain metastases. What systemic treatment would you recommend next?

a. Trastuzumab + chemotherapy
b. Trastuzumab + lapatinib
c. Neratinib
d. Neratinib + capecitabine
e. Neratinib + paclitaxel
f. Lapatinib + capecitabine
g. Tucatinib + trastuzumab/capecitabine
h. Trastuzumab deruxtecan
i. Other

Case Presentation – Dr Krop: 40-year-old woman with ER-positive, HER2-positive mBC

- 40 yo elementary school teacher initially presented in 2011 with mammographically detected mass in L breast
  - Core bx: IDC, grade 3, ER+ PR- HER2 3+
- Mastectomy: 2.1 cm poorly differentiated IDC.
  - SLNB: 1 positive LN
- Adjuvant TCH, started on tamoxifen/OS

Case Presentation – Dr Krop: 40-year-old woman with ER-positive, HER2-positive mBC (cont)

- 2015: left hip and mid back pain
  - Scans show multiple bone lesions, 2 cm liver lesion and sub-centimeter pulmonary nodules
  - Liver bx: ER+PR-HER2 3+ adenoCA c/w breast primary

- Started on paclitaxel/trastuzumab/pertuzumab
  - Had near complete response after 4 cycles
  - Asymptomatic
  - Continued two more cycles of THP, then stopped paclitaxel can continued HP alone

Case Presentation – Dr Krop: 40-year-old woman with ER-positive, HER2-positive mBC (cont)

- 3/2017 Progression in liver, remained asymptomatic
  - Reintroduced paclitaxel with HP
- 5/2017: further liver progression
  - Started T-DM1
- 9/2017: complete response in liver, bone lesions stable, pulmonary nodules no longer visible
  - Tolerating T-DM1 well

Case Presentation – Dr Krop: 40-year-old woman with ER-positive, HER2-positive mBC (cont)

- 8/18: Persistent R-sided headache
  - MRI: innumerable brain lesions, largest 0.7
  - Restaging CT: stable bone lesions, no other disease
  - Whole brain RT
  - Continue T-DM1
- 6/19: Headache returned
  - MRI: progression in 4 lesions, largest 1.4 cm

Case Presentation – Dr Krop: 40-year-old woman with ER-positive, HER2-positive mBC (cont)

- 7/19: Started on HER2CLIMB study
  - Headaches improved

- 9/19
  - MRI:PR in brain
  - CT: extracranial disease stable

- 6/20: continues on capecitabine/trastuzumab/tucatinib

Case Presentation – Dr Krop: 54-year-old woman with ER-negative, HER2-positive mBC

- 2017: 54 year old town clerk of a small town in NE. She presented with palpable R breast mass
  - Bx: ER-PR-HER2 3+ poorly differentiated ductal cancer
  - Neoadjuvant ACTHP
  - Lumpectomy/SLND: 2cm residual cancer, 1/3 nodes positive
  - Adjuvant radiation
  - Continued 1 year of HP
- 3/2019: RUQ abdominal pain
  - Scans show multiple liver lesions, largest 3.4cm
  - Liver bx demonstrates metastatic carcinoma, ER-PR-HER2 2+ FISH ratio 3.2
  - Started on vinorelbine/HP
  - Abdominal pain improved

Case Presentation – Dr Krop: 54-year-old woman with ER-negative, HER2-positive mBC (cont)

- 7 /2019: disease progression in liver
  - Started T-DM1

- 10/19: abdominal pain worsened, CT: modest progression in liver
  - Started eribulin/trastuzumab
  - Abdominal pain improved

Case Presentation – Dr Krop: 54-year-old woman with ER-negative, HER2-positive mBC (cont)

- 1/20: abdominal pain recurs
  - Scans: progression in liver, new adrenal lesion, grade 2 transaminase elevation
- 2/20: Started trastuzumab deruxtecan
  - Abdominal pain resolves, LFTs normalize
  - Initially had nausea, but resolved with ondansetron
  - Back to work
- 5/20: scans: no clearly defined liver lesions, adrenal lesion resolved

The Current and Future Role of Immune Checkpoint Inhibitors and Other Novel Therapies in Urothelial Bladder Cancer

Thursday, July 9, 2020

5:00 PM – 6:00 PM ET

Faculty

Arjun Balar, MD

Siamak Daneshmand, MD

Ashish M Kamat, MD, MBBS

Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME credit information will be emailed to each participant tomorrow morning.