

Personalizing Treatment Decisions in HER2-Altered Breast Cancer

*Strategies for Improving Equity
and Patient Outcomes Through
Individualized Targeted Therapy
Selection, Team-Based Care,
and Shared Decision-Making*

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Expert Faculty Panel:

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- Welcome to in-person and virtual attendees
- Thank you to:
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 - AstraZeneca, Daiichi Sankyo, Inc., Puma Biotechnology, Inc, and Seagen Inc. for providing the educational grants for this symposium
- Please take part in the audience polls that will be posed to you throughout the symposium
- You can submit your questions to the faculty both online and in the room via iPads, and we will address them during the Q&A session
- On the following slides are all the relevant disclosures

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Executive Director of METAvivor

Jamil Rivers

Patient Advocate, Founder, and CEO at The Chrysalis Initiative

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Agenda

- **Candid Conversations and Clinical Consults in HER2-Altered Breast Cancer**

During today's educational session, we will:

- Review Gaps, Disparities, Advances, and Opportunities for Improvement
 - Analyze the Evolving Evidence Base Underlying the Latest Advances in Treatment of HER2+ Breast Cancer
 - Share Case-Based Guidance for Navigating the Nuances of Personalized HER2-Targeted Treatment Selection/Sequencing in MBC and Providing Patient-Centered, Equitable Care
- **Key Take-Aways and Audience–Faculty Q&A**

Acknowledging Gaps, Disparities, Advances, and Opportunities for Improvement in HER2+ Breast Cancer



Later-line treatment of HER2+ metastatic breast cancer was largely not evidence based for many years, but new agents have emerged that have changed the standards of care



Many new therapeutic options and the quickly evolving evidence base make it difficult to stay current and know how to select and sequence the latest HER2-targeted therapies



Despite the remarkable progress made with advancing HER2-targeted therapies, the optimal role/use of these agents is not yet clear, and areas of unmet need remain that must be addressed, including treatment of HER2-low expressing and *HER2*-mutated breast cancer, overcoming de novo and acquired resistance, CNS and leptomeningeal metastases, etc



Disparities exist and persist in breast cancer clinical care and research; for example, racial and ethnic minorities are more likely to experience delays in therapy, less likely to obtain adequate treatment, and are also significantly underrepresented in clinical trials¹⁻⁵

We have partnered with **The Chrysalis Initiative**, **METAvivor**, and **GRASP** to integrate patient and advocate perspectives into this program and shine a light on disparities in breast cancer clinical care and research.

*Let's hear from **Jamil Rivers**, Founder and CEO of The Chrysalis Initiative, and representative of all 3 partner organizations*



METAVIVOR
Metastatic Breast Cancer Research, Support and Awareness



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NCCN v1.2022 Recommendations: Preoperative/Adjuvant Therapy for HER2+ Disease¹

Preferred Regimens

- Paclitaxel + trastuzumab
- TCH (docetaxel/carboplatin/trastuzumab)
- TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)
- If no residual disease after preoperative therapy or no preoperative therapy: complete up to 1 year of HER2-targeted therapy with trastuzumab (category 1) ± pertuzumab
- If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone; if ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete 1 year of therapy

Useful in Certain Circumstances

- Docetaxel + cyclophosphamide + trastuzumab
- AC followed by T + trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel + trastuzumab; various schedules)
- AC followed by T+ trastuzumab + pertuzumab (doxorubicin/cyclophosphamide followed by paclitaxel + trastuzumab + pertuzumab; various schedules)
- Neratinib (adjuvant setting only)
- Paclitaxel + trastuzumab + pertuzumab
- Ado-trastuzumab emtansine (adjuvant setting only)

Other Recommended Regimens

- AC followed by docetaxel + trastuzumab (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)
- AC followed by docetaxel + trastuzumab + pertuzumab (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

1. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

NCCN v1.2022 Recommendations: Advanced HER2+ Disease¹

Setting	Regimen	Evidence Level
First line	Pertuzumab + trastuzumab + docetaxel (THP)	
	Trastuzumab deruxtecan (T-DXd) (if recurrence <6 mo of neoadjuvant/adjuvant therapy or <12 mo of pertuzumab)	1
Second line	Trastuzumab deruxtecan (preferred)	1
	Trastuzumab emtansine (T-DM1) (other recommended)	2A
	Tucatinib/capecitabine/trastuzumab	
Third line and beyond (optimal sequence unknown)	Tucatinib/capecitabine/trastuzumab (preferred in those with systemic and CNS metastases)	1
	Trastuzumab deruxtecan (T-DXd) (if not used in the second line)	2A
	Trastuzumab emtansine (T-DM1) (no data regarding benefits after T-DXd)	
	Trastuzumab + docetaxel or vinorelbine or paclitaxel (± carboplatin)	2A
	Capecitabine + trastuzumab or lapatinib	2A
	Trastuzumab + lapatinib	2A
	Neratinib + capecitabine	2A
	Margetuximab + chemotherapy	2A

1. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

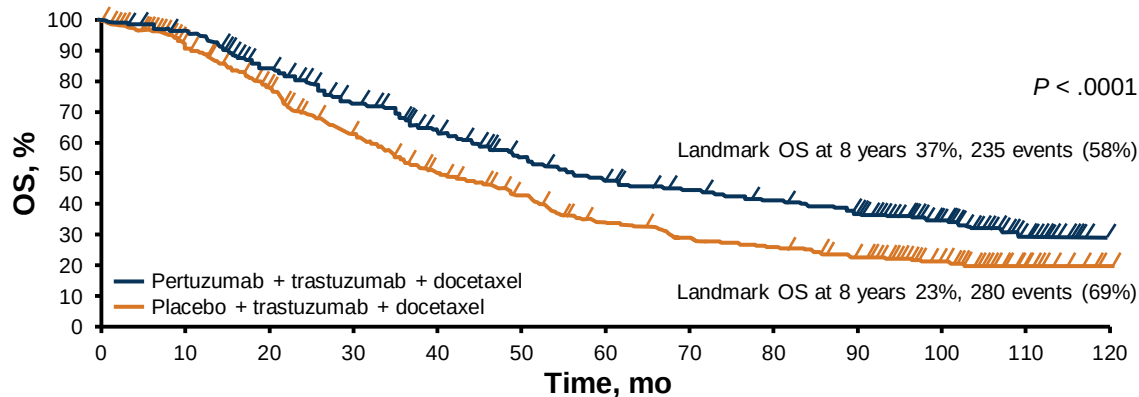


Standard First-Line Therapy

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Overall Survival in Patients With Advanced HER2+ mBC¹

CLEOPATRA End-of-Study Results (Median Follow-Up: ~100 mo)



Median OS
with TP-based initial therapy:
57.1 mo

No. at Risk (number censored)

Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)



Are There Other Alternative First-Line Approaches to De-Escalate Therapy?

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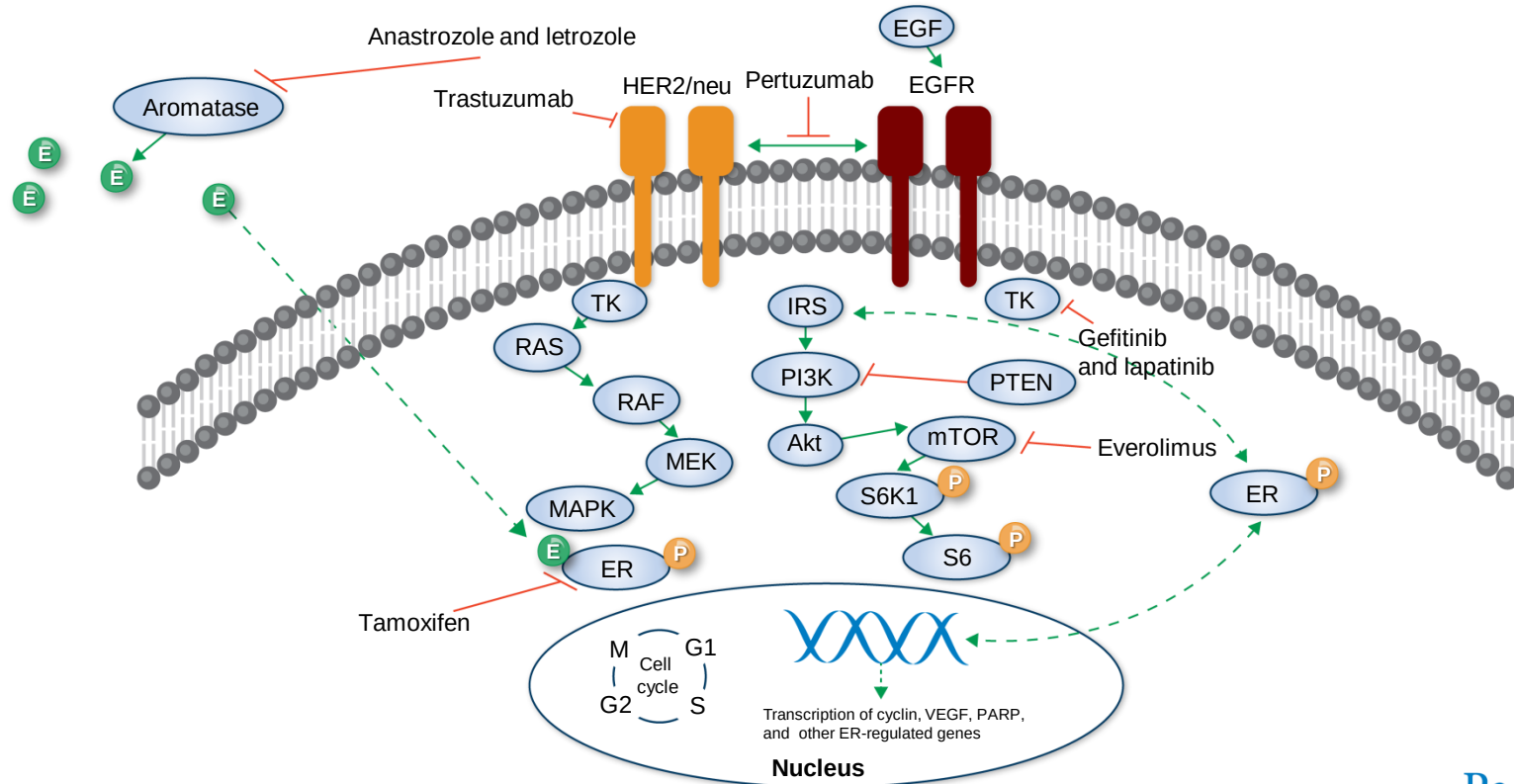
Reshma Mahtani, DO

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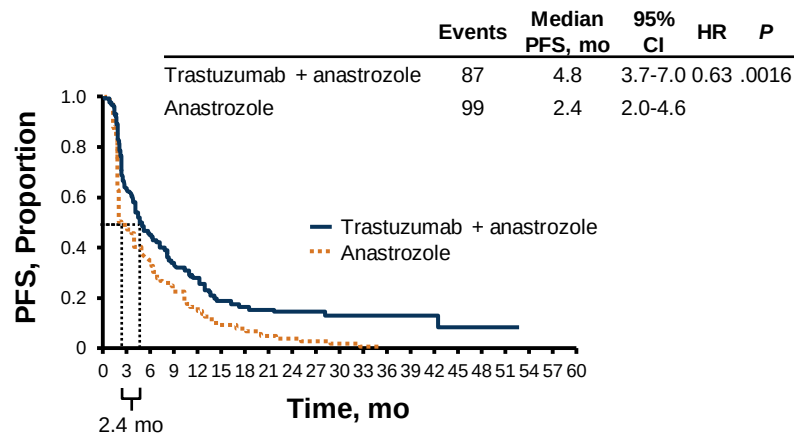
Crosstalk Between ER and HER2¹

Breast Cancer Cell



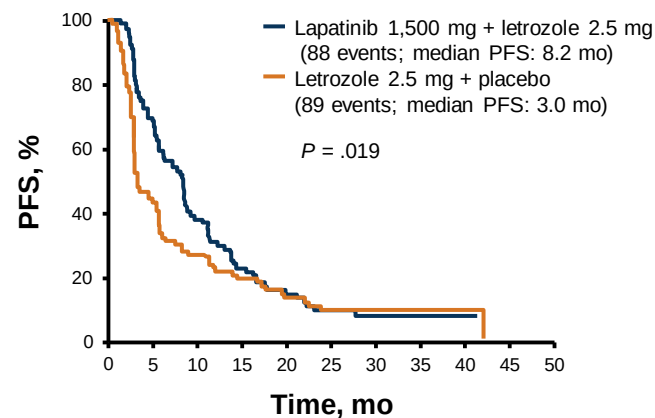
HER2-Targeted Therapy Adds Modestly to Endocrine Therapy^{1,2}

Trastuzumab + Anastrozole vs Anastrozole



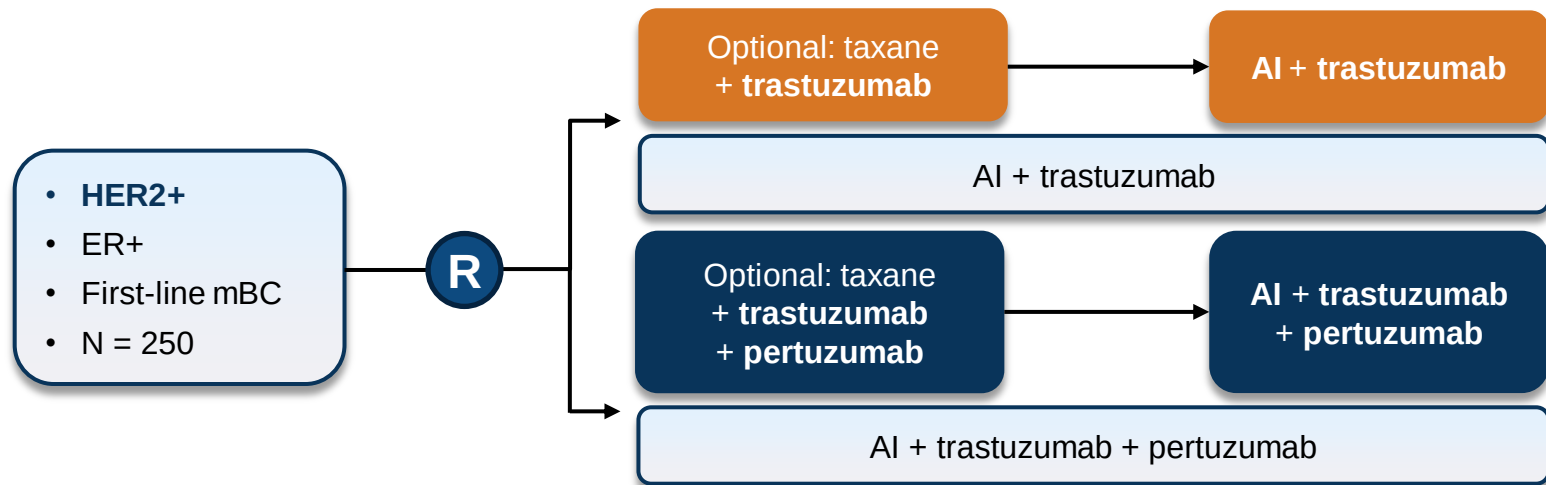
No. at Risk												
Trastuzumab + anastrozole	103	48	31	17	14	13	11	9	4	1	1	0
Anastrozole alone	104	36	22	9	5	4	2	1	0	0	0	0

Lapatinib + Letrozole vs Letrozole



No. at Risk										
Lapatinib + letrozole	111	69	33	20	12	8	4	1	1	
Letrozole alone	108	43	26	18	12	7	5	2	2	

PERTAIN Study Design¹



- **Primary endpoint:** PFS
- **Key secondary endpoints:** OS, ORR, CBR, DOR, time to response, safety, and QoL

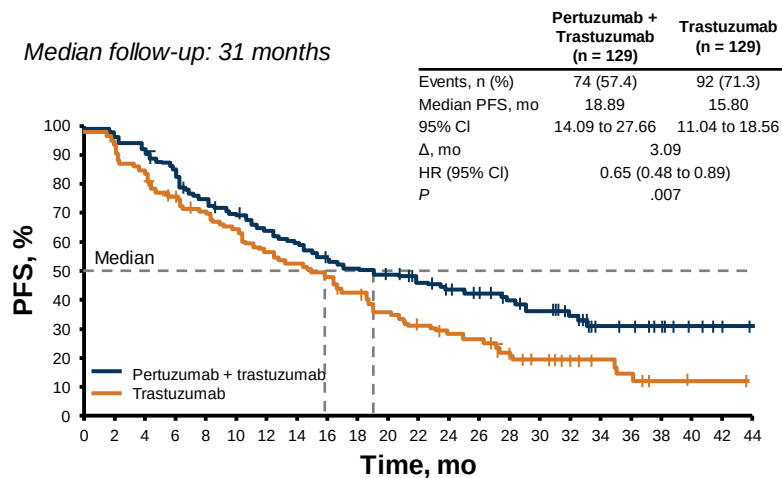
PERTAIN: PFS¹

PERTAIN Met Its Primary PFS Endpoint

Median PFS (ITT Population)
19 mo (trastuzumab and pertuzumab + AI)
vs 16 mo (trastuzumab + AI)

