Quali novità nel setting metastatico?

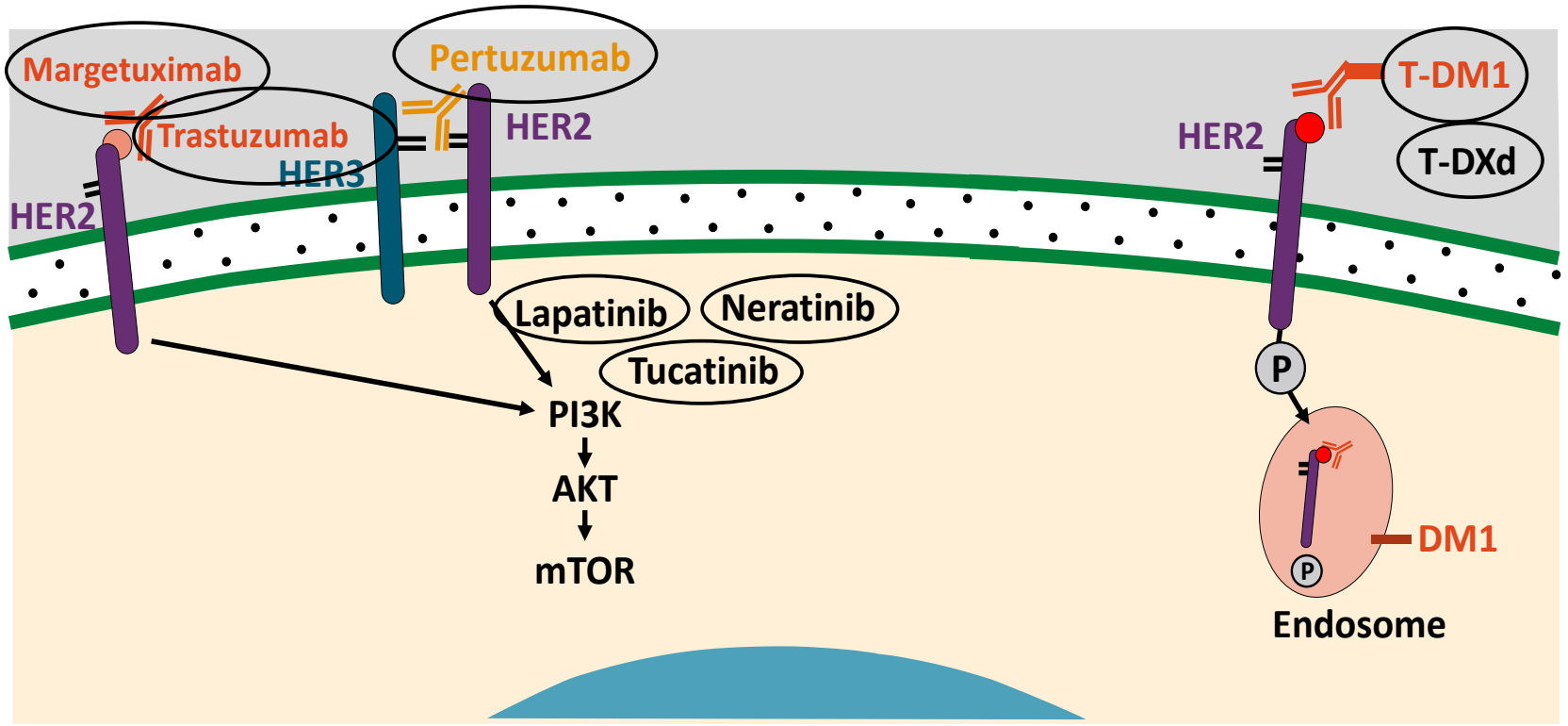
Laura Merlini

Vicenza

Disclosures

- Novartis
- Eli Lilly
- Amgen
- Roche

2021: 8 FDA-Approved HER2-Targeted Agents for MBC



Adapted from Gajria. *Expert Rev Anticancer Ther*. 2011;11:263.

Agenda

- **New oral tyrosine kinase inhibitors**

  -Neratinib

  - Tucatinib

- **Antibody drug coniugates**

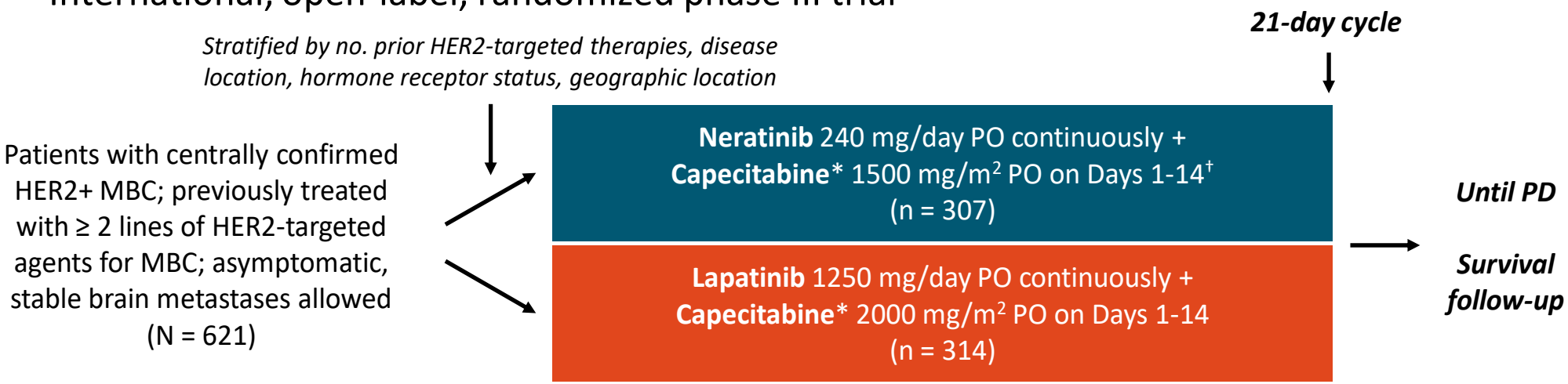
  - Trastuzumab deruxtecan

- **Fc engineered antibodies**

  - Margetuximab

NALA: Neratinib/Cape vs Lapatinib/Cape in HER2+ MBC With ≥ 2 Prior Lines of HER2-Targeted Agents

- International, open-label, randomized phase III trial



*BID in 2 evenly divided doses. †Loperamide administered at 4 mg with first neratinib dose followed by 2 mg Q4H for first 3 days, followed by 2 mg every 6-8 hrs through end of cycle 1; as needed thereafter.

- Coprimary endpoints: OS, PFS (centrally confirmed)
  - Study positive if either endpoint statistically significant (OS, $P < .04$; PFS, $P < .01$)
- Secondary endpoints: PFS (locally determined), ORR, DoR, CBR, intervention for CNS metastases, safety, PRO
- No endocrine therapy permitted

Saura. J Clin Oncol. 2020; 38:3138.