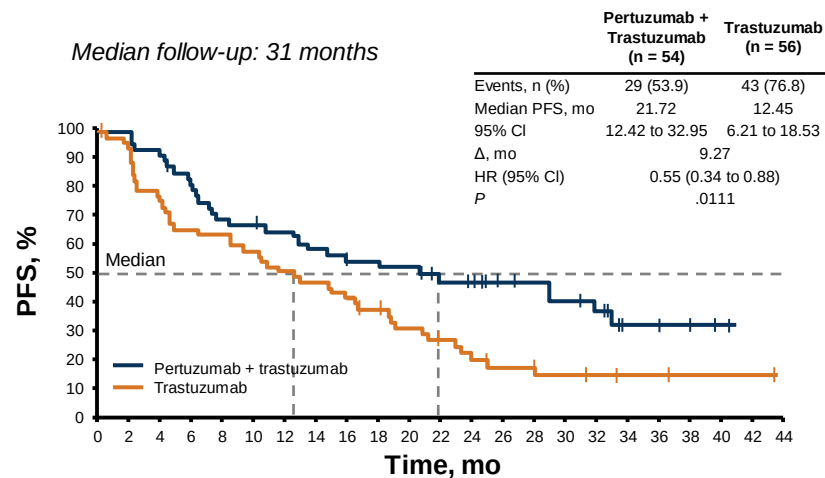
**Patients Who Did Not Receive
Induction Chemotherapy**
Change in Median PFS: +9.3 mo

Median follow-up: 31 months



No. at Risk	Pertuzumab + trastuzumab																									
	129	123	121	116	114	107	102	91	89	84	81	77	74	71	69	65	62	58	55	53	48	46	43	39	37	36
Trastuzumab																										
	129	122	116	108	104	93	90	81	80	75	73	67	64	61	60	56	54	47	47	39	36	33	32	29	26	26

Median follow-up: 31 months



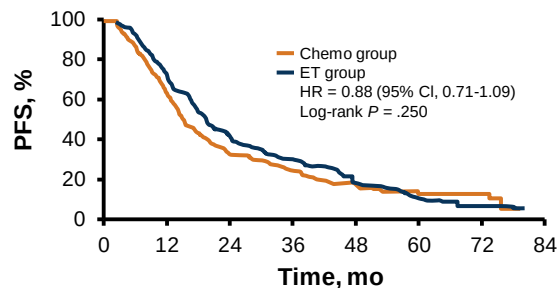
No. at Risk	Pertuzumab + trastuzumab																									
	54	50	50	47	46	42	39	36	34	33	33	31	31	29	28	27	25	25	24	24	24	22	20	19	16	15
Trastuzumab																										
	56	52	49	42	39	35	35	34	34	32	31	28	27	25	25	23	22	19	19	15	15	14	12	11	9	7

PERTAIN: Final Analysis¹

	Pertuzumab + Trastuzumab + AI	Trastuzumab + AI
Median PFS, mo HR (95% CI)		
ITT	21 0.7 (0.5-0.9); $P = .006$	16
With induction	17 0.7 (0.5-1.0); $P = .08$	17
No induction	27 0.7 (0.4-1.0); $P = .07$	12
Median OS, mo HR (95% CI)		
ITT	60 1.1 (0.7-1.5); $P = .8$	57
With induction	59 1.2 (0.7-1.9); $P = .5$	66
No induction	65 0.9 (0.5-1.6); $P = .7$	54

SYSUCC-002: Trastuzumab + ET or Chemotherapy as First-Line Treatment for HR+, HER2+ mBC¹

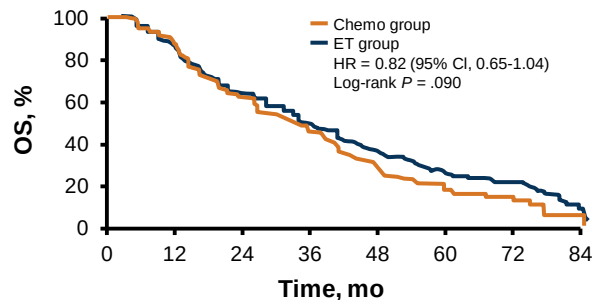
PFS (Primary Endpoint)



No. at Risk

Time, mo	0	12	24	36	48	60	72	84
Chemo	196	124	61	33	16	9	5	0
ET	196	142	73	50	28	11	4	0

Overall Survival



No. at Risk

Time, mo	0	12	24	36	48	60	72	84
Chemo	196	166	114	66	28	16	6	0
ET	196	166	118	78	49	33	22	2

Subgroup Analyses of PFS

Subgroup	ET Group (Events/n)	Chemo Group (Events/n)	HR (95% CI)	P
Age, y				.146
≤40	29/31	30/42	1.14 (0.67-1.91)	
>40	151/165	135/154	0.80 (0.63-1.00)	
Receptor status				.099
ER and PR positive	143/157	128/157	0.90 (0.71-1.15)	
ER or PR positive	37/39	37/39	0.76 (0.48-1.20)	
Visceral involvement				.487
Yes	106/114	103/119	0.95 (0.72-1.25)	
No	74/82	62/77	0.80 (0.57-1.12)	
Previous adjuvant endocrine therapy				.904
Als	74/83	66/83	0.98 (0.69-1.15)	
ORMs	56/59	51/59	0.97 (0.70-1.36)	
Metastasis number				.851
<2	127/140	111/139	0.89 (0.69-1.15)	
≥2	53/64	54/57	0.86 (0.59-1.27)	
DFS interval				.016
≤24 mo	59/64	64/78	1.39 (0.97-1.98)	
>24 mo	71/78	53/64	0.77 (0.53-1.10)	

0 0.5 1 1.5 2.0
ET better Chemo better

Let's Consider A Case to Frame Our Discussions Today

We will come back to this case later again

Patient

- 62-year-old Latina woman presents to clinic for newly diagnosed metastatic breast cancer
- Has no social support system; lives alone with her dog and is considering giving away her dog, as she does not have the energy to take him for walks twice a day
- Unemployed because of the pandemic

Presentation

- Originally diagnosed with 1.3-cm node-negative invasive breast cancer, ER+, PgR+, HER2+ 4 years ago
- Underwent breast-conserving surgery and then lost to follow-up; did not receive radiation or systemic therapy
- Developed abdominal fullness, RUQ pain, and significant fatigue
- Went to ER, where imaging revealed an 18-cm liver with multiple solid metastases
- Liver enzymes mildly elevated (3x ULN), but function is normal
- Biopsy demonstrates metastatic breast cancer, ER+, PgR+, HER2+, high grade



Discussion



- What option(s) is/are recommended for the frontline treatment of this patient, and which regimen would you recommend?
- How might her socioeconomic circumstances affect her outcomes, and what would you do to help optimize her outcome?
- Would you do brain imaging in a patient who has no headaches or neurological symptoms in the frontline setting?
- If you did imaging and it showed a metastasis, would your treatment approach be different?

The background is a solid dark blue. Overlaid on it is a faint, light blue graphic of a human silhouette from the waist up, facing right. The silhouette is semi-transparent, revealing internal organs like the heart and lungs. Behind the silhouette is a large, faint circular diagram with radial lines and tick marks, resembling a medical or scientific instrument. Centered over the silhouette is the main title in white text.

Expanding Options for Second-Line Therapy and Beyond

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T-DM1: EMILIA Trial¹

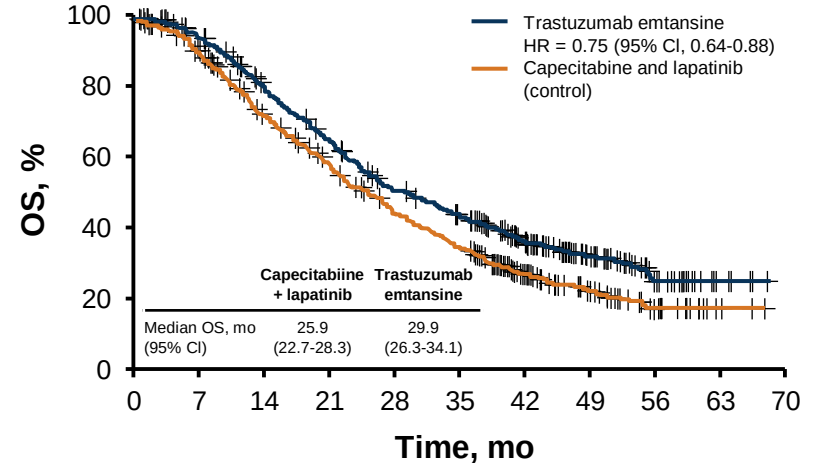
- **HER2+** (central) LABC or mBC
- Prior taxane and trastuzumab
- Progression on metastatic treatment or within 6 months of adjuvant treatment
- N = 980

R 1:1

T-DM1

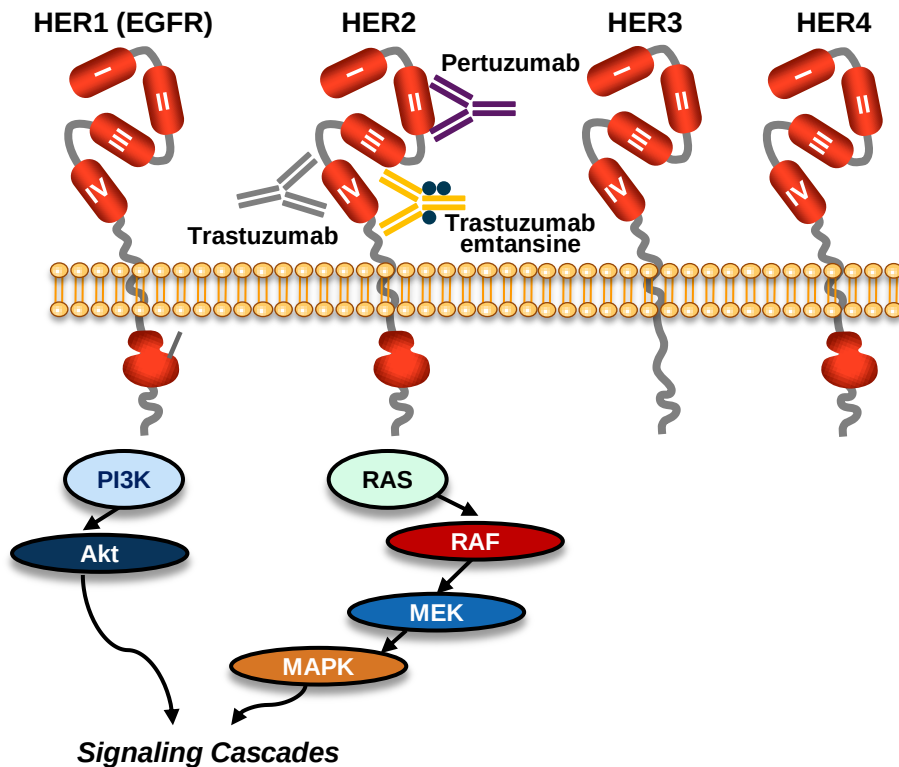
**Capecitabine +
lapatinib**

ITT Population



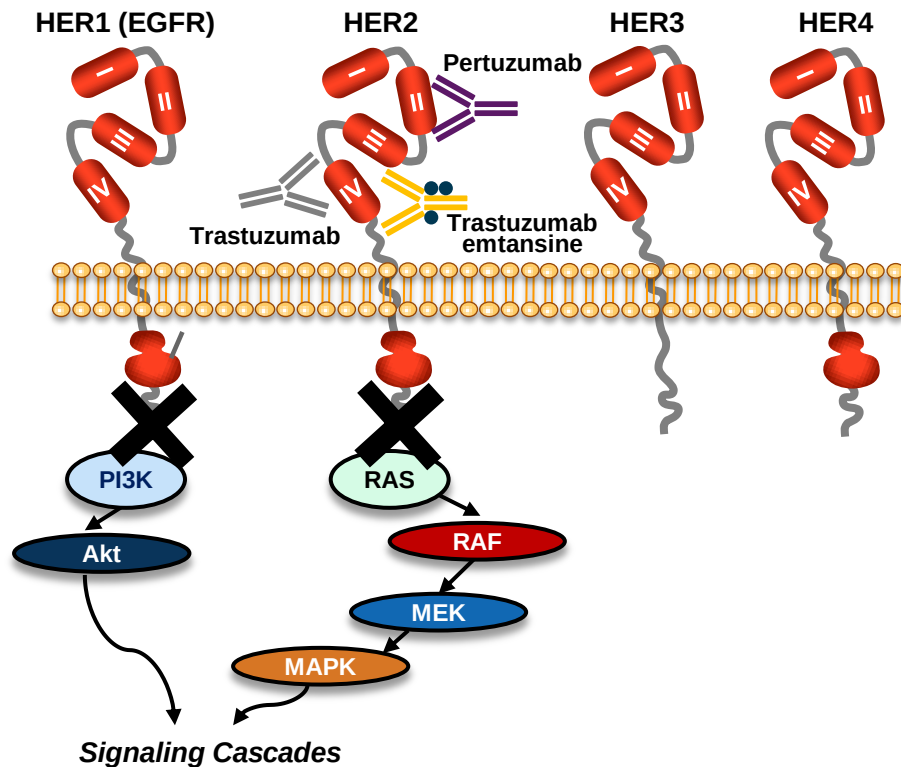
No. at Risk (censored)											
Capecitabine and lapatinib	496 (0)	418 (35)	326 (47)	258 (53)	195 (58)	153 (58)	82 (99)	48 (122)	19 (144)	3 (160)	0 (163)
Trastuzumab emtansine	495 (0)	452 (21)	374 (34)	302 (36)	231 (42)	194 (47)	127 (85)	68 (133)	23 (169)	5 (187)	0 (191)

Tyrosine Kinase Inhibitors for HER2+ Breast Cancer¹



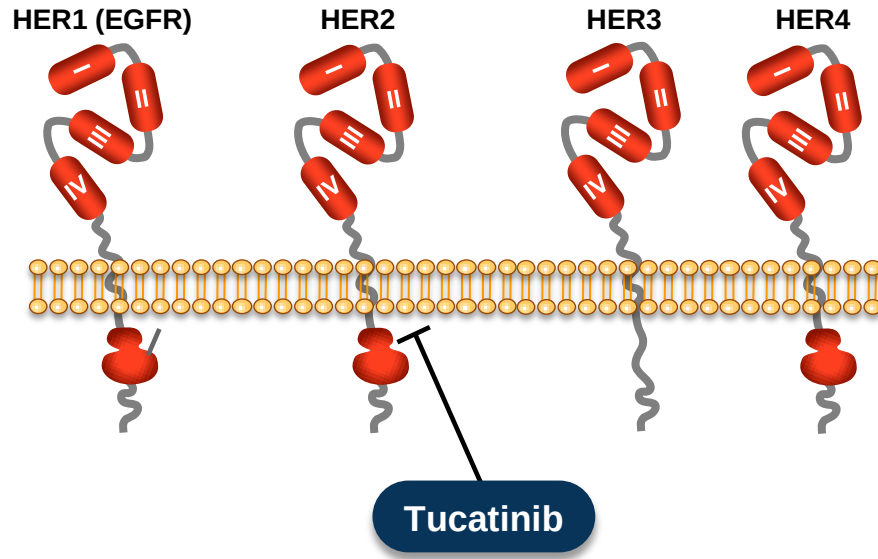
	Binding	Targets
Lapatinib	Reversible	HER1 HER2
Neratinib	Irreversible	Pan-HER
Pyrotinib	Irreversible	Pan-HER
Pozotinib	Irreversible	Pan-HER
Tucatinib	Reversible	HER2 specific

Tyrosine Kinase Inhibitors for HER2+ Breast Cancer¹



	Binding	Targets
Lapatinib	Reversible	HER1 HER2
Neratinib	Irreversible	Pan-HER
Pyrotinib	Irreversible	Pan-HER
Pozotinib	Irreversible	Pan-HER
Tucatinib	Reversible	HER2 specific

Tucatinib: A HER2-Selective TKI¹



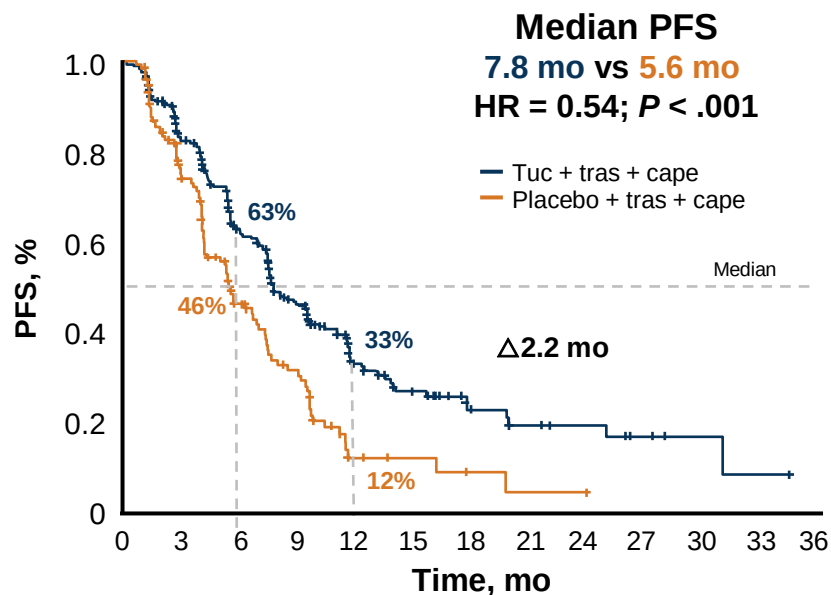
Phase 1b tucatinib + capecitabine + trastuzumab (n = 60)¹