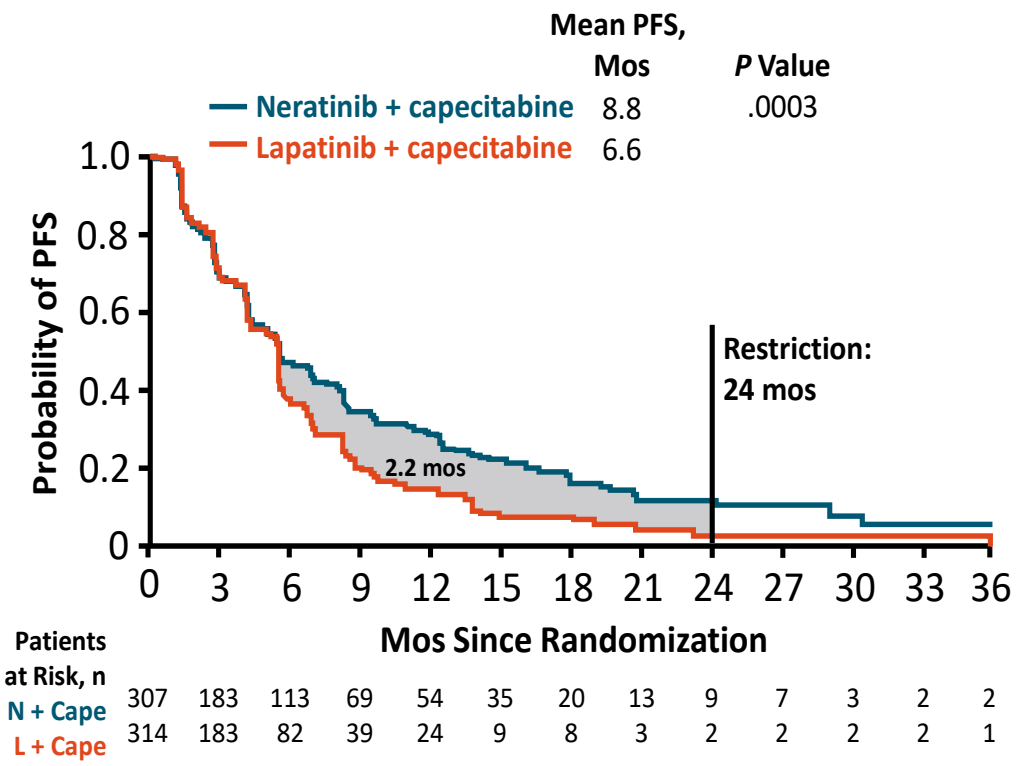
Baseline characteristics

	Neratinib + Capecitabine (n=307)	Lapatinib + Capecitabine (n=314)
Age <65 years, n (%)	244 (79)	248 (79)
Geographic region, n (%)		
Europe	121 (39)	123 (39)
North America	59 (19)	65 (21)
Rest of world	127 (41)	126 (40)
HR+ (ER+ and/or PR+), n (%)	181 (59)	186 (59)
Disease location at enrollment, n (%)		
Non-visceral only	60 (20)	61 (19)
Visceral	247 (80)	253 (81)
De novo metastatic disease, n (%)	139 (45)	136 (43)
No. of prior HER2 targeted therapies for MBC, n (%)		
2	215 (70)	215 (68)
≥3	92 (30)	99 (32)
Prior HER2 therapies for MBC, n (%)		
Trastuzumab only	124 (40)	113 (36)
Trastuzumab + pertuzumab	24 (8)	23 (7)
Trastuzumab + T-DM1	58 (19)	64 (20)
Trastuzumab + pertuzumab + T-DM1	101 (33)	114 (36)

Presented By Cristina Saura at 2019 ASCO Annual Meeting

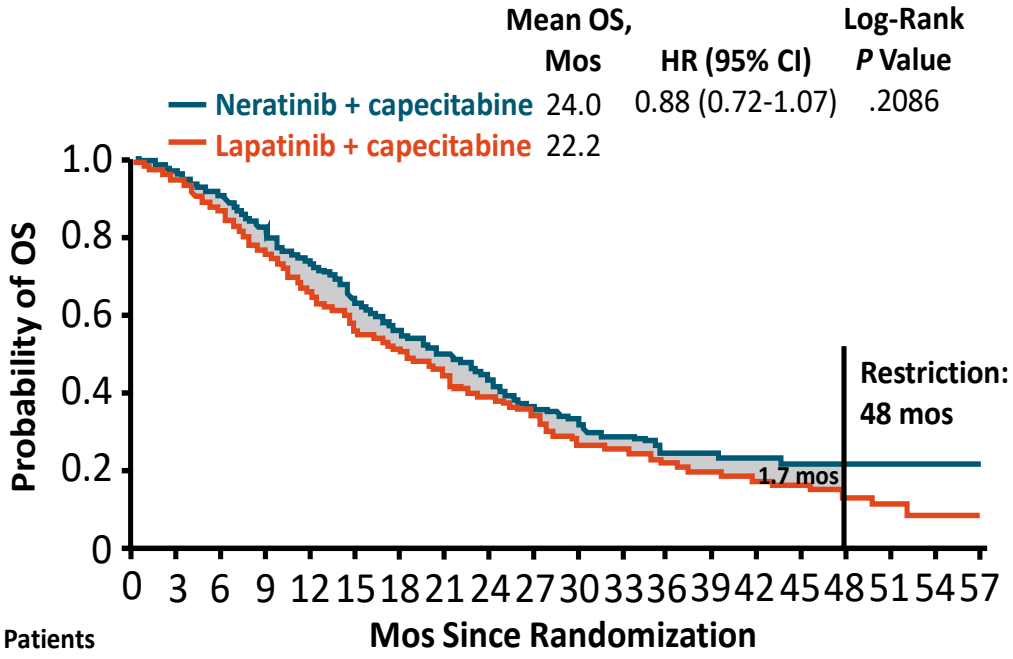
NALA: Survival

PFS (Prespecified Means Analysis)



Patients at Risk, n													
N + Cape	307	183	113	69	54	35	20	13	9	7	3	2	2
L + Cape	314	183	82	39	24	9	8	3	2	2	2	2	1

OS (Coprimary Endpoint)

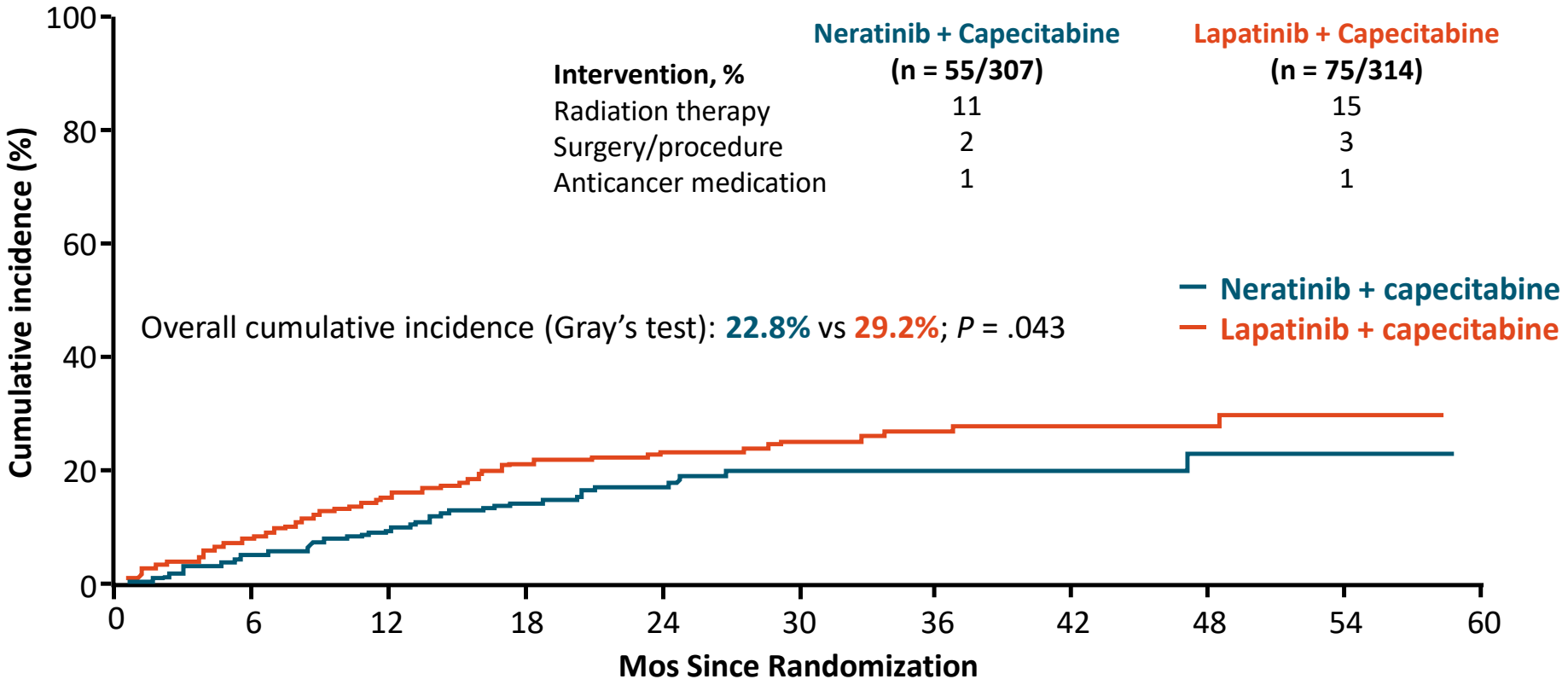


Patients at Risk, n																			
N + Cape	307	294	275	244	220	182	142	112	82	64	47	34	28	18	15	13	6	4	2	1
L + Cape	314	303	273	240	208	170	132	107	84	67	47	36	27	22	17	12	8	4	3	1

Saura. J Clin Oncol. 2020;38:3138.

NALA: Time to Intervention for CNS Metastases

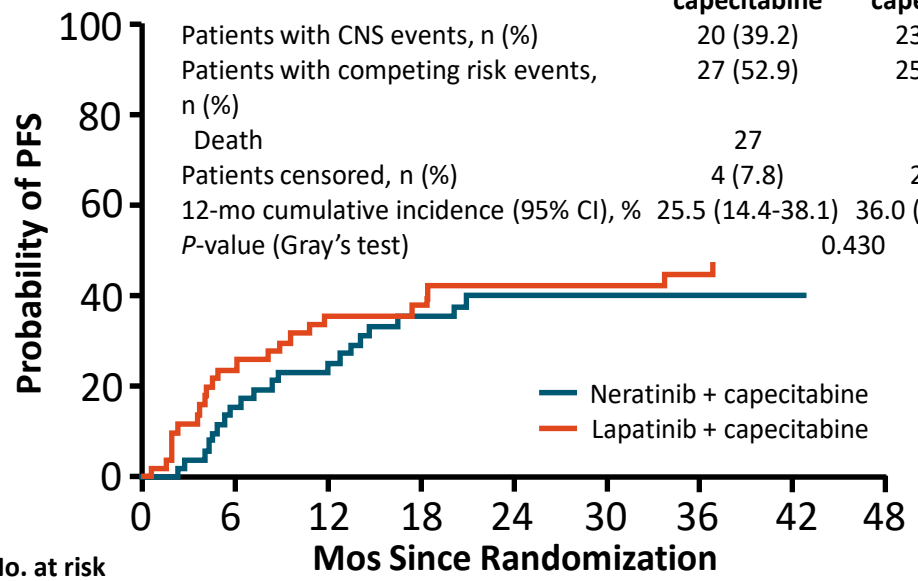
Intervention, %	Neratinib + Capecitabine (n = 55/307)	Lapatinib + Capecitabine (n = 75/314)
Radiation therapy	11	15
Surgery/procedure	2	3
Anticancer medication	1	1



Saura. J Clin Oncol. 2020;38:3138.

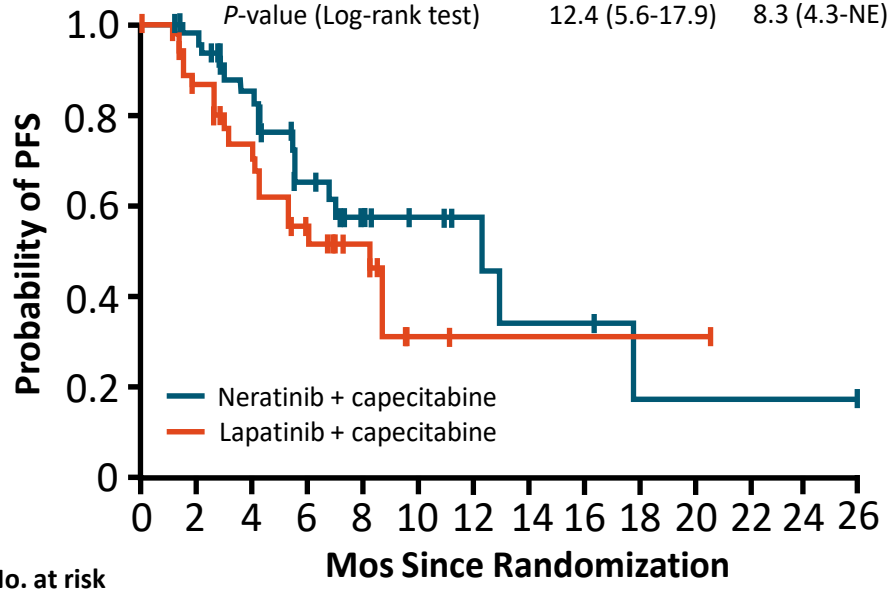
NALA: CNS-Specific Outcomes in Patients with CNS Metastases at Baseline

	Neratinib + capecitabine	Lapatinib + capecitabine
Patients with CNS events, n (%)	20 (39.2)	23 (46.0)
Patients with competing risk events, n (%)	27 (52.9)	25 (50.0)
Death	27	25
Patients censored, n (%)	4 (7.8)	2 (4.0)
12-mo cumulative incidence (95% CI), %	25.5 (14.4-38.1)	36.0 (22.9-49.3)
P-value (Gray's test)	0.430	



No. at risk									
Neratinib + capecitabine	51	39	21	10	3	2	1	1	0
Lapatinib + capecitabine	50	34	17	10	4	2	1	0	0

Patients with events, n (%)	Neratinib + capecitabine	Lapatinib + capecitabine
Median (95% CI), mos	17 (33.3)	21 (42.0)
HR (95% CI)	12.4 (5.6-17.9)	8.3 (4.3-NE)
P-value (Log-rank test)		



No. at risk														
Neratinib + capecitabine	51	46	30	17	12	8	5	3	3	1	1	1	1	1
Lapatinib + capecitabine	50	36	25	15	10	2	1	1	1	1	1	0	0	0

Leptomeningeal disease (LMD): pts with LMD at enrollment (n=3):

- 2 pts received N+C; disease progression:5.6 & 9.8 mos; OS 17.4 &19.8 mos
- 1 pt received L+C; disease progression: 4.3 mos; OS 6.5 mos.

Saura. J Clin Oncol. 2020; 38:3138. Saura. SABCS 2020. Abstr. PD-13-09.

NALA: Safety

- Median duration of treatment numerically longer with neratinib vs lapatinib (5.7 vs 4.4 mos)
- D/c due to treatment-emergent AEs: neratinib arm, 10.9%; lapatinib arm, 14.5%

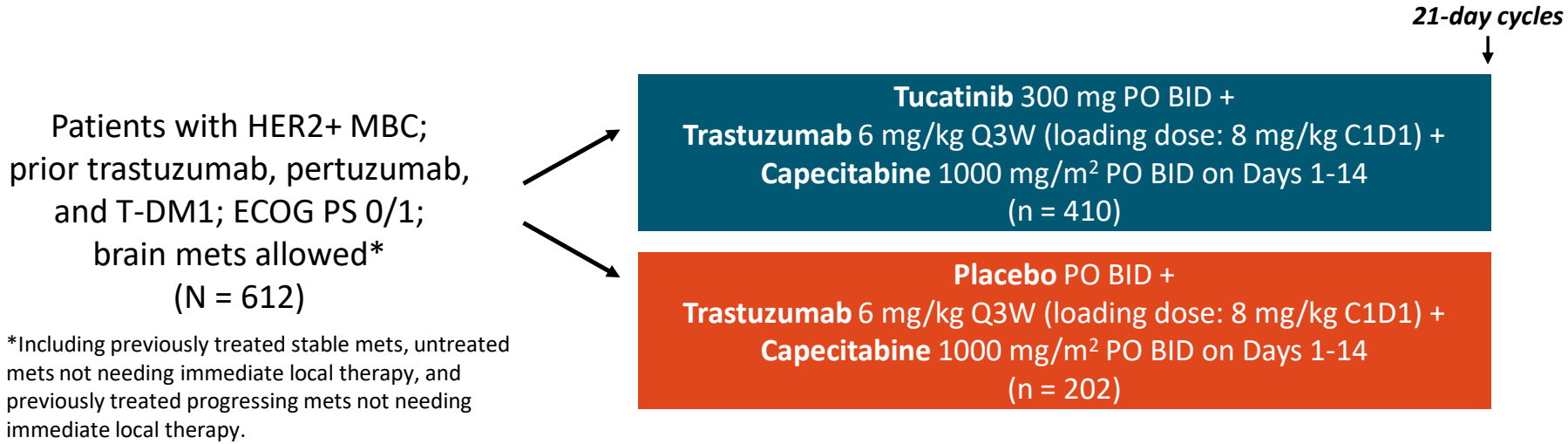
Treatment-Emergent AE, %	Neratinib + Capecitabine (n = 303)		Lapatinib + Capecitabine (n = 311)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Overall	100	61	99	60
▪ Diarrhea	**83**	**24***	66	13*
▪ Hand–foot syndrome	46	10	**56**	11
▪ Hypokalemia	12	5	14	6
▪ Nausea	**53**	4	42	3
▪ Vomiting	**46**	4	31	2
▪ 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

*No grade 4 diarrhea observed

Saura. J Clin Oncol. 2020; 38:3138. Saura. SABCS 2020. Abstr. PD-13-09.