- **Prior treatment**
 - 100% trastuzumab
 - 65% pertuzumab
 - 97% T-DM1
 - 55% lapatinib
 - 56% with CNS metastasis
- **ORR**
 - 61% (14/23)
 - 42% (5/12) with CNS metastasis
- **PFS**
 - 7.8 months
 - 6.7 months with CNS metastasis
- **Diarrhea**
 - 33% grade 1-2
 - 0% grade 3-4

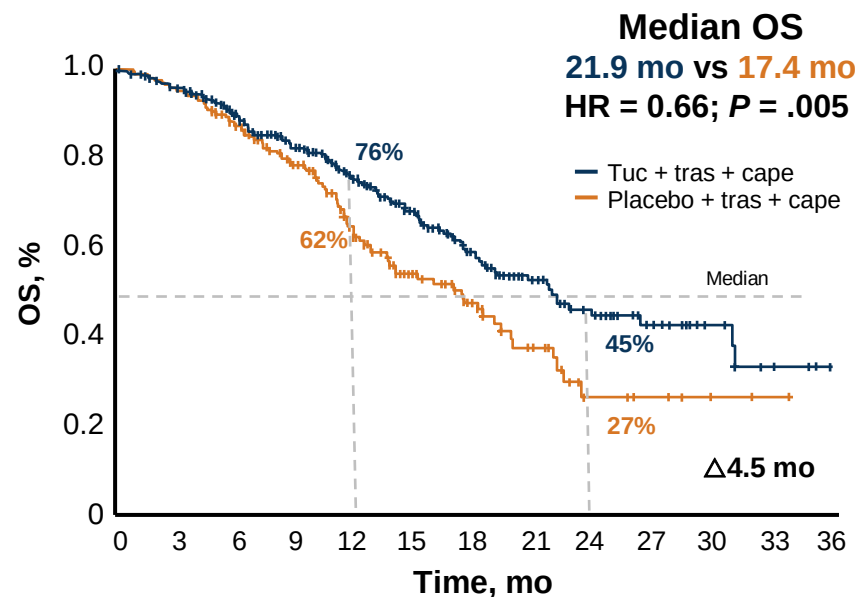
HER2CLIMB: Randomized Phase 2 Trial of Tucatinib¹

Tucatinib + Capecitabine + Trastuzumab vs Capecitabine + Trastuzumab

Tucatinib Improves PFS and OS

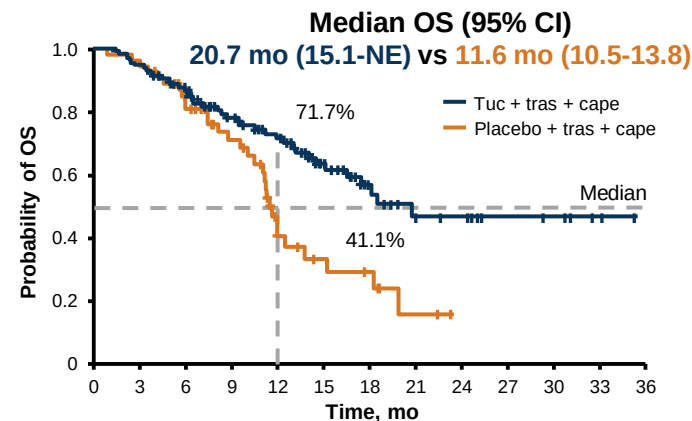
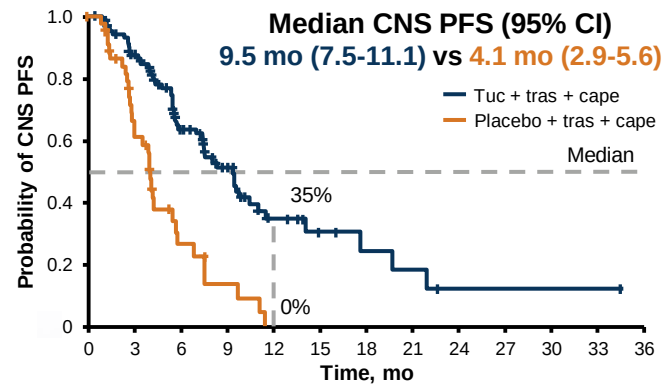
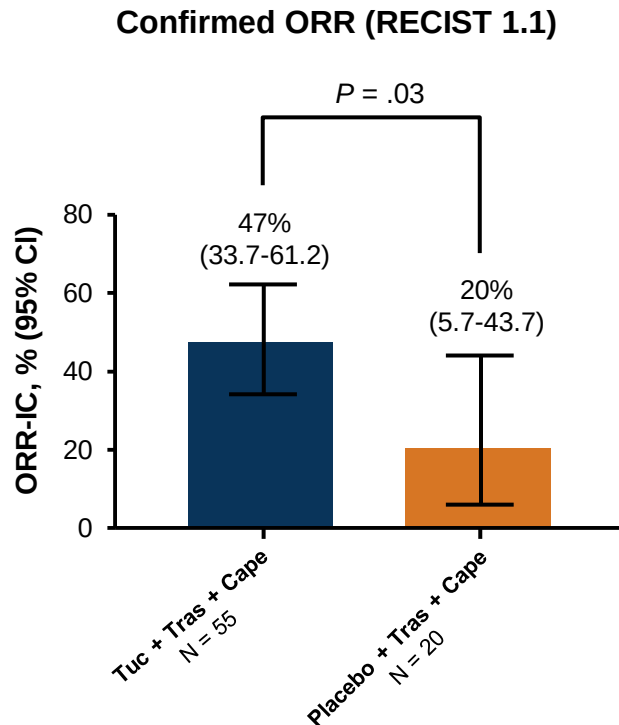


No. at Risk	320	235	152	96	40	29	15	10	8	4	2	1	0
Tuc + tras + cape	320	235	152	96	40	29	15	10	8	4	2	1	0
PBO + tras + cape	160	94	45	27	6	4	2	1	1	0	0	0	0

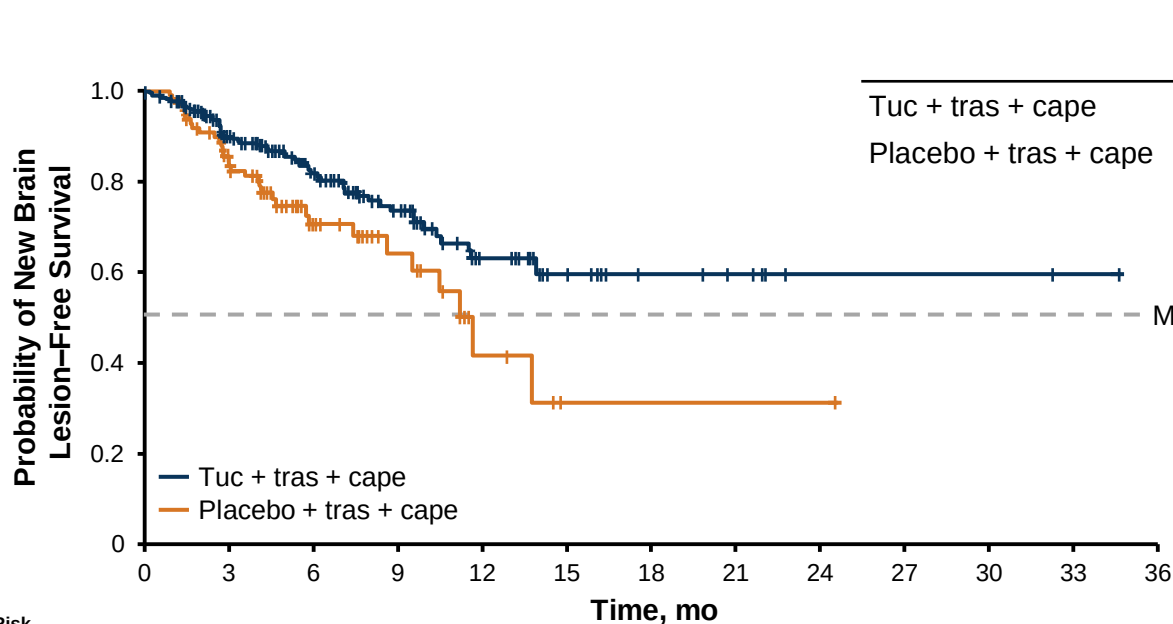


No. at Risk	410	388	322	245	178	123	80	51	34	20	10	4	0
Tuc + tras + cape	410	388	322	245	178	123	80	51	34	20	10	4	0
PBO + tras + cape	202	191	160	119	77	48	32	19	7	5	2	1	0

Tucatinib for Active Brain Metastases: Improves ORR, CNS PFS, and OS¹



Time to New Brain Lesions or Death in All HER2CLIMB Patients^{1,2}



	Events, n (N = 612)	HR (95% CI)	P
Tuc + tras + cape	52/410	0.52	.005
Placebo + tras + cape	33/202	(0.33-0.82)	

Median New Brain Lesion-Free Survival (95% CI)

Tuc + Tras + Cape	Placebo + Tras + Cape
NR (13.9, -)	11.7 mo (9.5, -)

- Rate of new brain lesions in all patients: 6.1% vs 9.4%
- Rate of death similar between arms

No. at Risk

Tuc + tras + cape	410	182	105	66	25	14	8	6	2	2	2	1	0
Placebo + tras + cape	202	77	31	17	5	1	1	1	1	0	0	0	0

Time to new brain lesion-free survival: time from randomization to new lesion 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.

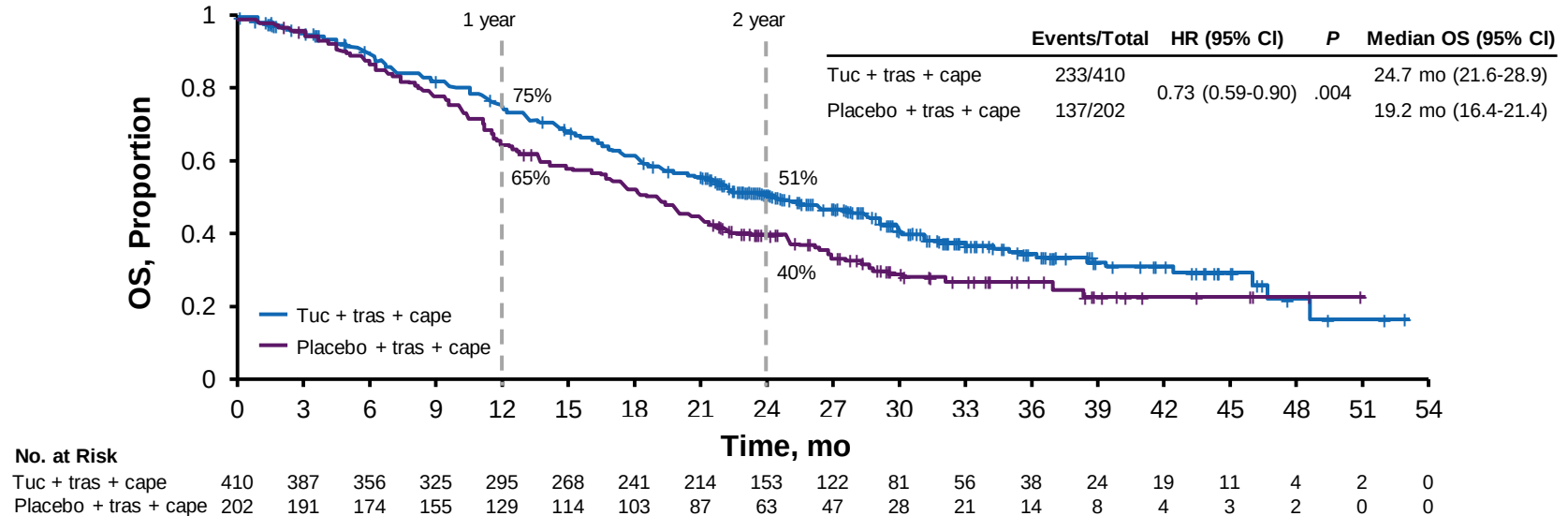
All P are nominal.

1. Lin N et al. Society for NeuroOncology Second Annual Conference on Brain Metastases (SNO 2020). Abstract 53.

2. Bachelot T et al. European Society for Medical Oncology Congress 2020 (ESMO 2020). Abstract 293P.

HER2CLIMB: Updated OS Results¹

Overall Survival^a

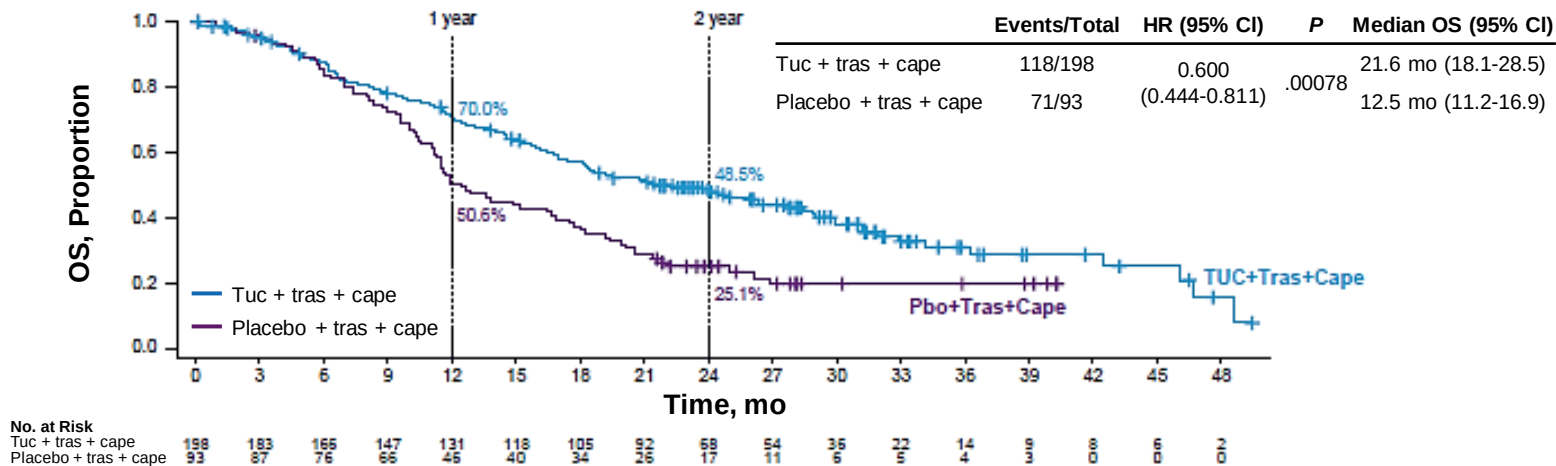


- OS benefit with tucatinib was maintained with longer follow-up, with a 5.5-month improvement in median OS in the tucatinib arm compared with the placebo arm
- Sensitivity analyses accounting for crossover showed consistent results with ITT analysis

^a Median overall study follow-up: 29.6 months.
 1. Gurigiano G et al. ASCO 2021. Abstract 1043.