HER2CLIMB: Tucatinib + Trastuzumab + Capecitabine in Previously Treated HER2-Positive MBC

- Randomized, double-blind, placebo-controlled, active comparator phase II trial



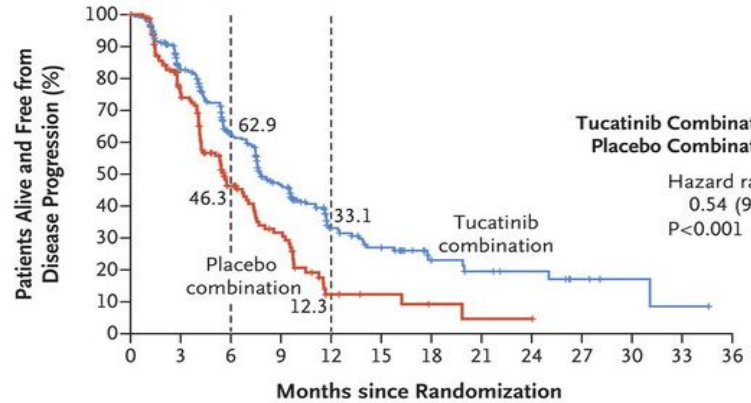
- Primary endpoint: PFS (RECIST v 1.1 by BICR) among first 480 randomized patients

HR+ ~60%; median previous lines of Tx 4; 100% received trast, pert and T-DM1

- Secondary endpoints (total population): OS, PFS in patients with brain mets, ORR in patients with measurable disease, safety in patients who received ≥ 1 dose of study tx

Murthy. NEJM. 2020;382:597.

A Kaplan–Meier Estimates of Progression-free Survival



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	178/320	7.8 (7.5–9.6)
Placebo Combination	97/160	5.6 (4.2–7.1)

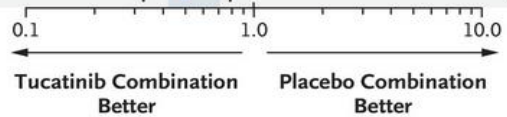
Hazard ratio for disease progression or death, 0.54 (95% CI, 0.42–0.71)
P<0.001

No. at Risk

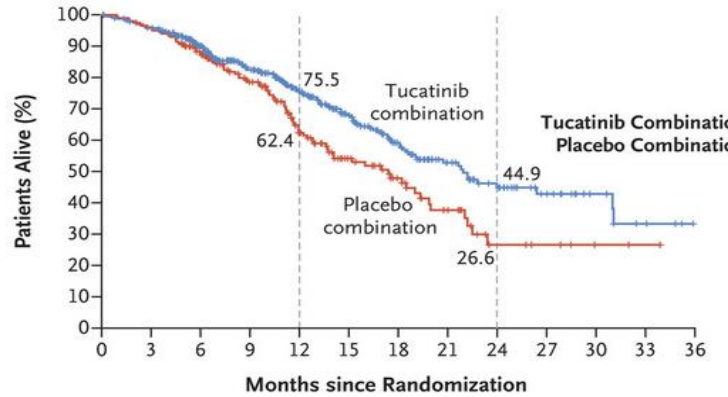
Tucatinib combination	320	235	152	98	40	29	15	10	8	4	2	1	0
Placebo combination	160	94	45	27	6	4	2	1	1	0	0	0	0

B Subgroup Analysis of Progression-free Survival

Subgroup	No. of Events/ Total No.	Hazard Ratio for Disease Progression or Death (95% CI)
Total	275/480	0.54 (0.42–0.71)
Age		
≥65 yr	51/96	0.59 (0.32–1.11)
<65 yr	224/384	0.54 (0.41–0.72)
Race		
White	206/350	0.57 (0.42–0.77)
Nonwhite	69/130	0.46 (0.26–0.82)
Hormone-receptor status		
Positive for ER, PR, or both	172/289	0.58 (0.42–0.80)
Negative for ER and PR	103/191	0.54 (0.34–0.86)
Baseline brain metastasis		
Yes	138/219	0.46 (0.31–0.67)
No	136/260	0.62 (0.44–0.89)
ECOG performance-status score		
0	134/235	0.56 (0.39–0.80)
1	141/245	0.55 (0.38–0.79)
Geographic region		
United States and Canada	179/307	0.57 (0.41–0.78)
Rest of the world	96/173	0.51 (0.33–0.79)



A Kaplan–Meier Estimates of Overall Survival



	No. of Deaths/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	130/410	21.9 (18.3–31.0)
Placebo Combination	85/202	17.4 (13.6–19.9)

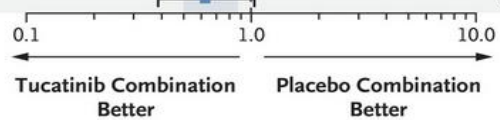
Hazard ratio for death, 0.66 (95% CI, 0.50–0.88)
P=0.005

No. at Risk

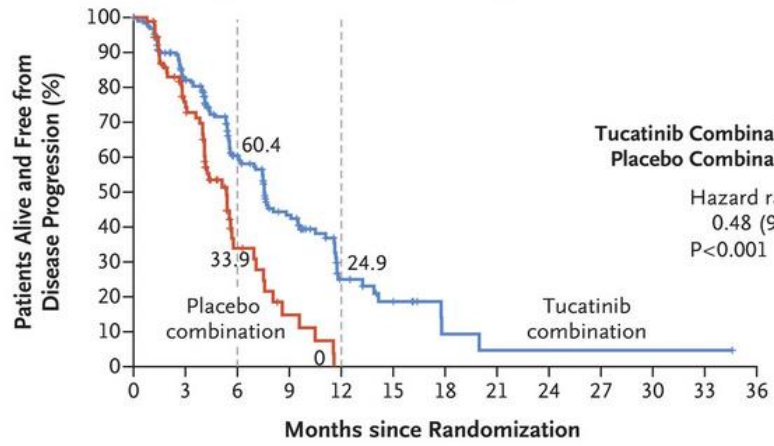
Tucatinib combination	410	388	322	245	178	123	80	51	34	20	10	4	0
Placebo combination	202	191	160	119	77	48	32	19	7	5	2	1	0

B Subgroup Analysis of Overall Survival

Subgroup	No. of Deaths/ Total No.	Hazard Ratio for Death (95% CI)
Total	215/612	0.66 (0.50–0.88)
Age		
≥65 yr	53/116	0.58 (0.32–1.06)
<65 yr	162/496	0.69 (0.50–0.95)
Race		
White	160/444	0.69 (0.50–0.96)
Nonwhite	55/168	0.51 (0.28–0.93)
Hormone-receptor status		
Positive for ER, PR, or both	128/370	0.85 (0.59–1.23)
Negative for ER and PR	87/242	0.50 (0.31–0.80)
Baseline brain metastasis		
Yes	114/291	0.58 (0.40–0.85)
No	101/319	0.72 (0.48–1.08)
ECOG performance-status score		
0	81/298	0.51 (0.33–0.80)
1	134/314	0.84 (0.59–1.20)
Geographic region		
United States and Canada	148/369	0.68 (0.48–0.95)
Rest of the world	67/243	0.63 (0.39–1.03)



A Kaplan–Meier Estimates of Progression-free Survival among Patients with Brain Metastases



	No. of Events/ No. of Patients	Median Duration (95% CI)
		mo
Tucatinib Combination	106/198	7.6 (6.2–9.5)
Placebo Combination	51/93	5.4 (4.1–5.7)

Hazard ratio for disease progression or death, 0.48 (95% CI, 0.34–0.69)
P<0.001

No. at Risk

Tucatinib combination	198	144	78	45	14	8	2	1	1	1	1	1	0
Placebo combination	93	49	12	4	0	0	0	0	0	0	0	0	0

B Subgroup Analysis of Progression-free Survival among Patients with Brain Metastases

Subgroup	No. of Events/ Total No.	Hazard Ratio for Disease Progression or Death (95% CI)
Total	157/291	0.48 (0.34–0.69)
Age		
≥65 yr	24/48	0.41 (0.17–1.01)
<65 yr	133/243	0.51 (0.35–0.76)
Race		
White	112/199	0.49 (0.32–0.75)
Nonwhite	45/92	0.45 (0.23–0.90)
Hormone-receptor status		
Positive for ER, PR, or both	92/166	0.48 (0.31–0.75)
Negative for ER and PR	65/125	0.50 (0.27–0.95)
ECOG performance-status score		
0	76/130	0.68 (0.41–1.15)
1	81/161	0.34 (0.21–0.55)
Geographic region		
United States and Canada	97/177	0.43 (0.27–0.67)
Rest of the world	60/114	0.60 (0.33–1.08)