HER2CLIMB: Updated Results in Patients With Brain Metastases¹

Overall Survival in Patients With Brain Metastases



- OS benefit with tucatinib was improved with additional follow-up: median OS was 9.1 mo longer in the tucatinib arm compared with the control arm in all patients with brain metastases
 - Median OS was 9.6 mo longer in the tucatinib arm compared with control in patients with active brain metastases
 - Median OS was 5.2 mo longer in the tucatinib arm compared with control in patients with treated stable brain metastases

HER2CLIMB: Most Common Adverse Events¹

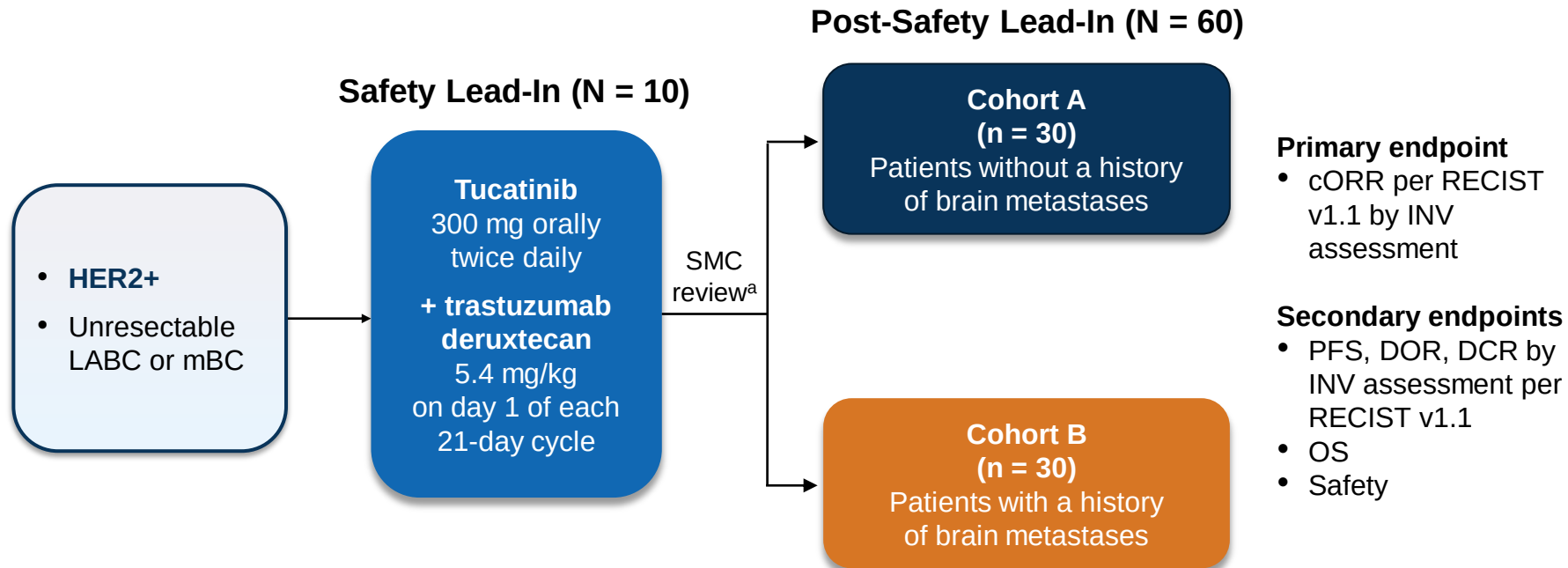
- Rates of the most common adverse events remained stable with longer follow-up

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

Preferred Term	Tuc + Tras + Cape, n (%) (n = 404)		Placebo + Tras + Cape, n (%) (n = 197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any event	401 (99.3)	245 (60.6)	191 (97.0)	101 (51.3)
Diarrhea	331 (81.9)	53 (13.1)	106 (53.8)	17 (8.6)
Palmar-plantar erythrodysesthesia syndrome	264 (65.3)	57 (14.1)	105 (53.3)	18 (9.1)
Nausea	243 (60.1)	16 (4.0)	88 (44.7)	7 (3.6)
Fatigue	193 (47.8)	22 (5.4)	87 (44.2)	8 (4.1)
Vomiting	152 (37.6)	13 (3.2)	51 (25.9)	8 (4.1)
Decreased appetite	105 (26.0)	3 (0.7)	41 (20.8)	0
Stomatitis	105 (26.0)	10 (2.5)	28 (14.2)	1 (0.5)
Headache	96 (23.8)	3 (0.7)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	89 (22.0)	19 (4.7)	22 (11.2)	1 (0.5)
Anemia	88 (21.8)	17 (4.2)	24 (12.2)	5 (2.5)
Alanine aminotransferase increased	85 (21.0)	23 (5.7)	13 (6.6)	1 (0.5)
Blood bilirubin increased	81 (20.0)	4 (1.0)	21 (10.7)	5 (2.5)

HER2CLIMB-04: Phase 2 Trial of Tucatinib + T-Dxd in HER2+ LABC and mBC With or Without Brain Metastases¹

HER2CLIMB-04 Study Design



^a If there are no safety signals in the safety lead-in, 50 additional patients will be enrolled in the postsafety lead-in.

1. Krop I et al. ASCO 2021. Abstract TPS1097.

A011801 (CompassHER2 RD) Trial: Postneoadjuvant T-DM1 + Tucatinib in Residual HER2+ Invasive BC¹

- **HER2+** invasive residual BC, ER+, and ER-
- cT1-4, N0-3 at *diagnosis*
- ER-: any amount of residual disease
- ER+: lymph node positive disease post op
- Received ≥ 6 cycles of chemotherapy (preop $\pm$ postop; including ≥ 9 weeks neoadjuvant taxane and trastuzumab) prior to registration

Residual invasive HER2+ breast cancer after neoadjuvant chemotherapy and HER2-directed treatment

REGISTRATION

R 1:1

T-DM1 and placebo
x14 cycles

T-DM1 and tucatinib
x14 cycles

Stratification factors

- Receipt of postoperative chemotherapy (yes/no)
- HR status: positive (ER and/or PgR positive) vs negative (ER negative and PgR negative)
- Pathologic lymph node status (positive/negative)

Primary objective: IDFS *HER2+* (all)

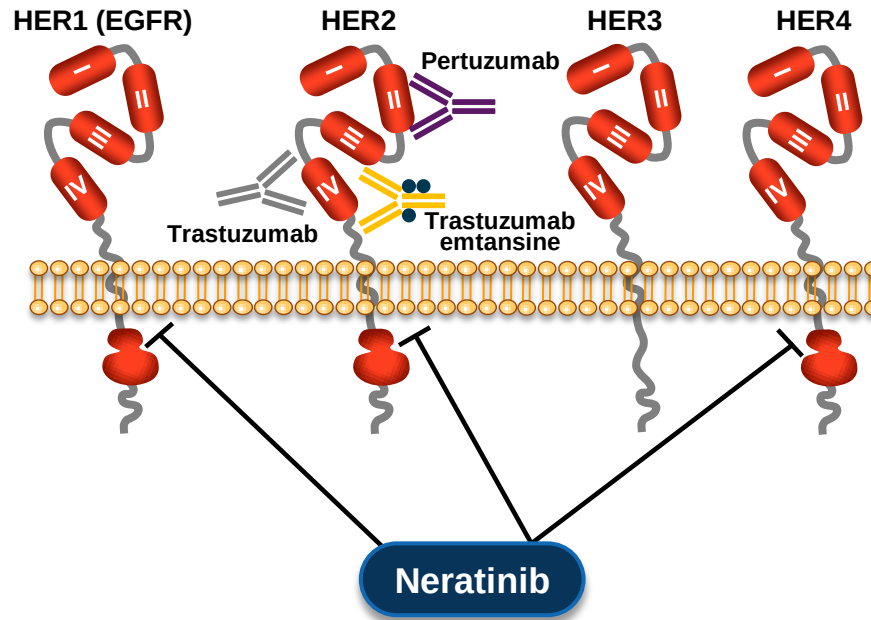


Joyce O'Shaughnessy, MD

Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

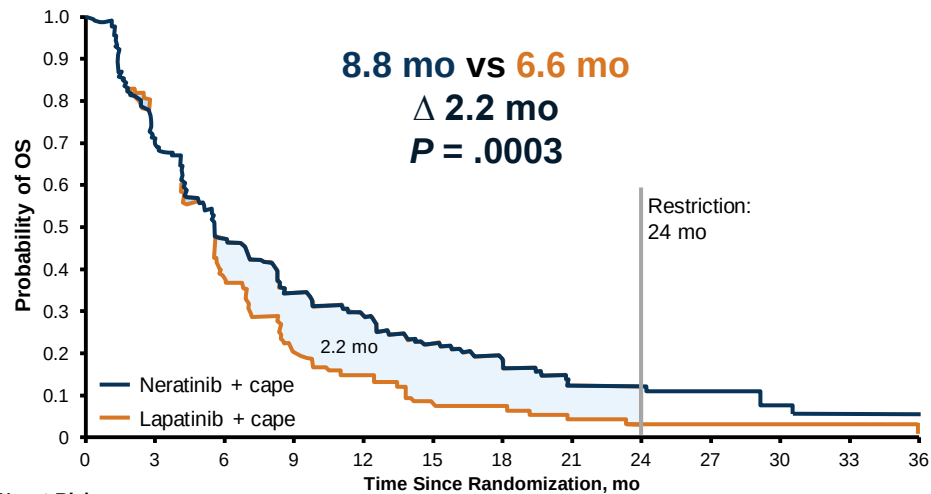
PeerView
Live

Neratinib: A Pan-HER Kinase Inhibitor¹⁻⁴

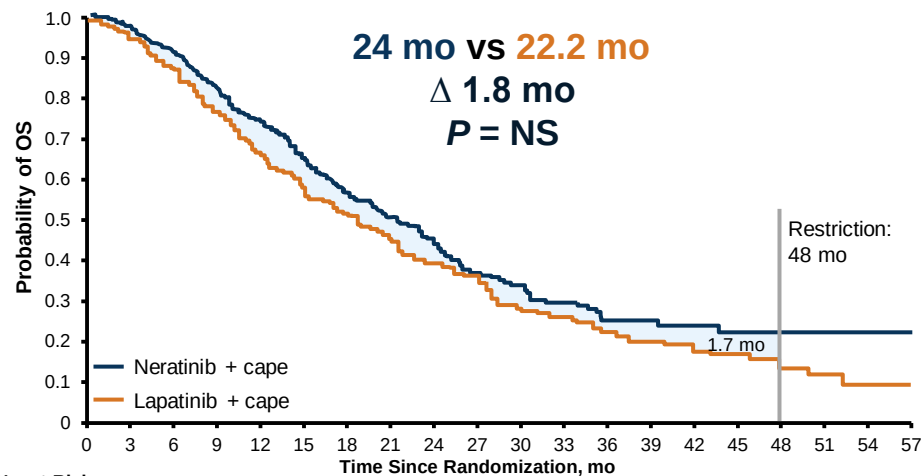


NALA Trial: A Phase 3 Trial of Neratinib + Capecitabine vs Lapatinib + Capecitabine¹

Centrally Confirmed PFS

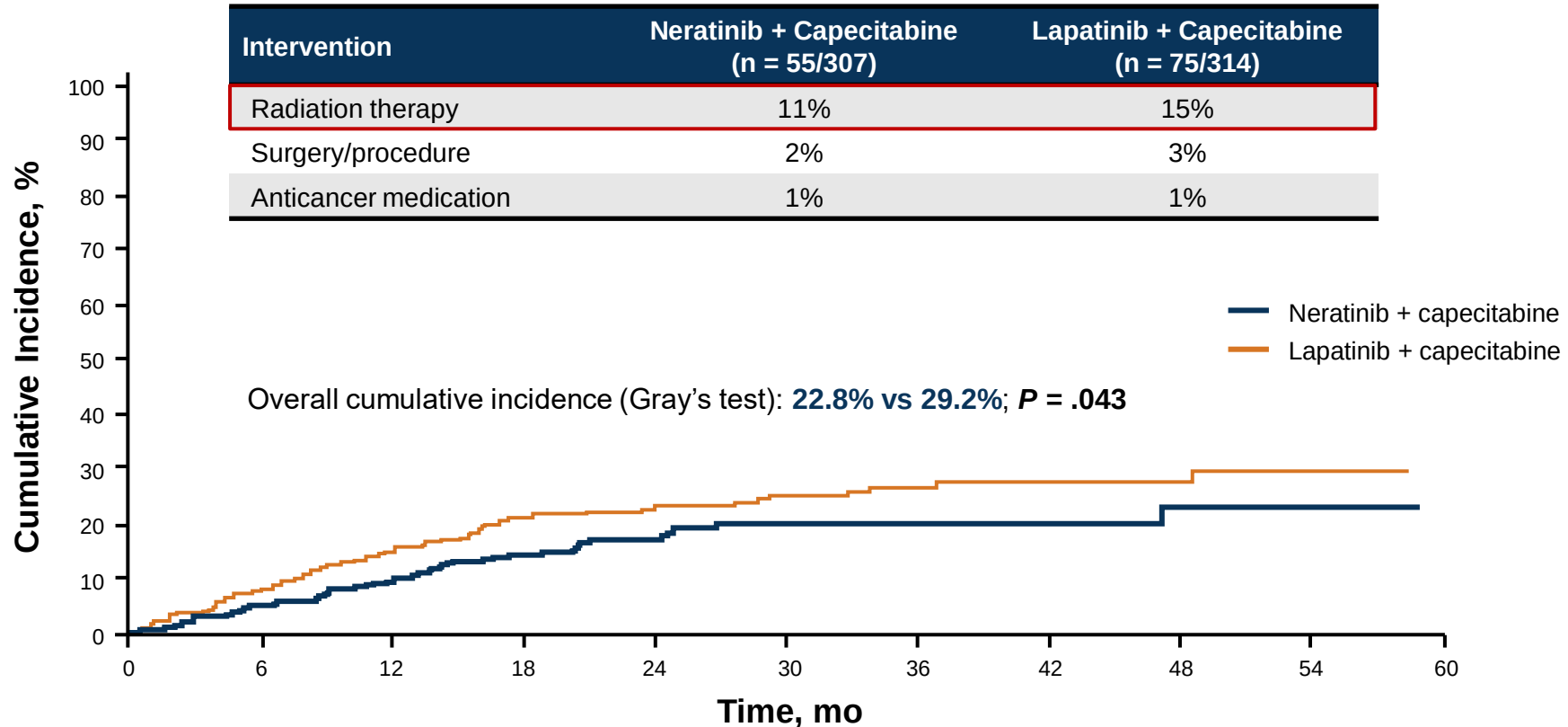


Overall Survival



- 1-y PFS: **29%** vs 15%
- ORR: **33%** vs 27% ($P = .1201$)
- Median DOR: **8.5 mo** vs 5.6 mo (HR = 0.50, 95% CI, 0.33-0.74; $P = .0004$)

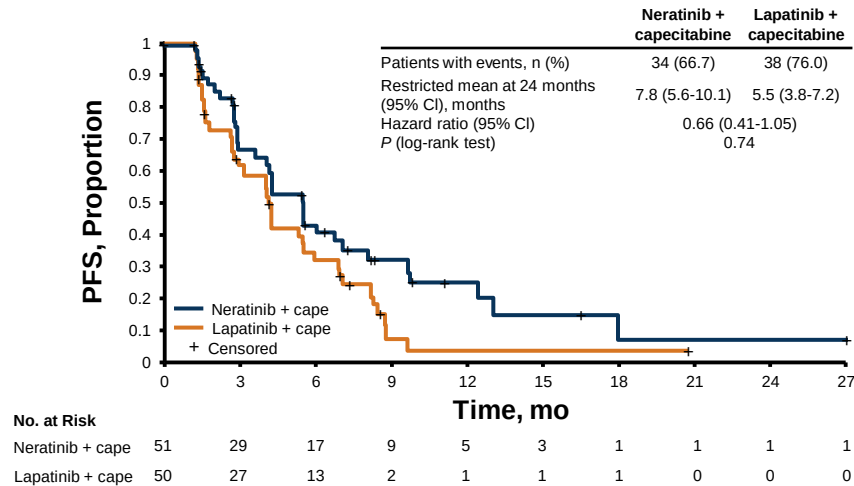
Time to Intervention for CNS Metastases¹



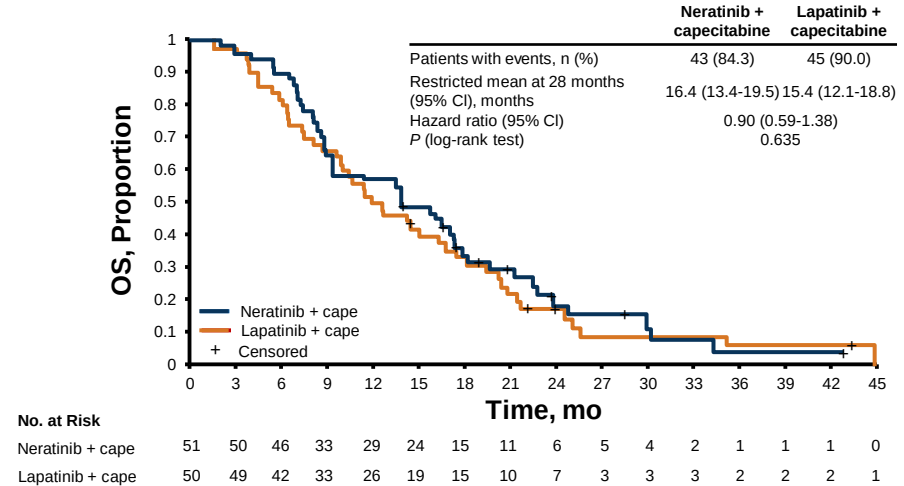
Efficacy of Neratinib + Capecitabine in NALA Subgroup With CNS Involvement¹

- Subgroup analyses suggest improved PFS and CNS outcomes with N + C versus L+ C in patients with CNS metastases from HER2+ mBC