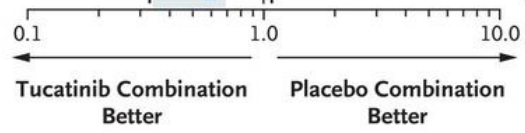
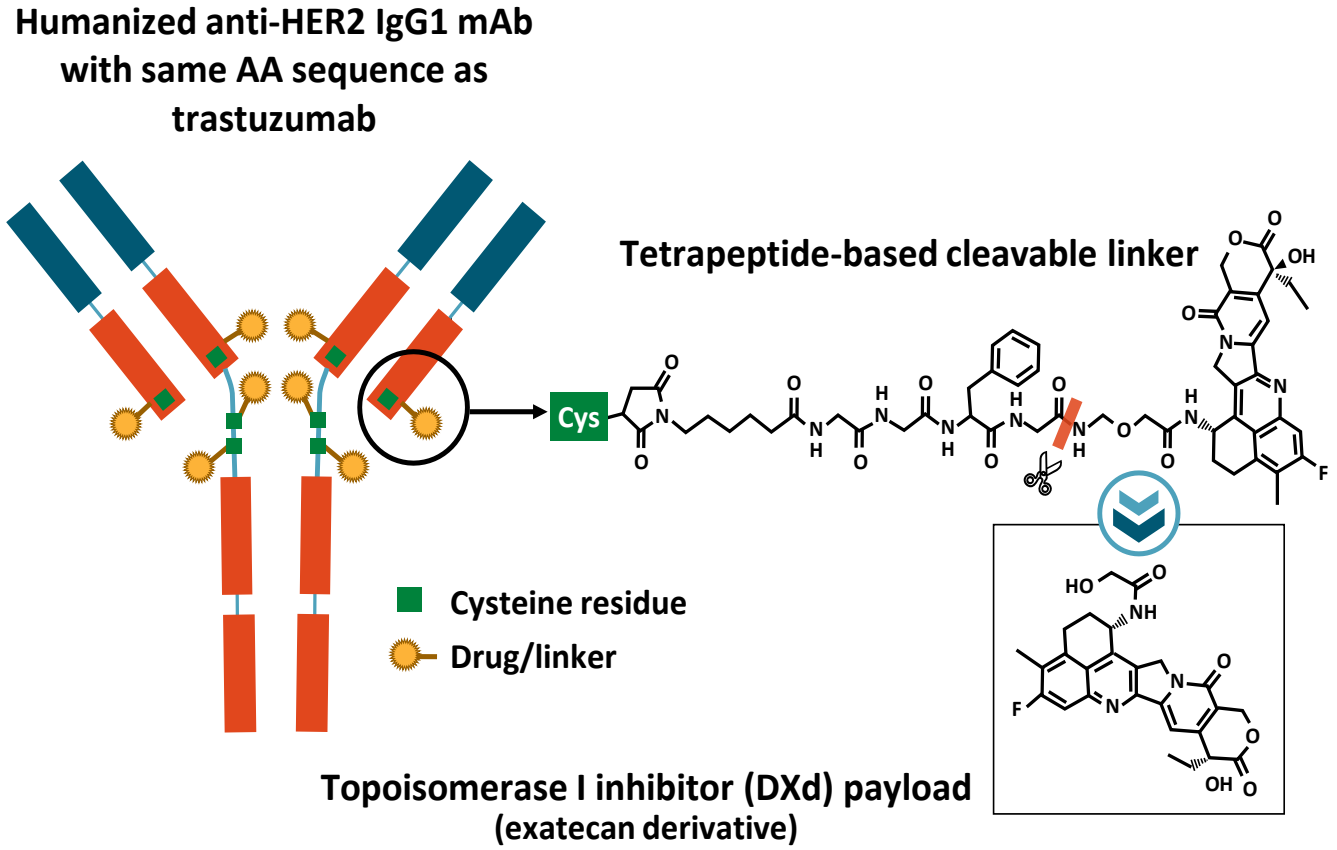


Table 2. Most Common Adverse Events.*

Event	Tucatinib-Combination Group (N=404)		Placebo-Combination Group (N=197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

HER2-Targeted ADC: Trastuzumab Deruxtecan (DS-8201)

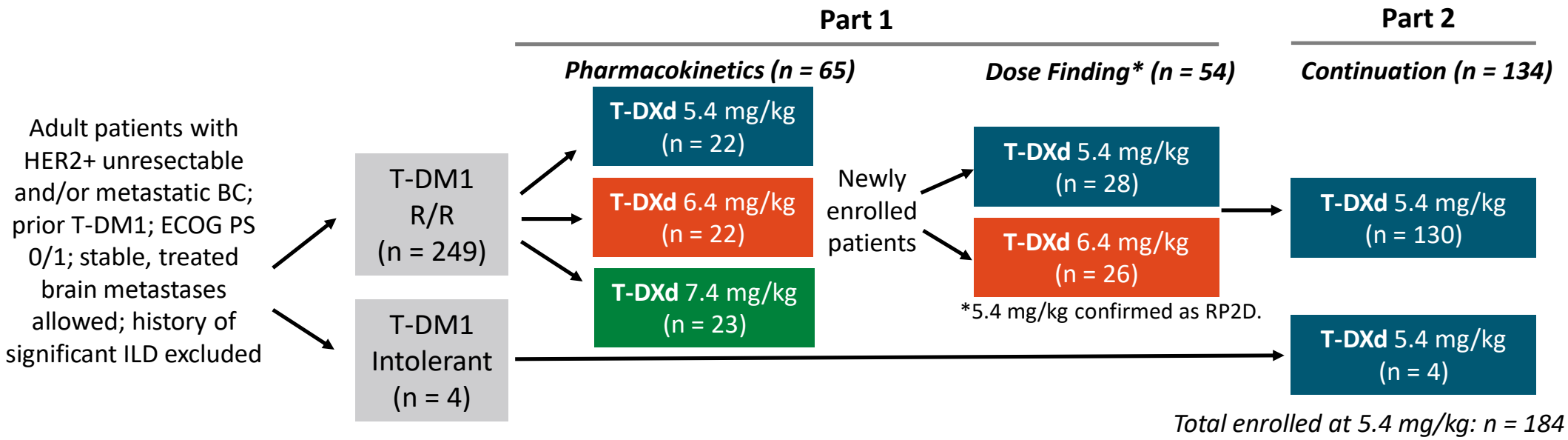


- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

DESTINY-Breast01: Trastuzumab Deruxtecan (T-DXd) in Advanced HER2-Positive Breast Cancer

- Open-label, multicenter, randomized, 2-part phase II study



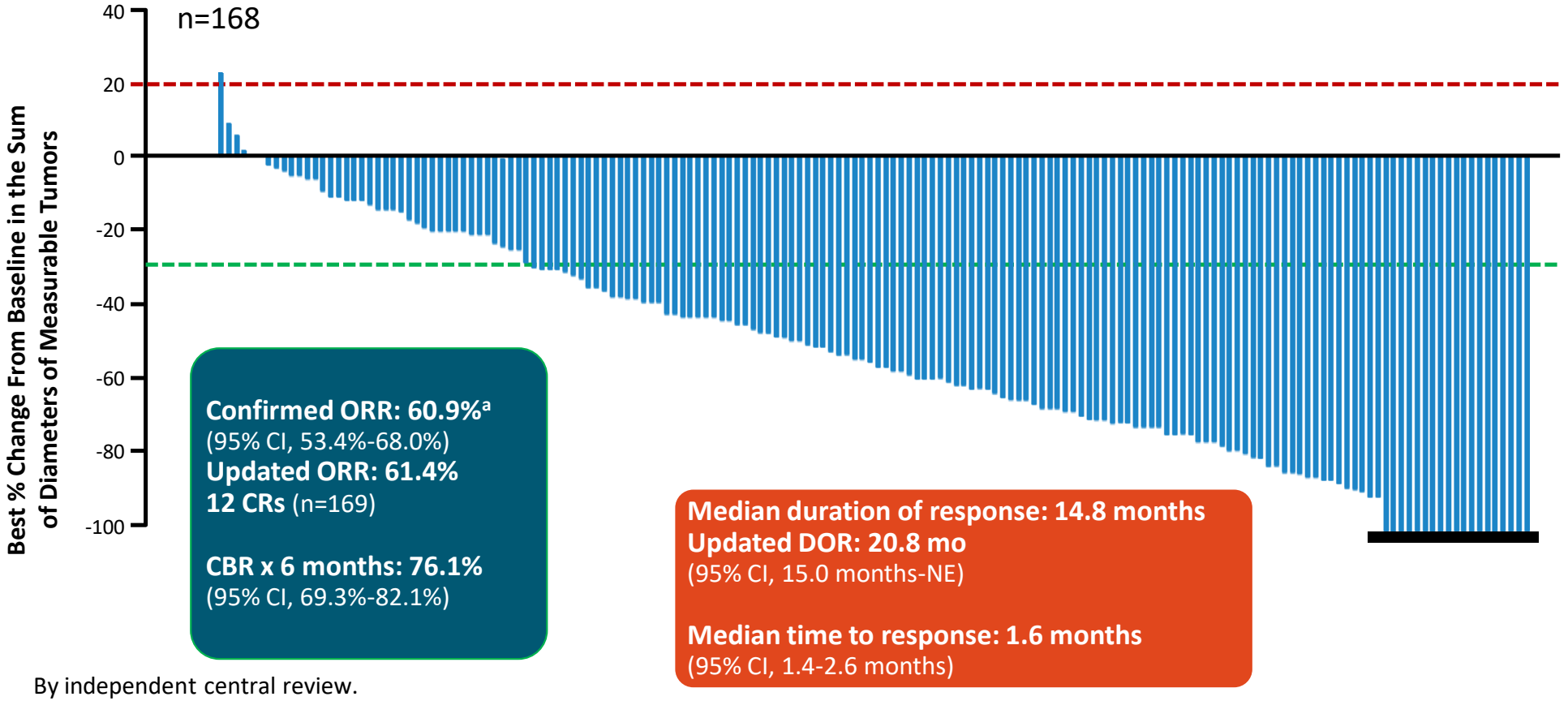
- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: investigator-assessed ORR, DCR, DoR, CBR, PFS, OS, PK, safety
- Data cutoff: August 1, 2019
  - 79 (42%) continuing treatment
  - 105 (57.1%) d/c (mostly for PD, 28.8%)

Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2020;382:610.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients (N = 184)
Age	
Median (range) — yr	55.0 (28.0–96.0)
≥65 yr — no. (%)	44 (23.9)
Female sex — no. (%)	184 (100)
Race — no. (%)†	
Asian	70 (38.0)
White	101 (54.9)
Other	9 (4.9)
Missing data	4 (2.2)
Region — no. (%)	
Europe	68 (37.0)
Asia	63 (34.2)
North America	53 (28.8)
ECOG performance-status score — no. (%)‡	
0	102 (55.4)
1	81 (44.0)
2	1 (0.5)
Hormone-receptor status — no. (%)	
Positive	97 (52.7)
Negative	83 (45.1)
Unknown	4 (2.2)
HER2 expression — no. (%)§	
IHC 3+	154 (83.7)
IHC 1+ or 2+, ISH-positive	28 (15.2)
Missing data	2 (1.1)
Median sum of diameters of target lesions (range) — cm	5.5 (1.2–24.5)
Median no. of previous cancer regimens (range)	6 (2–27)
Previous systemic cancer therapy — no. (%)	
Trastuzumab	184 (100)
Trastuzumab emtansine¶	184 (100)
Pertuzumab	121 (65.8)
Other anti-HER2 therapy	100 (54.3)
Hormone therapy	90 (48.9)
Other systemic therapy	183 (99.5)
Best response to trastuzumab emtansine therapy — no. (%)	
Complete or partial response or stable disease	79 (42.9)
Progressive disease	66 (35.9)
Could not be evaluated	39 (21.2)

DESTINY-Breast01: Updated Best Change in Tumor Size



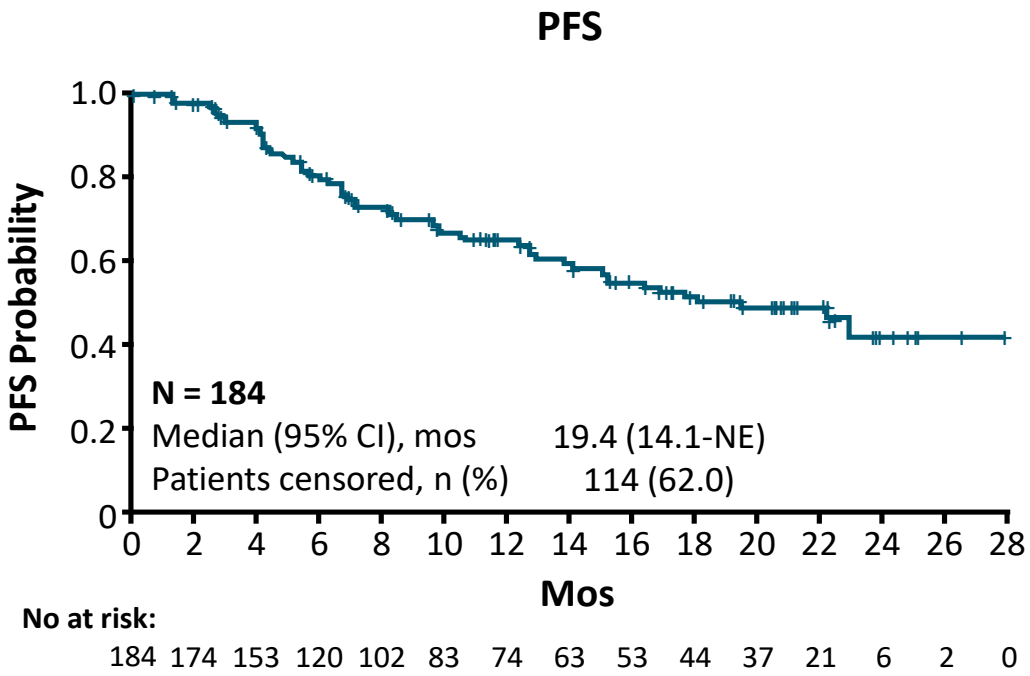
By independent central review.

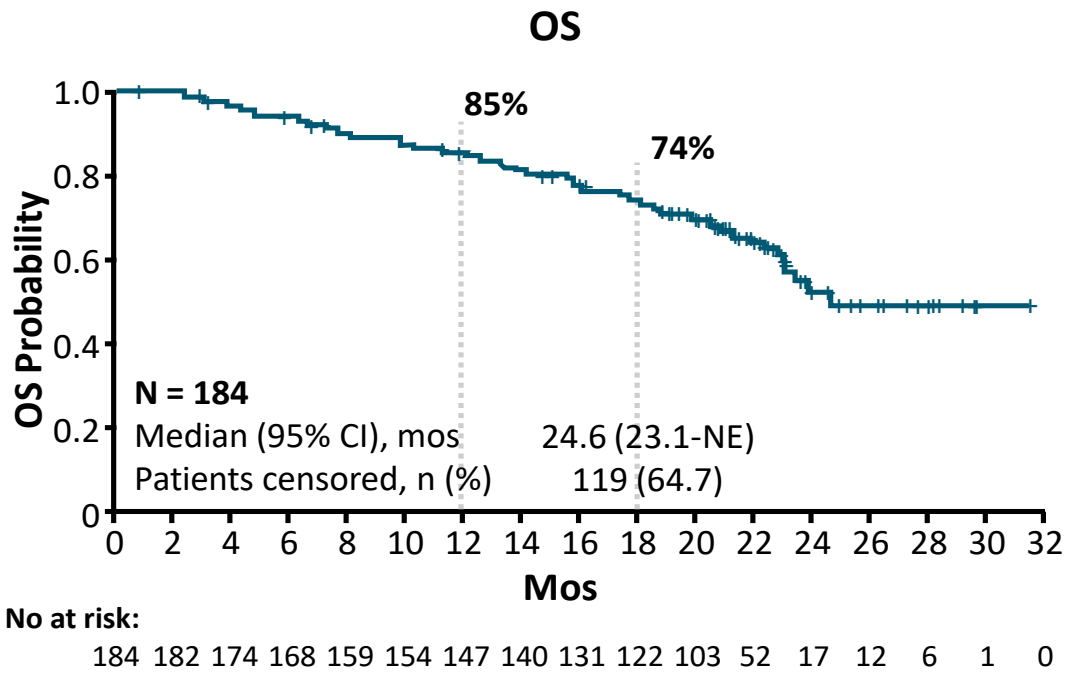
The line at 20% indicates progressive disease; the line at −30% indicates partial response.

[a]Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Modi. NEJM. 2020;382:610. Modi. SABCS 2020. Abstr. PD3-06.