PFS With CNS Metastases at Baseline



OS With CNS Metastases at Baseline

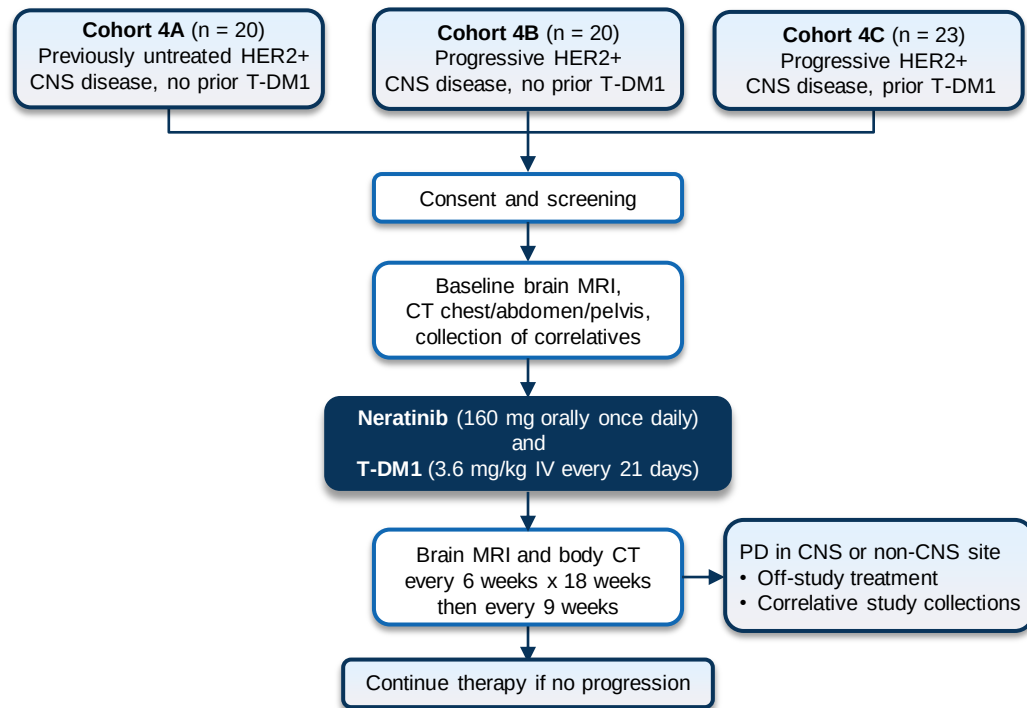


TBCRC 022: Phase 2 Trial of Neratinib + Capecitabine in Patients With HER2+ Breast Cancer and Brain Metastases^{1,2}

TBCRC 022 Cohorts 3A and 3B

- 49 pts with measurable, progressive, HER2+ brain metastases received N + C in cohort A (lapatinib-naïve; n=37) and cohort B (lapatinib-treated; n=12)
- Cohort 3A composite CNS ORR=49% (95% CI, 32%-66%)
- Cohort B CNS ORR=33% (95% CI, 10%-65%)
- Median PFS: 5.5 and 3.1 mo in cohorts 3A and 3B, respectively; median survival: 13.3 and 15.1 mo

TBCRC 022 (Cohort 4) (All Require Measurable Disease)



Details on and Efficacy of Neratinib + Capecitabine in Patients With Leptomeningeal Metastases in NALA¹

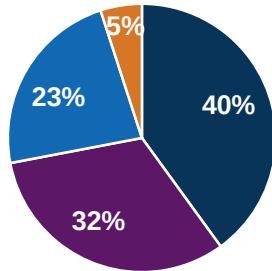
	Patient 1	Patient 2	Patient 3
Demographics	60-year-old white female	40-year-old white female	62-year-old white female
HR status	HR+	HR-	HR-
Randomization	June 14, 2016	November 21, 2016	April 4, 2014
Treatment group	Neratinib + capecitabine	Neratinib + capecitabine	Lapatinib + capecitabine
First dose study drug	June 16, 2016	November 22, 2016	April 10, 2014
Prior CNS-directed treatment	Palliative WBRT from September 10-26, 2014; no prior intrathecal therapy for LMD	Palliative WBRT from May 24 to June 9, 2016; no prior intrathecal therapy for LMD	Palliative WBRT from February 10-27, 2014; no prior intrathecal therapy for LMD
Concomitant CNS medications at enrollment	Anti-epileptic agents	–	Dexamethasone
First intervention for CNS disease	Radiotherapy	–	Dexamethasone
End of treatment	March 8, 2017	October 3, 2017	August 22, 2014
End of study	November 25, 2017	July 15, 2018	October 19, 2014
Post-treatment anti-cancer therapy	Lapatinib	Capecitabine, gemcitabine, and cisplatin	–
Efficacy			
PFS	5.6 mo	9.8 mo (censored)	4.3 mo
OS	17.4 mo	19.8 mo	6.5 mo

NALA: Most Frequent Grade 3/4 Adverse Events¹

	Neratinib + Cape (n = 303)		Lapatinib + Cape (n = 311)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Treatment-emergent AE, (%)	100	61	99	60
Diarrhea	83	24	66	13
Hand-foot syndrome	46	10	56	11
Hypokalemia	12	5	14	6
Nausea	53	4	42	3
Vomiting	46	4	31	2
Fatigue	34	3	31	3
Neutropenia	7	3	5	2
Asthenia	12	3	12	2
Decreased appetite	35	3	22	2
Dehydration	6	2	6	2
Treatment discontinuation due to treatment-emergent AEs: N + C: 10.9%; L + C: 14.5%				

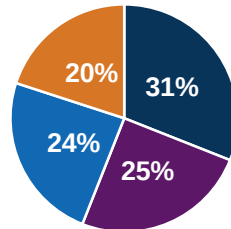
Antidiarrheal Prophylaxis Reduces Diarrhea With Neratinib: CONTROL Trial¹⁻³

**ExteNET: Adjuvant Neratinib
in Trastuzumab-Treated
HER2+ Early-Stage BC
(N = 1,408)**

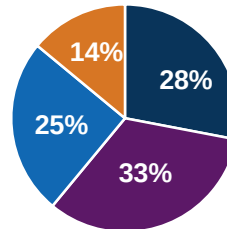


Control

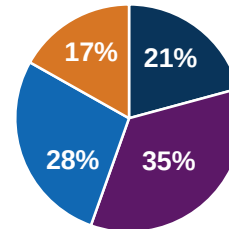
**Loperamide
(n = 137)**



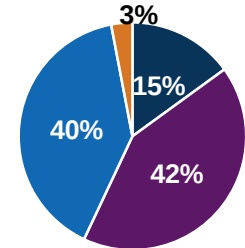
**LPM + Budesonide
(n = 64)**



**LPM + Colestipol
(n = 136)**



**Neratinib Dose Escalation
+ LPM prn (n = 60)**



**Discontinuation rate
due to diarrhea:**

20.4%

10.9%

3.7%

3.3%

None Grade 1 Grade 2 Grade 3



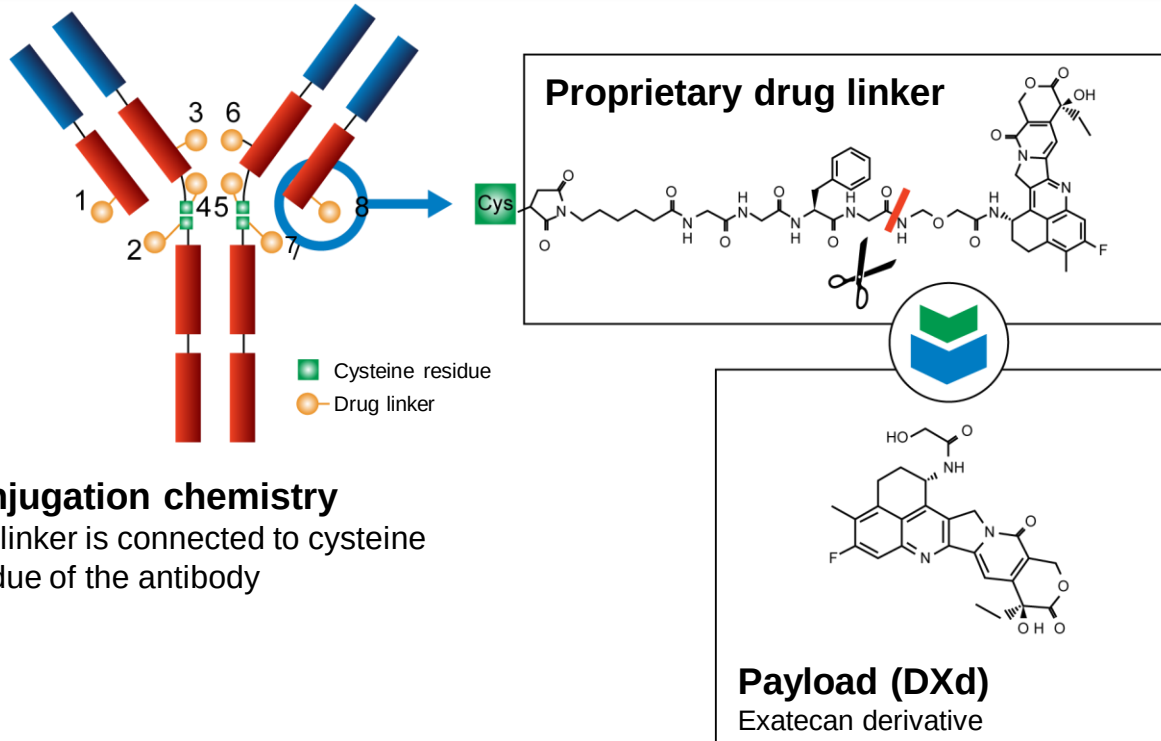
Javier Cortés, MD, PhD

Head

International Breast Cancer Center (IBCC)
Barcelona, Spain

PeerView
Live

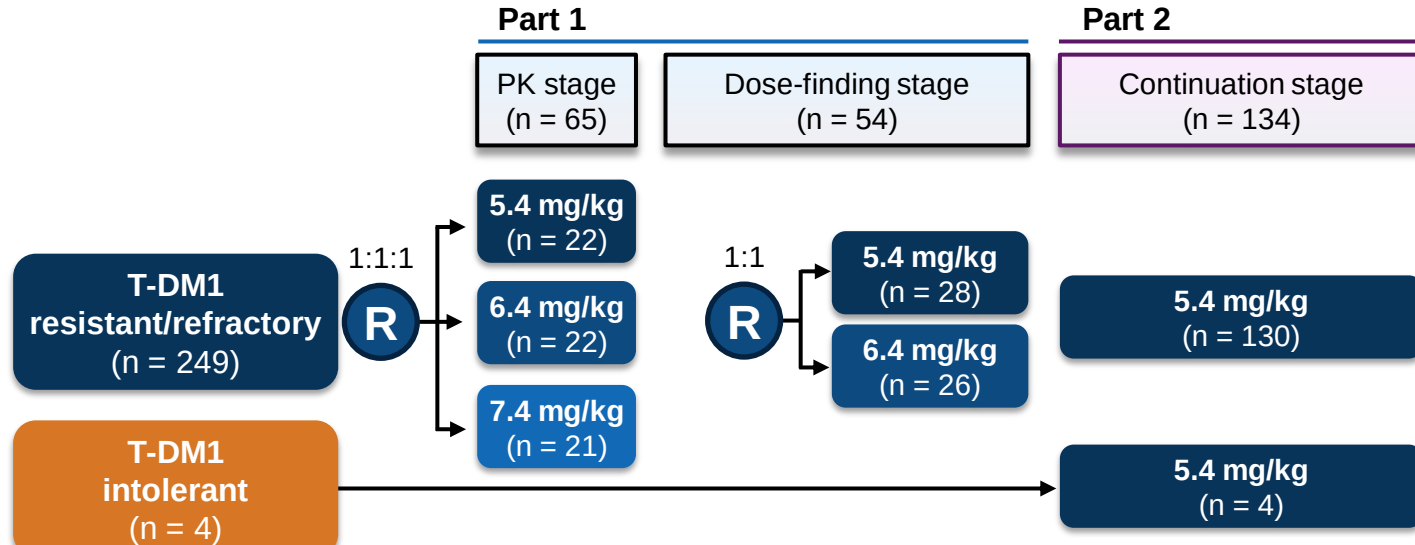
Trastuzumab Deruxtecan (T-DXd; DS8201a) Is a Novel HER2 ADC^{1,2}



	T-DXd	T-DM1
Antibody	Anti-HER2 mAb	Trastuzumab
Payload	Topoisomerase I inhibitor	Tubulin inhibitor
DAR	7-8	3.5
Membrane Permeability	Yes (bystander effect)	No

DESTINY-Breast01: Phase 2 Study of T-DXd in HER2+ mBC¹

- ≥18 years of age
- Unresectable and/or metastatic BC
- **HER2+**
(centrally confirmed on archival tissue)
- **Prior T-DM1**
- Excluded patients with history of significant ILD
- Stable, treated brain metastases were allowed



- **Primary endpoints:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary endpoints:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK, and safety

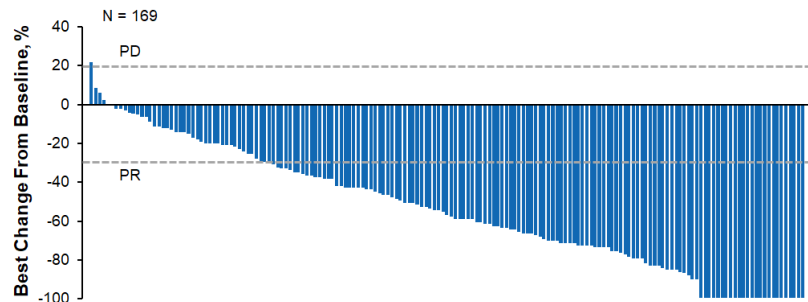
Median lines of therapy = 6 (range: 2-27)

- 100% received prior trastuzumab
- 100% received prior T-DM1
- 66% received prior pertuzumab
- 54% received other HER2 therapies

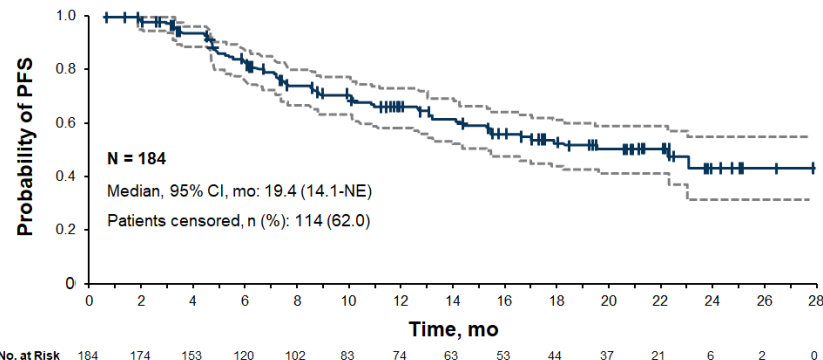
184 patients

DESTINY-Breast01: Efficacy of T-DXd in HER2+ mBC¹⁻³

ORR



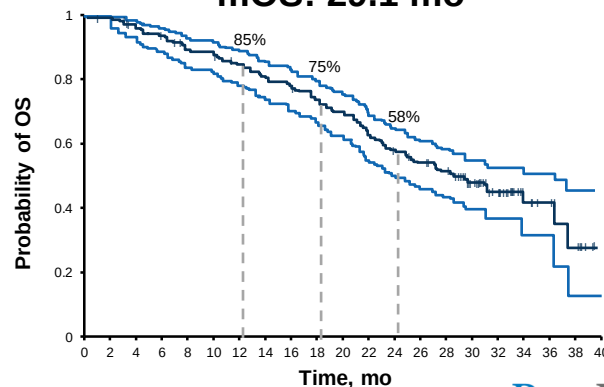
mPFS: 19.4 mo



Intent-to-treat analysis

	August 2019 DCO T-DXd 5.4 mg/kg (N=184)	June 2020 DCO T-DXd 5.4 mg/kg (N=184)	March 2021 DCO T-DXd 5.4 mg/kg (N=184)
Median duration of follow up (range), months	11.1 (0.7-19.9)	20.5 (0.7-31.4)	26.5 (0.7-39.1)
Patients remaining on treatment, n (%)	79 (42.9)	37 (20.1)	28 (15.2)
Confirmed ORR^a by ICR, n (%)	112 (60.9)	113^b (61.4)	114 (62.0)
95% CI	53.4-68.0	54.0-68.5	54.5-69.0
CR	11 (6.0)	12 (6.5)	13 (7.1)
PR	101 (54.9)	101 (54.9)	101 (54.9)
SD	67 (36.4)	66 (35.9)	65 (35.3)
PD	3 (1.6)	3 (1.6)	3 (1.6)
Not evaluable	2 (1.1)	2 (1.1)	2 (1.1)
Median DOR (95% CI), months	14.8 (13.8-16.9)	20.8 ^b (15.0-NE)	18.2 (15.0-NE)
Median time to response (95% CI), months	1.6 (1.4-2.7)	1.6 (1.4-2.7)	1.6 (1.4-2.7)
Median PFS (95% CI), months	16.4 (12.7-NE)	19.4 (14.1-NE)	19.4 (14.1-25.0)
Median OS (95% CI), months	NE (NE-NE)	24.6 (23.1-NE)	29.1 (24.6-36.1)

mOS: 29.1 mo



1. Modi S et al. *N Engl J Med*. 2020;387:610-621.

2. Modi S et al. 2020 San Antonio Breast Cancer Symposium (SABCS 2020). Abstract PD3-06. 3. Saura C. ESMO 2021. Abstract 279P.

T-DXd: Interstitial Lung Disease¹

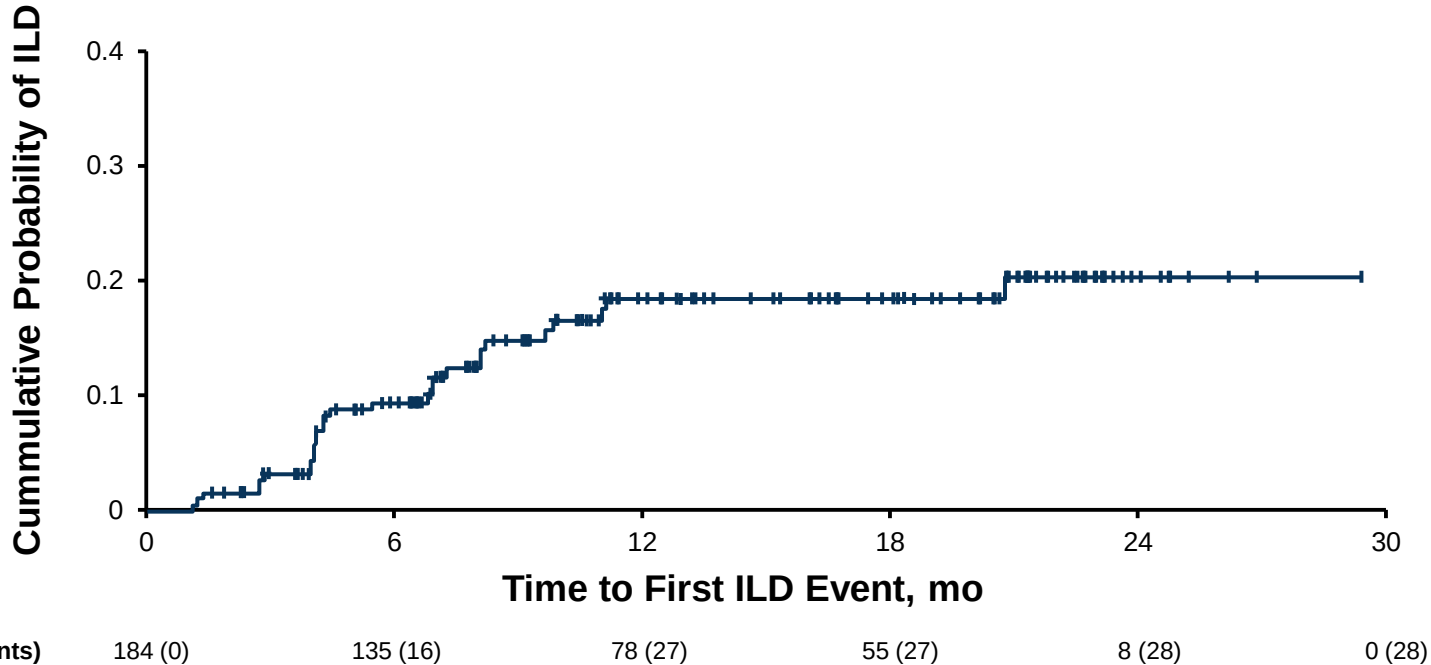
Drug-Related ILD/Pneumonitis^a

ILD, n (%)	T-DXd 5.4 mg/kg (N = 184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	28 (15.2)

^a As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.
1. Modi S et al. SABCS 2020. Abstract PD3-06.

T-DXd: Timing to Onset of ILD¹

Cumulative Probability of Adjudicated Drug-Related Any-Grade ILD^a



^a In patients with HER2+ breast cancer (T-DXd 5.4 mg/kg).

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

Trastuzumab Deruxtecan: Black Box Warning¹

Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with T-DXd. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. **Permanently discontinue T-DXd in all patients with grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms** [see Dosage and Administration (2.2), Warnings and Precautions (5.1)].

Severity	Treatment Modification
Asymptomatic ILD/pneumonitis (grade 1)	- Interrupt T-DXd until resolved to grade 0, then: - If resolved in 28 days or less from date of onset, maintain dose - If resolved in greater than 28 days from date of onset, reduce dose one level (see Table 1) - Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected [see Warnings and Precautions (5.1)]
Symptomatic ILD/pneumonitis (grade 2 or greater)	- Permanently discontinue T-DXd - Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected [see Warnings and Precautions (5.1)]

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761139s000lbl.pdf.

DESTINY-Breast03: First Randomized Phase 3 Study of T-DXd

An Open-label, Multicenter Study (NCT03529110)

- Unresectable or metastatic HER2^a breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting^b
- Could have clinically stable, treated brain metastases

Stratification

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R

1:1

T-DXd
5.4 mg/kg Q3W
(n = 261)

T-DM1
3.6 mg/kg Q3W
(n = 263)

- **Primary endpoint:** PFS (BICR)
 - Efficacy boundary for superiority: $P < .000204$ (based on 245 events)
 - IDMC recommendation to unblind study (July 30, 2021)
- **Key secondary endpoint:** OS
 - boundary for efficacy: $P < .000265$ (based on 86 events)
- **Secondary endpoints:** ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety

^a HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. ^b Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Baseline Characteristics¹

	T-DXd (n = 261)	T-DM1 (n = 263)
Age, median (range), y	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, %	99.6	99.6
Region, %		
Europe	20.7	19.0
Asia	57.1	60.8
North America	6.5	6.5
Rest of world	15.7	13.7
HER2 status (IHC^a, %)		
3+	89.7	88.2
2+ (ISH amplified)	9.6	11.4
1+ Not evaluable Not examined	0.4 0.4 0	0 0.4 0
ECOG PS, %		
0 1 Missing	59.0 40.6 0.4	66.5 33.1 0.4
Hormone receptor, %		
Positive Negative	50.2 49.8	51.0 49.0
Brain metastases, %		
Yes No	23.8 76.2	19.8 80.2
Visceral disease, %		
Yes No	70.5 29.5	70.3 29.7

^a HER2 status as evaluated by central lab. 1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Prior Therapies¹

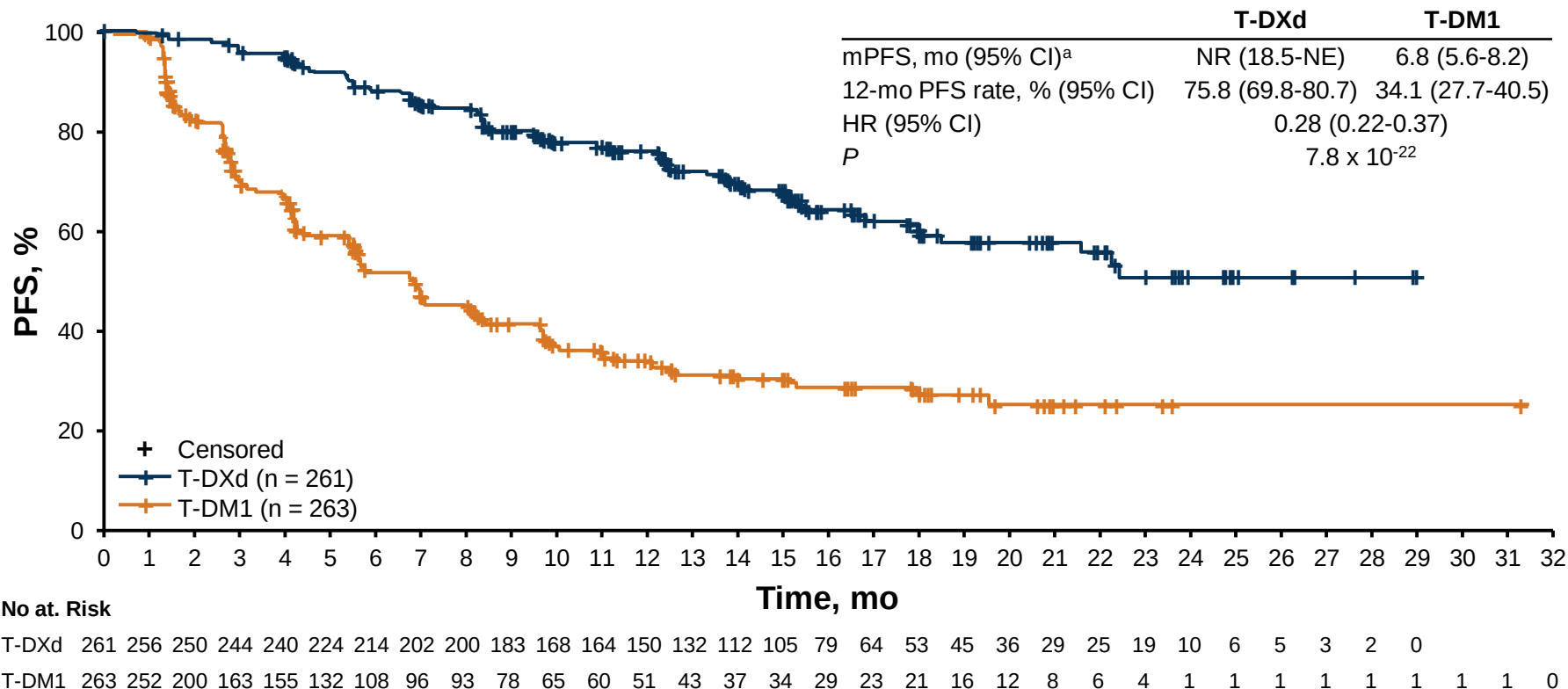
	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)^a, n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy^b, %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

^a Rapid progressors defined as progression within 6 mo of (neo)adjuvant therapy or 12 mo if regimen contained pertuzumab. Line of therapy does not include endocrine therapy.

^b All patients received at least 1 prior cancer therapy. One patient with prior T-DM1 treatment was enrolled in error in the T-DXd arm.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

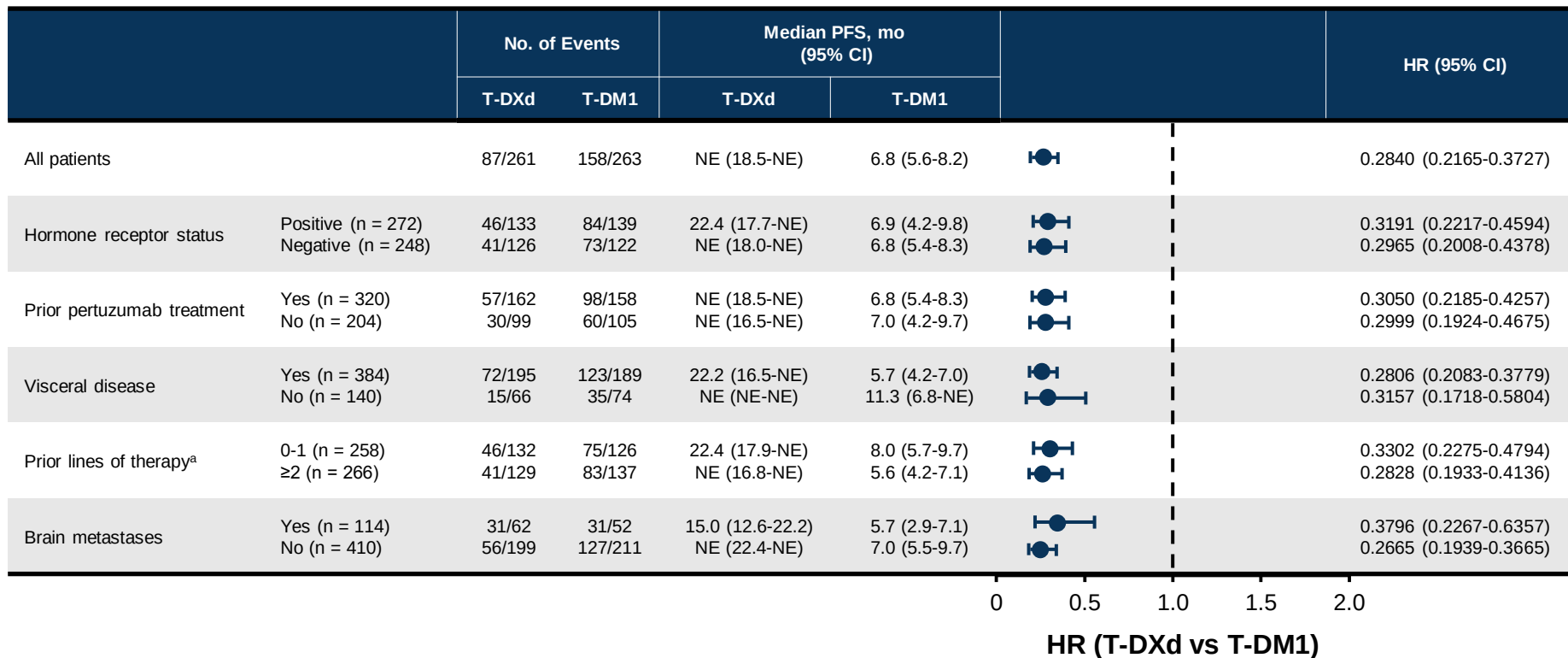
DESTINY-Breast03 Primary Endpoint: PFS by BICR¹



^a Median PFS follow-up was 15.5 months (range, 15.1-16.6) for T-DXd and 13.9 months (range, 11.8-15.1) for T-DM1.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

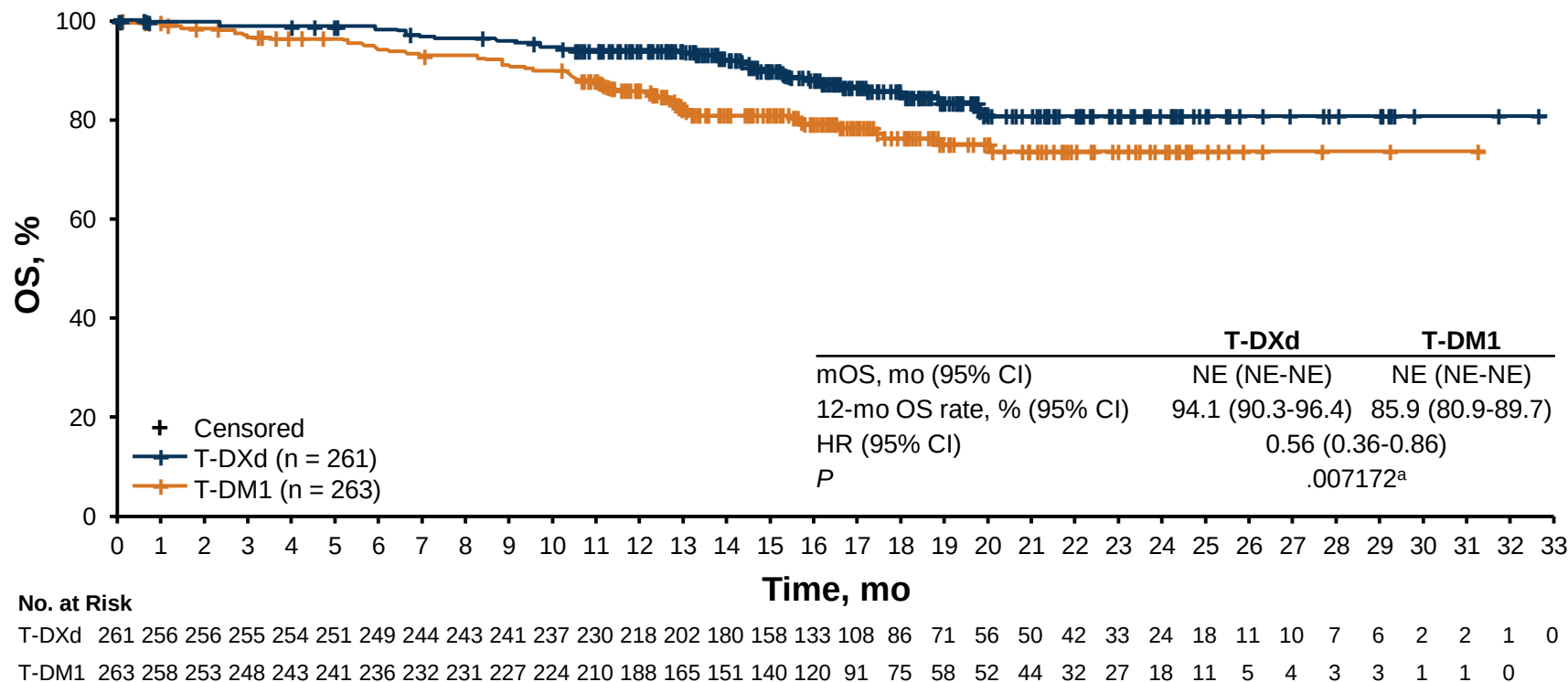
DESTINY-Breast03: PFS in Key Subgroups¹



^a Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03 Key Secondary Endpoint: OS¹