DESTINY-Breast01: Updated PFS and OS

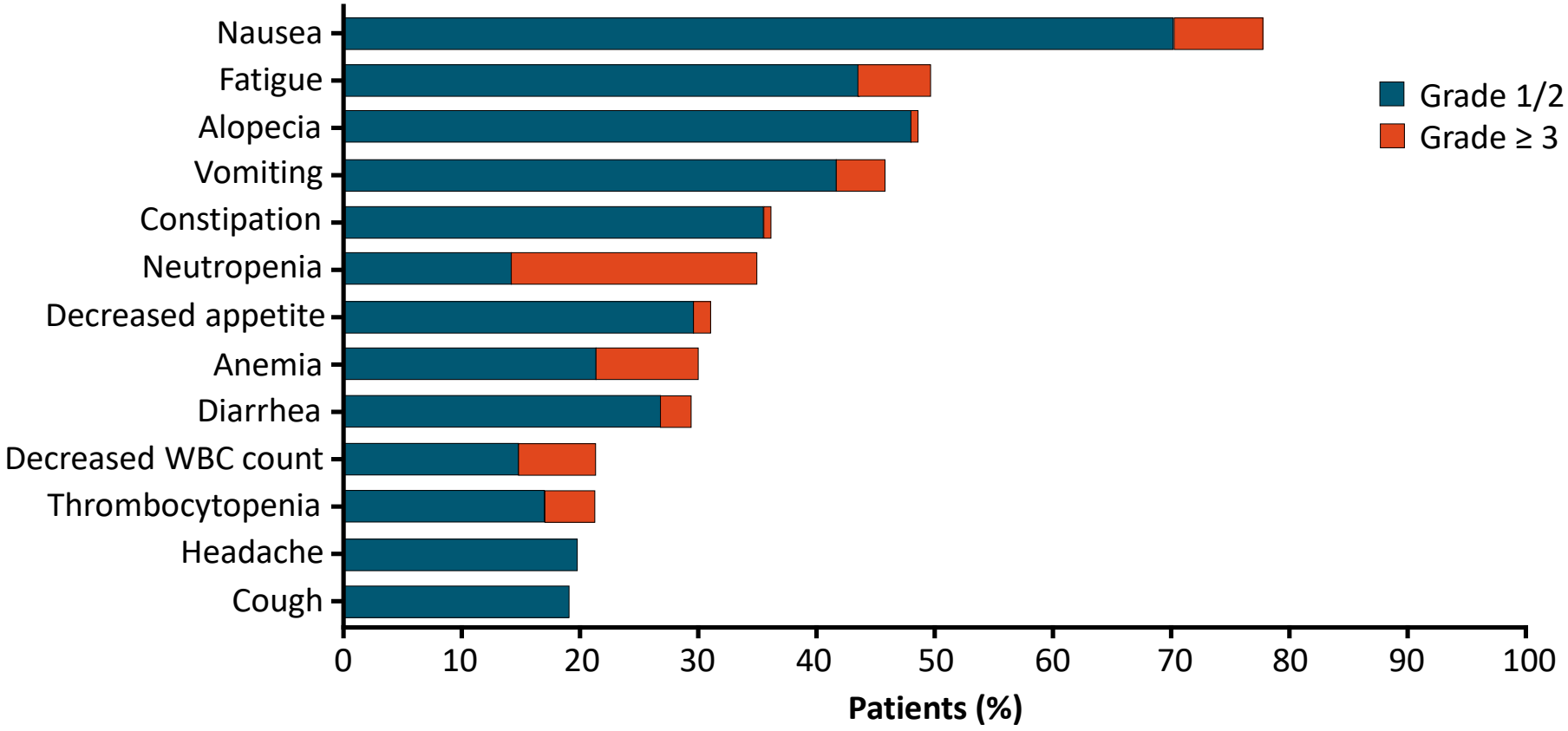




- 20.5 month median follow up (11.1 month at initial reporting)

Modi. NEJM. 2020;382:610. Modi. SABCS 2020. Abstr. PD3-06.

DESTINY-Breast01: AEs in Overall Population



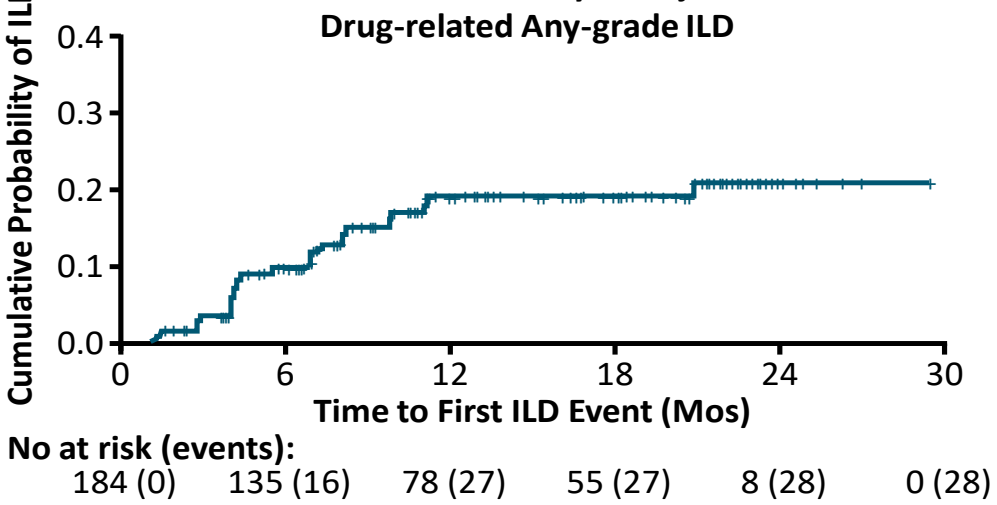
Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2020;382:610.

Warnings and Precautions: ILD/Pneumonitis Monitoring and Management

Interstitial lung disease, 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)**

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.

Cumulative Probability of Adjudicated Drug-related Any-grade ILD



No at risk (events):

184 (0) 135 (16) 78 (27) 55 (27) 8 (28) 0 (28)

Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

Fam-trastuzumab deruxtecan-nxki PI. 2021.

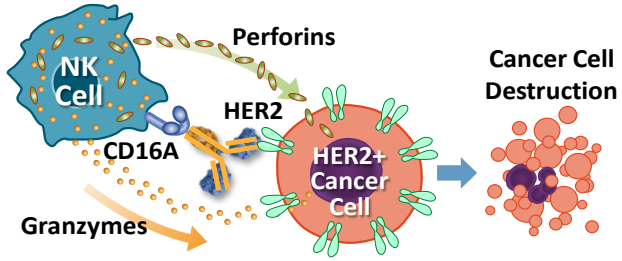
ONGOING TRIALS WITH T-DXT

NCT number	Acronym	Setting	PHASE	Drug(s)	Accrual
NCT03523585	DESTINY-Breast02	aBC, HER2+	III	T-DXT vs trast-cape or lap cape	600
NCT03529110	DESTINY-Breast03	aBC, HER2+	III	T-DXT vs T-DM1	500
NCT03734029	DESTINY-Breast04	aBC, HER2-low	III	T-DXT vs TPC	540
NCT04622319	DESTINY-Breast05	eBC HER2+, post NACT	III	T-DXT vs T-DM1	1600
NCT04494425	DESTINY-Breast-06	HER2-low, HR+ aBC	III	T-DXT vs TPC	850
NCT04538742	DESTINY-Breast07	aBC, HER2+	I/2	T-DXT plus durv. pert. and and pacli.	350
--	DESTINY-Beast09	aBC, HER2+ 1° line	III	T-DXT vs T-DXT+ P vs THP	--
NCT04556773	DESTINY-Breast08	aBC, HER2-low	I	T-DXT with other drugs	185
NCT04420598	DEBBRAH	aBC with CNS met, HER2+	II	T-DXT	39
NCT04539938	HER2CLIMB-04	aBC HER2+	II	T-DXT+Tucatinib	70
NCT04042701	KEYNOTE KN-797	aBC, NSCLS	I	T-DXT with pembrolizumab	115

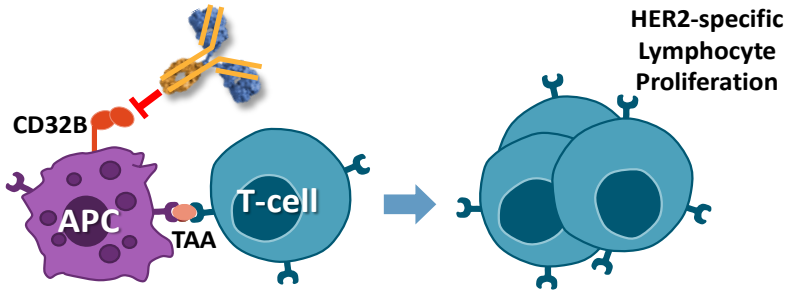
Margetuximab: Fc Engineering Alters Fc Receptor Affinities and Activates the Immune Response

- Margetuximab has the same specificity, affinity to HER2 as trastuzumab with similar ability to disrupt signaling
- However, via Fc engineering with intent to activate immune responses, margetuximab has altered Fc receptor affinity
  - Trastuzumab: WT IgG1 effector domains; binds and activates immune cells
  - Margetuximab: Increased affinity for activating Fcγ RIIIA (CD16A) and decreased affinity for inhibitory Fcγ RIIB (CD32B)

Increased CD16A Affinity:
Enhance Innate Immunity/More Potent ADCC Stimulation



Decreased CD32B Affinity:
Enhance Adaptive Immunity/Increase Immune Activation



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Stavenhagen. Cancer Res. 2007;67:8882.