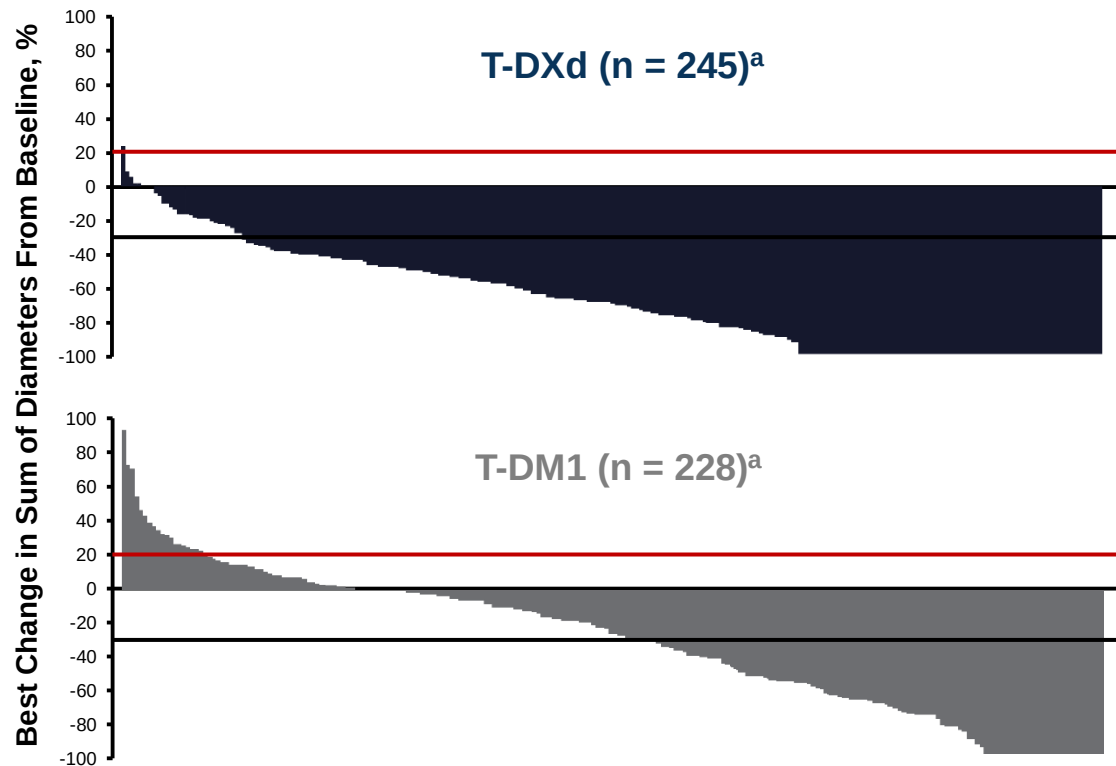


Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

^a P = .007172, but does not cross prespecified boundary of P < .000265.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Confirmed ORR and Best Overall Response¹



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%) ^b	208 (79.7)	90 (34.2)
95% CI	74.3-84.4	28.5-40.3
<i>P</i> <.0001		
CR	42 (16.1)	23 (8.7)
PR	166 (63.6)	67 (25.5)
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

^a Only participants with measurable disease at baseline and at least one postbaseline target lesion assessment are included. ^b Based on BICR.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Drug-Related TEAEs in $\geq 20\%$ of Patients¹

System Organ Class Preferred Term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Blood and lymphatic system disorders				
Neutropenia ^a	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia ^b	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia ^c	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia ^d	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue ^e	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous skin disorders				
Alopecia ^f	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

^a This category includes the preferred terms neutrophil count and neutropenia. ^b This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. ^c This category includes the preferred terms white blood cell count decreased and leukopenia. ^d This category includes platelet count decreased and thrombocytopenia.

^e This category includes the preferred terms fatigue, asthenia, and malaise. ^f Grade 1 alopecia: T-DXd = 26.5%, T-DM1 = 2.3%; grade 2, T-DXd = 9.3%.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Adverse Events of Special Interest¹

Adjudicated as Drug-Related ILD/Pneumonitis ^a , n (%)						
n (%)	Grade 1	Grade2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF Decrease, n (%)						
n (%)	Grade 1	Grade2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4) ^b	6 (2.3) ^c	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4) ^c	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

^a Patients with prior history of ILD/pneumonitis requiring steroids were excluded. ^b Left ventricular dysfunction. ^c Decreased ejection fraction.

1. Cortés J et al. ESMO 2021. Abstract LBA1.

DESTINY-Breast03: Conclusions¹

In the first randomized phase 3 trial in breast cancer, T-DXd demonstrated:

- Highly clinically meaningful and statistically significant improvement in PFS compared with T-DM1 in patients with HER2+ mBC
 - PFS HR of 0.28 ($P = 7.8 \times 10^{-22}$)
 - Consistent benefit seen across key subgroups and efficacy endpoints, with a confirmed ORR for T-DXd of 79.7% versus 34.2% for T-DM1 (CR, 16.1% vs 8.7%)

Encouraging OS trend at the time of first interim analysis

- 12-month OS rate for T-DXd was 94.1% vs 85.9% for T-DM1

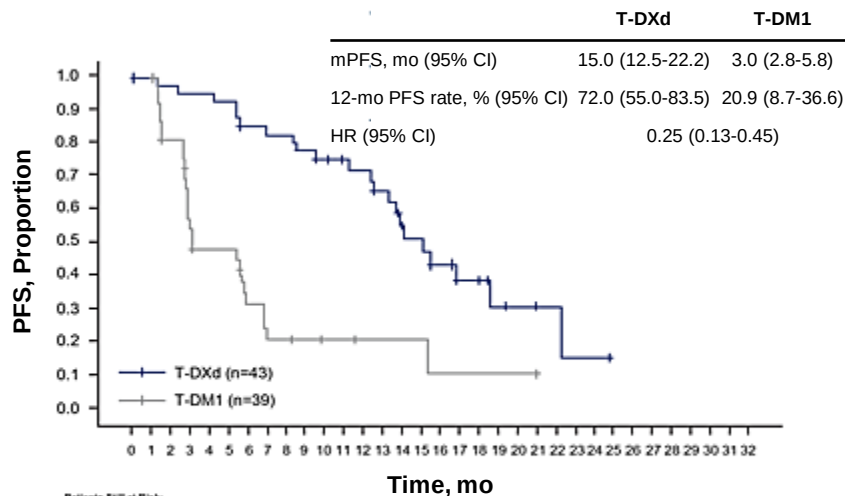
A safety profile that is comparable between the 2 arms

- Similar rates of all grade and grade ≥ 3 drug-related TEAEs between arms
- There were no grade 4 or 5 ILD/pneumonitis events in either arm

These data support T-DXd becoming the standard of care for 2L HER2+ mBC

DESTINY-Breast03: PFS in Patients With and Without Brain Mets¹

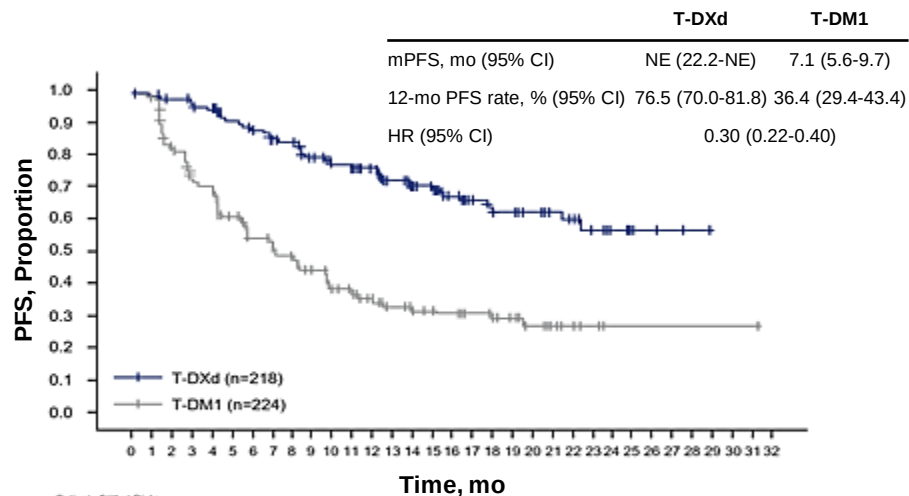
Brain Metastases at Baseline



In patients with BM at baseline, PD was observed:

- In 48.8% (21/43) treated with T-DXd versus 69.2% (27/39) with T-DM1
- In the brain in 42.9% (9/21) treated with T-DXd versus 40.7% (11/27) with T-DM1

No Brain Metastases at Baseline



In patients without BM at baseline, PD was observed:

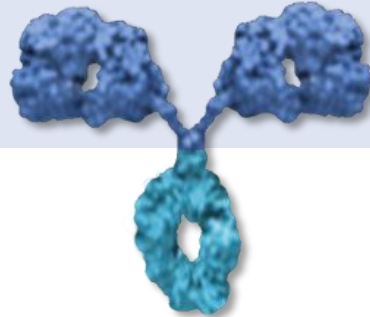
- In 28.9% (63/218) treated with T-DXd versus 57.1% (128/224) with T-DM1
- In the brain in 6.3% (4/63) treated with T-DXd versus 0.8% (1/128) with T-DM1

Margetuximab: A Novel HER2 mAB With a Modified Fc Domain^{1,2}

Trastuzumab

Fab

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



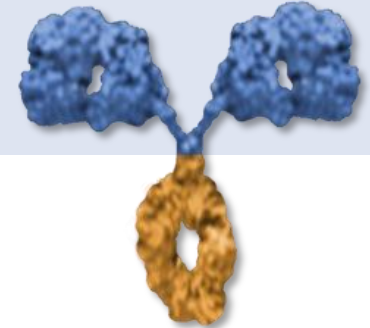
Fc

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

Margetuximab^{1,2}

Fab

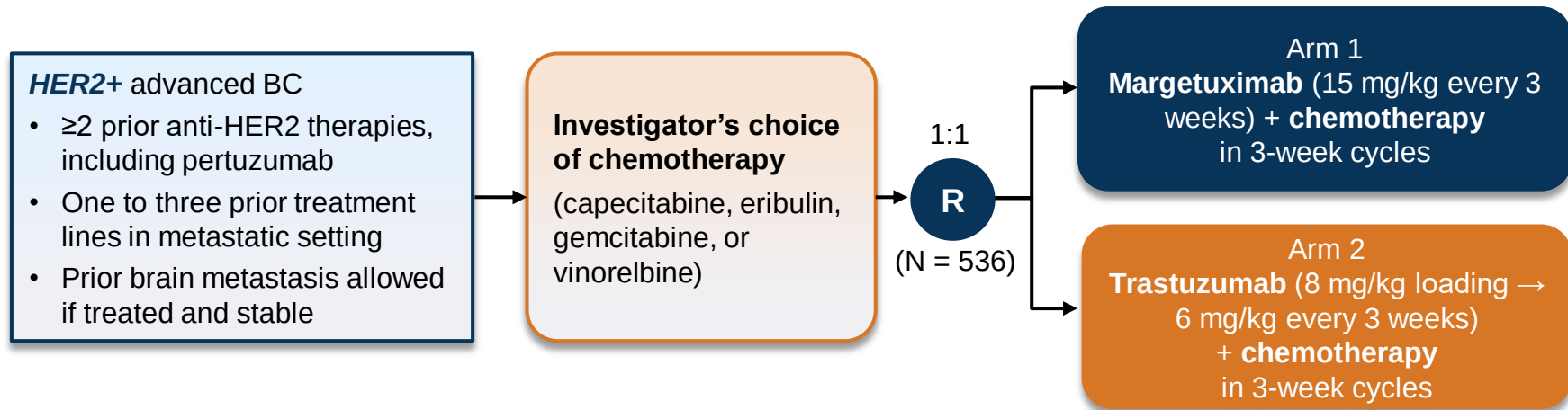
- Same specificity and affinity
- Similarly disrupts signaling



Fc engineering

- ↑ Affinity for activating $\text{Fc}\gamma$ RIIIA (CD16A)
- ↓ Affinity for inhibitory $\text{Fc}\gamma$ RIIB (CD32B)

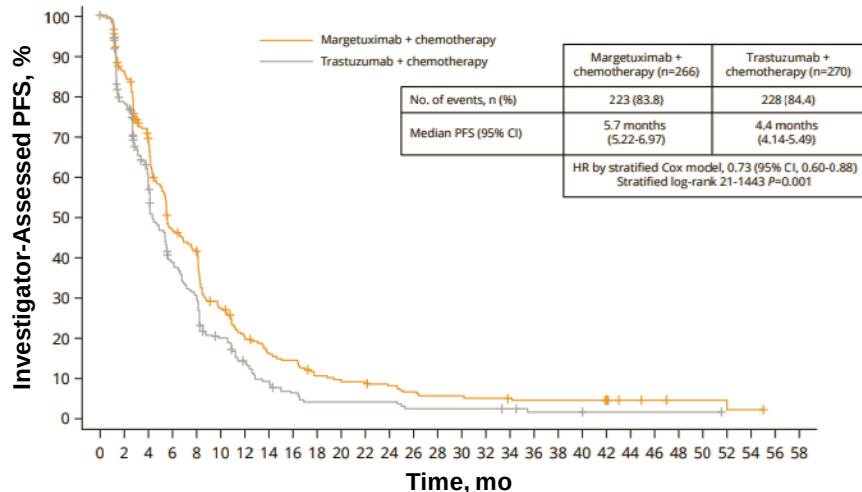
SOPHIA Study: Randomized Phase 3 Design¹



SOPHIA: Final PFS and OS in the ITT Population¹

Final PFS

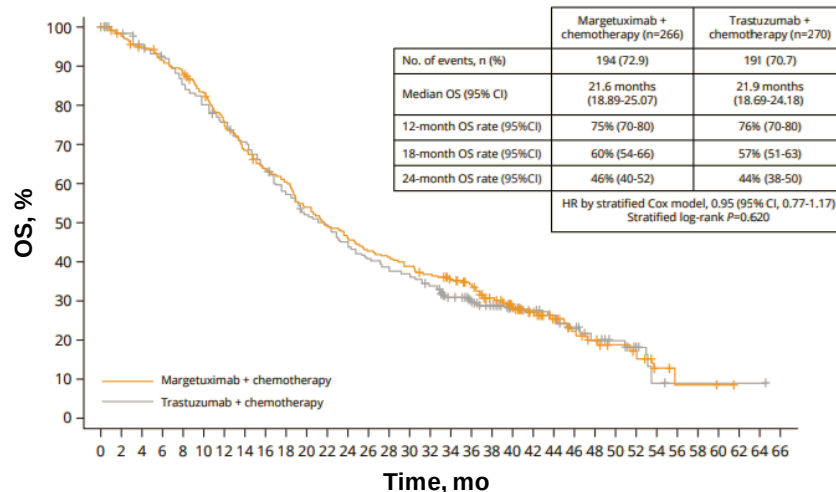
ITT Population (N = 536)



Margetuximab 266 215 169 110 97 62 45 35 31 22 20 19 16 13 11 11 10 9 8 8 7 4 3 2 2 1 1 0
Trastuzumab 270 196 144 89 69 43 29 19 12 8 8 8 5 5 5 4 2 2 2 1 1 1 1 1 1 0

Final OS

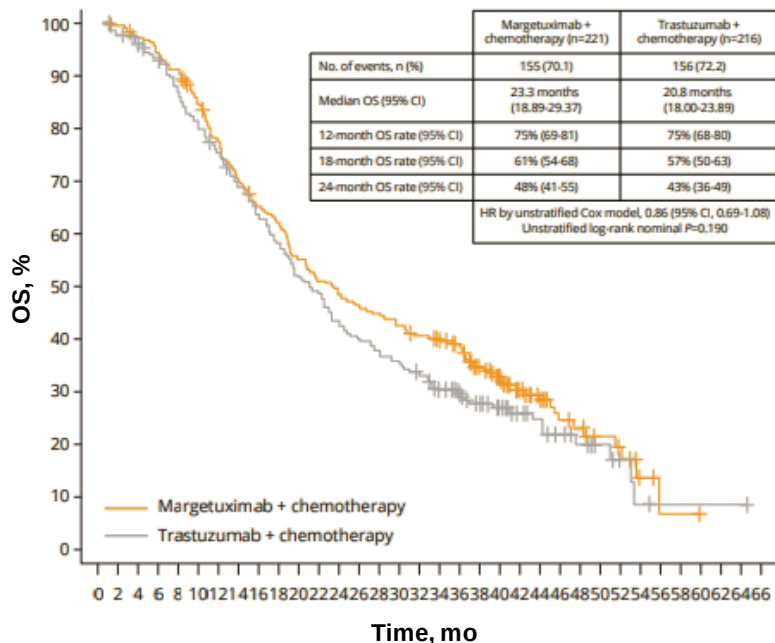
ITT Population (N = 536)



Margetuximab 266 259 249 239 230 214 193 176 163 154 138 126 117 109 105 99 93 85 75 61 45 37 27 21 17 12 8 4 2 2 1 0
Trastuzumab 270 261 248 238 220 207 194 180 161 146 131 124 111 103 95 91 84 72 61 52 41 32 25 19 13 10 5 2 1 1 1 1 1 0

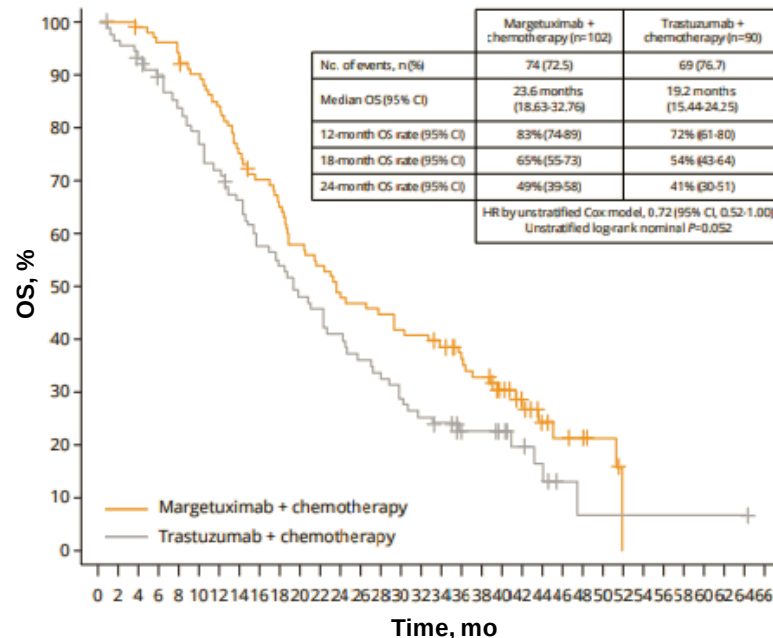
SOPHIA Trial: Exploratory OS in CD16A-185 F Carriers and Homozygotes¹