January 22, 2021

Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer

A Phase 3 Randomized Clinical Trial

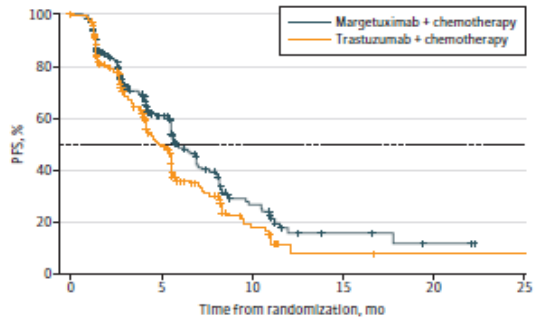
Hope S. Rugo, MD[1]; Seock-Ah Im, MD, PhD[2]; Fatima Cardoso, MD[3]; et al

» Author Affiliations | Article Information

JAMA Oncol. Published online January 22, 2021. doi:10.1001/jamaoncol.2020.7932

Figure 2. Progression-Free Survival (PFS) in the Intention-to-Treat Population

A PFS by CBA, October 2018 cutoff



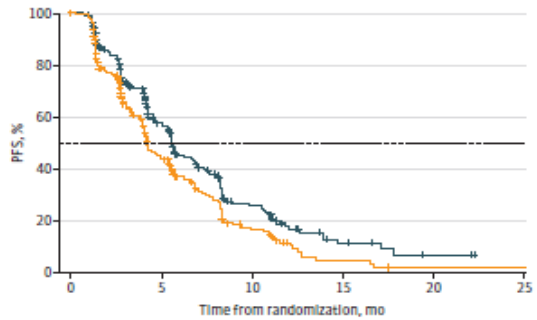
No. at risk

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)
Stratified log-rank $P = .03$
24% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

B PFS by Investigator, October 2018 cutoff



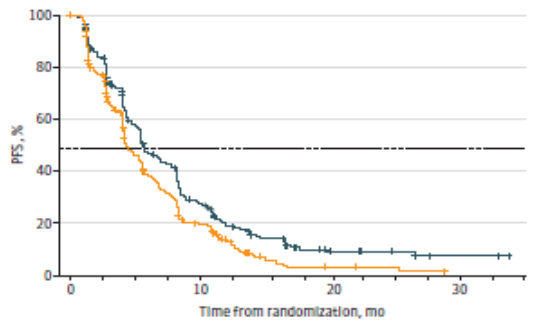
No. at risk

Margetuximab	266	206	155	112	72	61	33	32	16	13	8	7	3	2	2	0
Trastuzumab	270	184	130	87	59	45	25	21	10	5	4	3	1	1	1	1	1	0

	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	160	177
Median PFS (95% CI)	5.6 mo (5.06-6.67)	4.2 mo (3.98-5.39)
3-mo PFS rate	73% (67%-78%)	65% (58%-71%)
6-mo PFS rate	45% (38%-52%)	37% (31%-44%)
9-mo PFS rate	27% (20%-34%)	19% (13%-25%)

HR by stratified Cox model, 0.70 (95% CI, 0.56-0.87)
Stratified log-rank $P = .001$
30% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

C PFS by Investigator, September 2019 cutoff



No. at risk

Margetuximab	266	210	137	100	62	36	25	14	11	6	5	3	2	2	0
Trastuzumab	270	192	108	72	42	20	8	4	3	2	2	1	0		

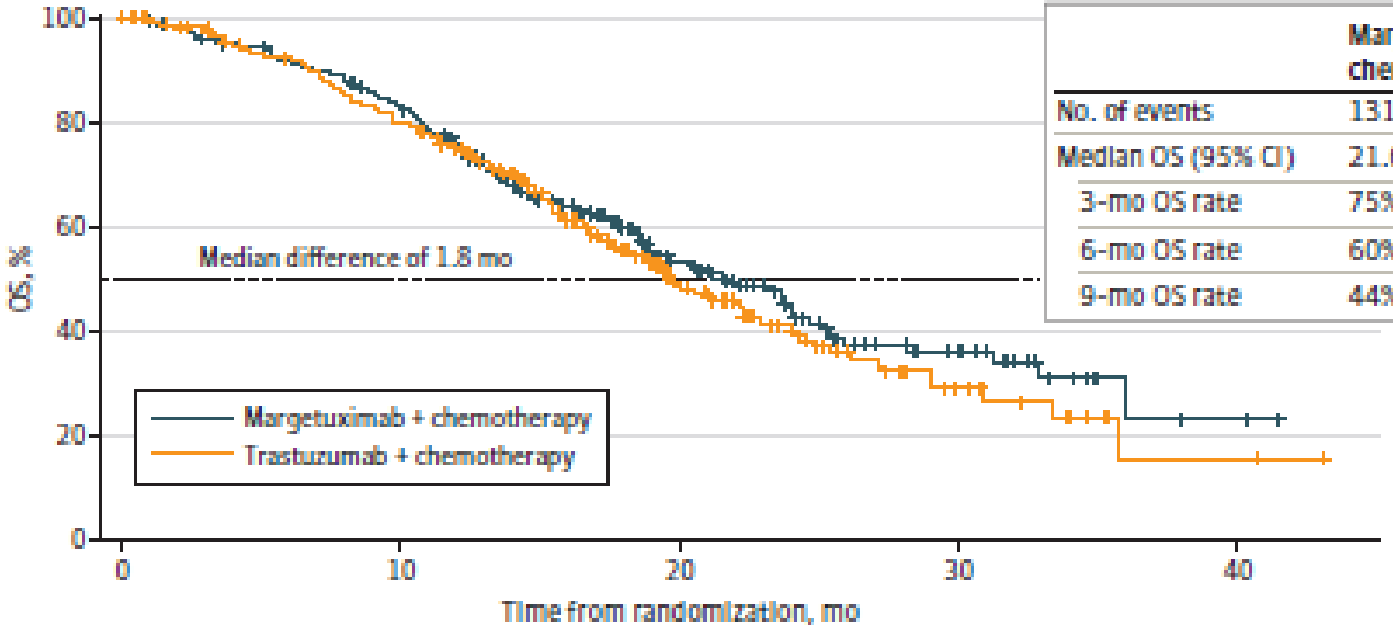
	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	208	222
Median PFS (95% CI)	5.7 mo (5.22-6.97)	4.4 mo (4.14-5.45)
3-mo PFS rate	74% (68%-79%)	67% (61%-72%)
6-mo PFS rate	47% (41%-53%)	38% (32%-45%)
9-mo PFS rate	29% (24%-35%)	20% (16%-26%)

HR by stratified Cox model, 0.71 (95% CI, 0.58-0.86)
Stratified log-rank $P < .001$
29% Risk reduction of disease progression[b]

[a] PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred.

[b] PFS analysis performed as of September 10, 2019, after 430 PFS events occurred.

Figure 3. Overall Survival (OS) in the Intention-to-Treat Population (September 2019 Cutoff)*



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86–24.05)	19.8 mo (17.54–22.28)
3-mo OS rate	75% (70%–80%)	75% (70%–80%)
6-mo OS rate	60% (53%–66%)	56% (49%–62%)
9-mo OS rate	44% (36%–51%)	40% (33%–48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69–1.13)
Stratified log-rank $P = .33$
Median follow-up, 15.6 mo

No. at risk

Margetuximab	266	259	249	239	230	214	188	159	131	107	80	64	47	35	31	22	14	9	3	2	2	0
Trastuzumab	270	260	246	236	218	205	183	160	126	102	74	57	43	30	22	16	10	6	2	2	2	1	0

*OS analysis performed as of September 10, 2019, data cutoff, after 270 of 385 (70%) events needed for final OS analysis had occurred.

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