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



Margetuximab 2212192122041961811611481381301171081029794908579705742342519161173110
Trastuzumab 21621020119217616515414112811710598878175716657464031231814107421111110

CD16A-158FF Homozygotes, n = 192 (38%)



Margetuximab 1021021009794908375696457534846444140373229201697640
Trastuzumab 908581767166615548454038343027242119151410752111111110

NCCN v1.2022 Recommendations: Advanced HER2+ Disease¹

Setting	Regimen	Evidence Level
First line	Pertuzumab + trastuzumab + docetaxel (THP)	
	Trastuzumab deruxtecan (T-DXd) (if recurrence <6 mo of neoadjuvant/adjuvant therapy or <12 mo of pertuzumab)	1
Second line	Trastuzumab deruxtecan (preferred)	1
	Trastuzumab emtansine (T-DM1) (other recommended)	2A
	Tucatinib/capecitabine/trastuzumab	
Third line and beyond (optimal sequence unknown)	Tucatinib/capecitabine/trastuzumab (preferred in those with systemic and CNS metastases)	1
	Trastuzumab deruxtecan (T-DXd) (if not used in the second line)	2A
	Trastuzumab emtansine (T-DM1) (no data regarding benefits after T-DXd)	
	Trastuzumab + docetaxel or vinorelbine or paclitaxel (± carboplatin)	2A
	Capecitabine + trastuzumab or lapatinib	2A
	Trastuzumab + lapatinib	2A
	Neratinib + capecitabine	2A
	Margetuximab + chemotherapy	2A

1. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Case Continues

Patient

- She connected with a local cancer support community and initiates therapy with docetaxel, trastuzumab, and pertuzumab

Presentation

- After two cycles, she is symptomatically much improved and able to walk her dog twice daily again
- After four cycles she has 70% reduction in tumor burden, and after 6 cycles, she has a CR in the liver
- She is developing moderate neuropathy as well as edema related to the taxane; drops docetaxel but continues trastuzumab and pertuzumab
- She initiates an aromatase inhibitor concurrently with the trastuzumab and pertuzumab

20 Months Later

- She has progression in the liver, with a new 1-cm metastasis, as well as new lung metastases



Discussion



- What would you recommend for this patient for second-line therapy?
- Do you use brain imaging to help select therapy in second-line and later settings?
- How would you sequence the next options after this line of therapy?
- Where are you currently using neratinib in the metastatic setting?
- When/where are you using margetuximab? Should we be testing patients for the FcGR11A genotype?
- Any strategies you would recommend to avoid treatment-related toxicities associated with the different HER2-targeted therapies?

*Let's hear from **Jamil Rivers** again, who presents a call to action from our 3 patient advocacy partner organizations*

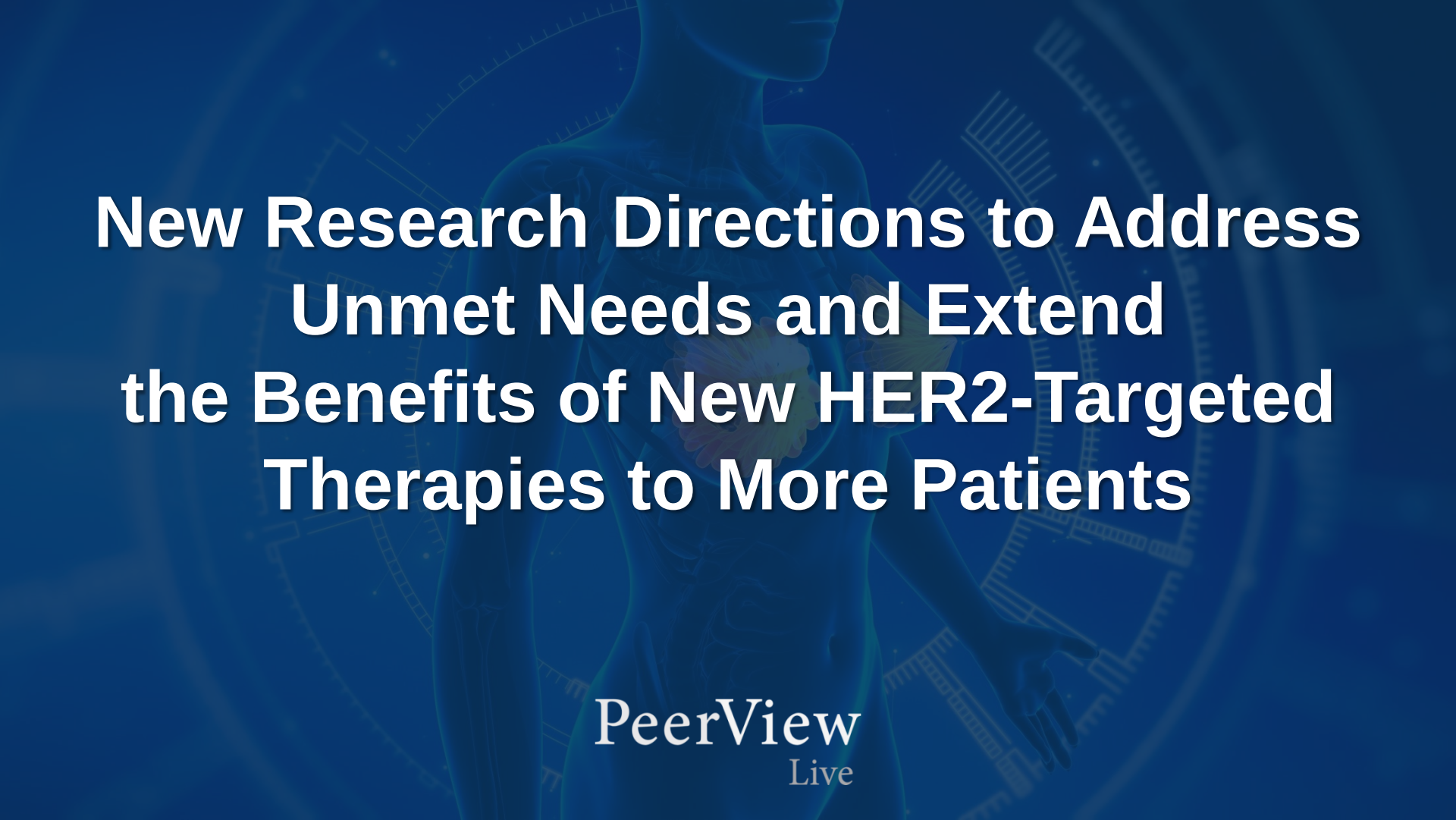


METAVIVOR

Metastatic Breast Cancer Research, Support and Awareness



PeerView
Live

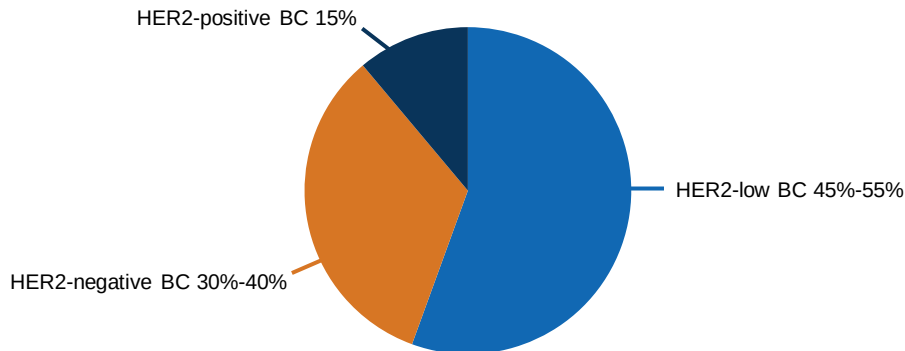
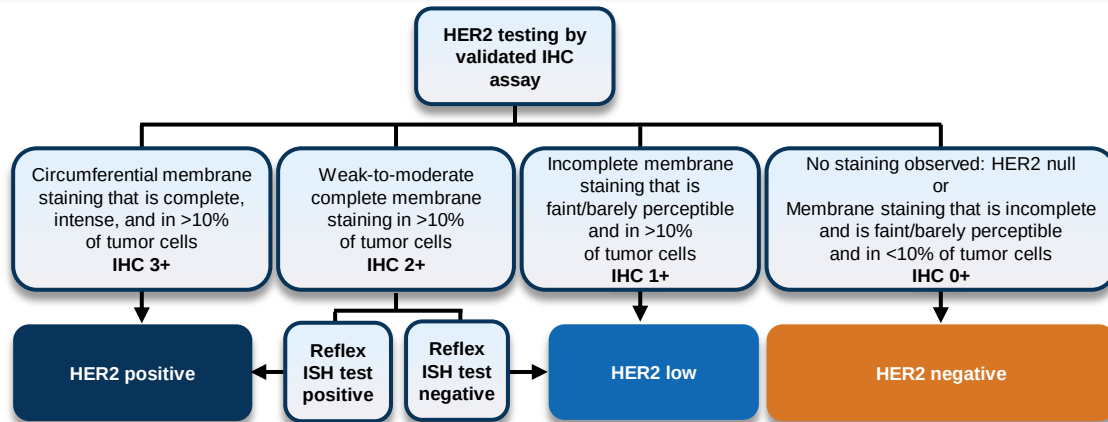


New Research Directions to Address Unmet Needs and Extend the Benefits of New HER2-Targeted Therapies to More Patients

PeerView
Live

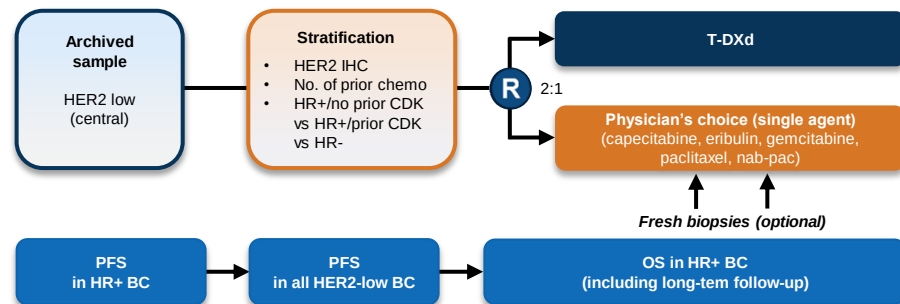
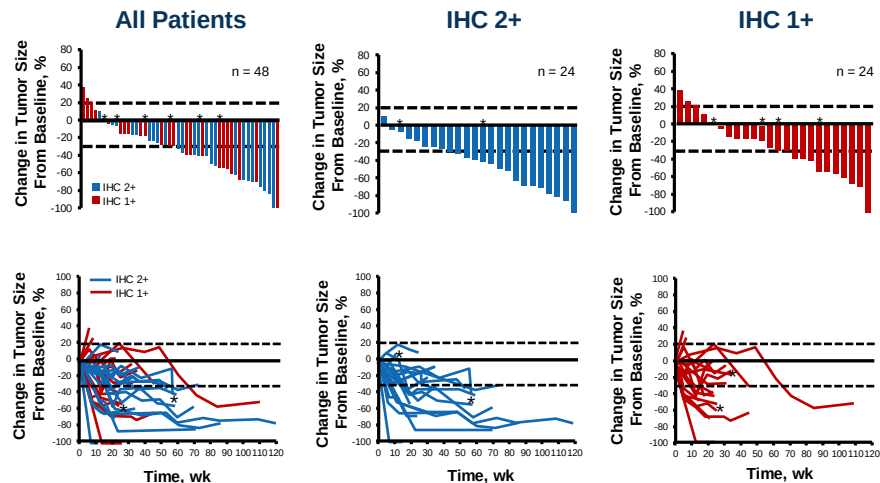
Defining and Detecting HER2-Low Breast Cancer¹

- HER2-low breast cancers (IHC 1+ or 2+ with negative ISH) account for about half of all breast cancers and currently have no indication for HER2-targeted treatment
- Is there an opportunity to change that?



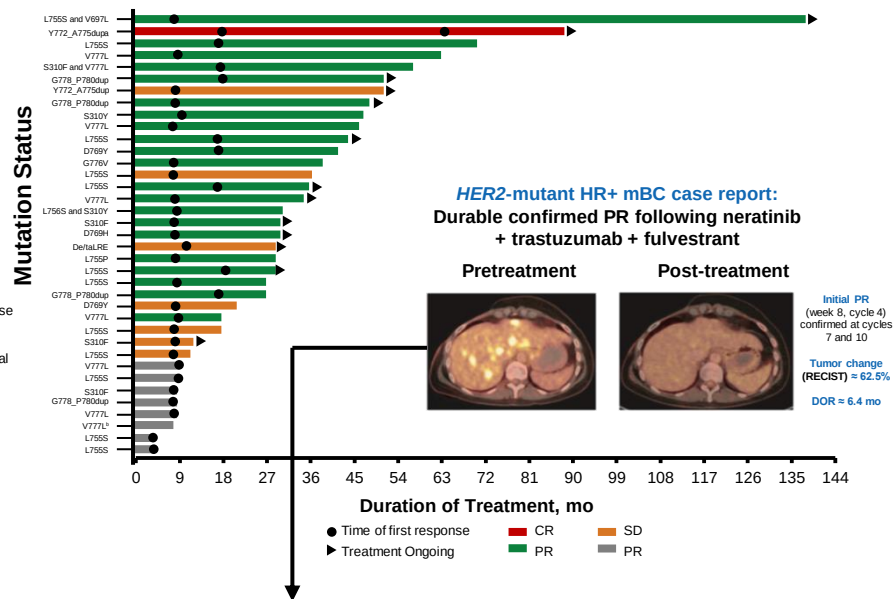
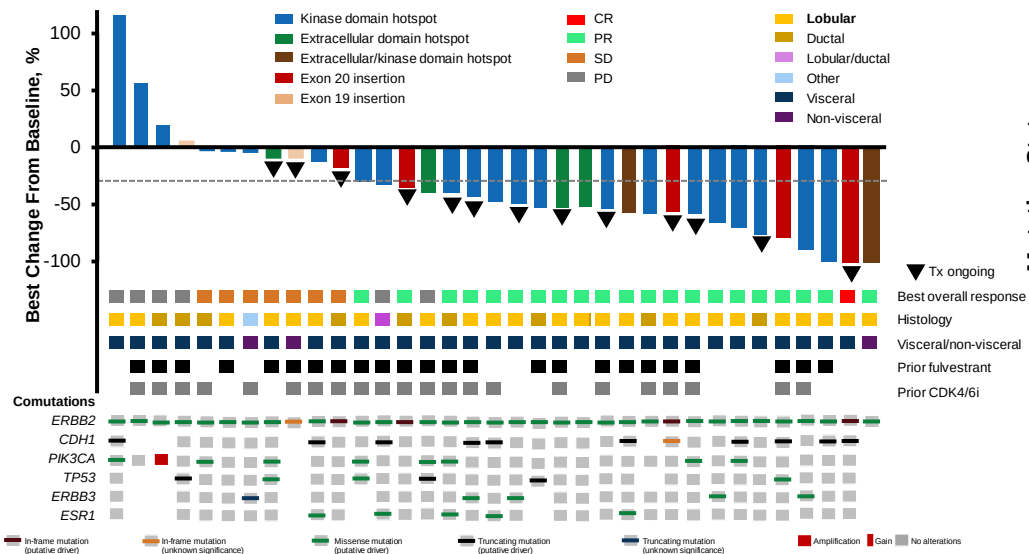
Progress in Targeted Treatment of HER2-Low Breast Cancer¹

- Recent phase 1 trials of anti-HER2 ADCs have shown promising activity in HER2-low mBC¹
- DESTINY-Breast04: trastuzumab deruxtecan vs chemotherapy in HER2-low (IHC 2+/ISH- or IHC 1+) breast cancer



- If activity of HER2-targeted therapies is confirmed in HER2-low BC, the % of BC patients deriving benefit from these agents could reach up to 60%-70% → evolution from the current HER2-binary paradigm to a spectrum of expression

SUMMIT Trial: Neratinib for *HER2*-Mutant mBC¹



Updated data from the SUMMIT trial will be presented on
Friday, December 10 at 11:00-11:15 AM CT.
Jhaveri K et al. SABCS 2021. Abstract GS4-10

38-year-old female, diagnosed Nov. 2013:
ER+/HER2- (V777L), stage T2N0M0 invasive lobular carcinoma, ECOG PS 0
4 prior lines of tx for mBC (including prior CDK4/6i and fulvestrant)



Final Open Discussion, Key Takeaways, and Audience–Faculty Q&A

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