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Futuras terapias para el cáncer de mama HER2+ y HER3+

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by SOLTI

Outline:

- HER2:

  Current standard treatment landscape in HER2+ mBC

  Third line options and beyond:

  -Guidelines recommendations:

  -Recent efficacy and safety results in the post

  T-DM1 setting

  Margetuximab – SOPHIA

  Neratinib – NALA

  DS8201 – DESTINY-Breast01

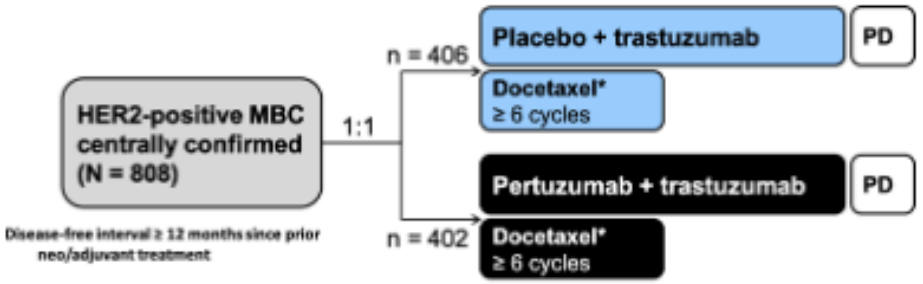
  Tucatinib – HER2CLIMB

- HER3:

  Signaling and targeted therapy in BC

Current standard treatment: First Line:

CLEOPATRA TRIAL

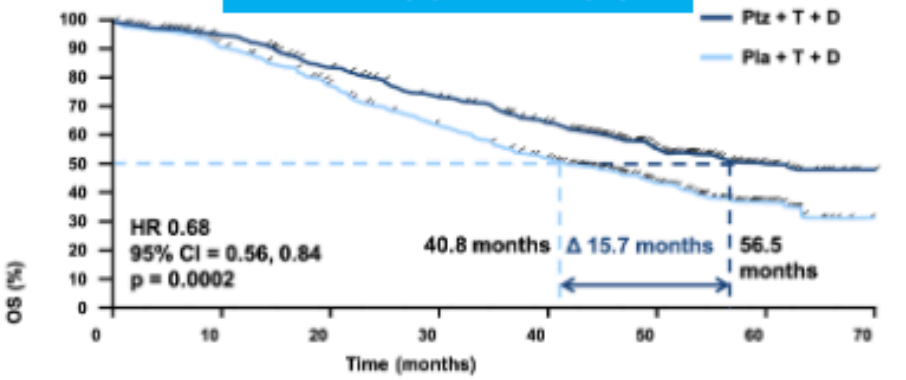


Randomization stratified by:

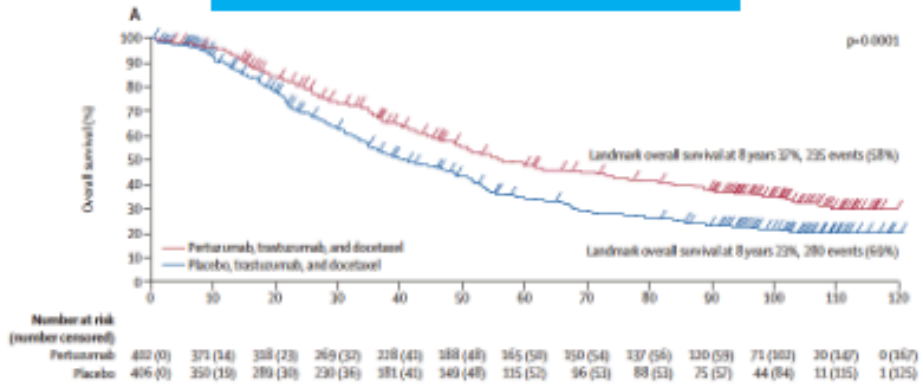
-geographic region

-neo/adjuvant chemotherapy

FINAL OS ANALYSIS

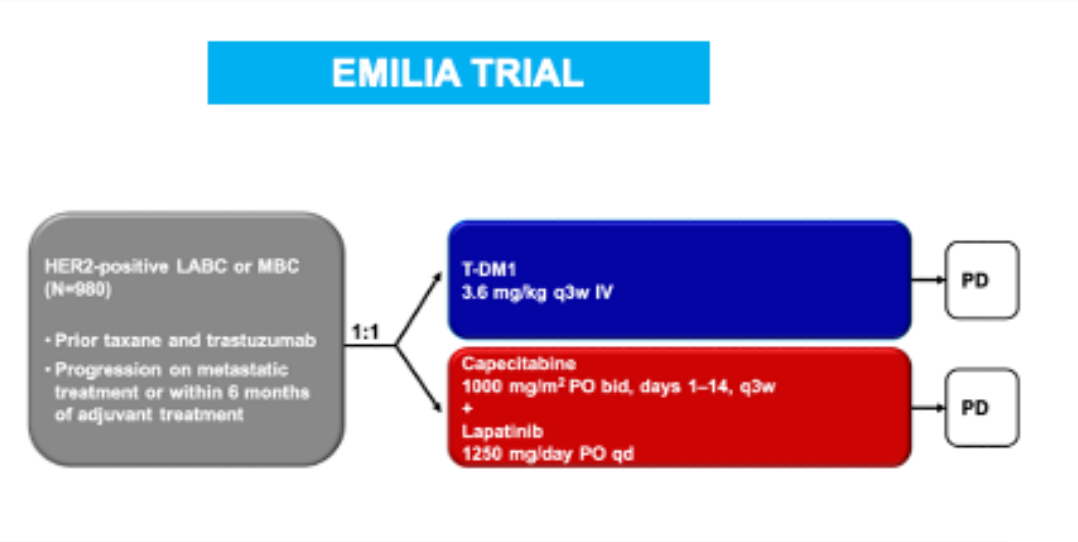


END-OF-STUDY RESULTS

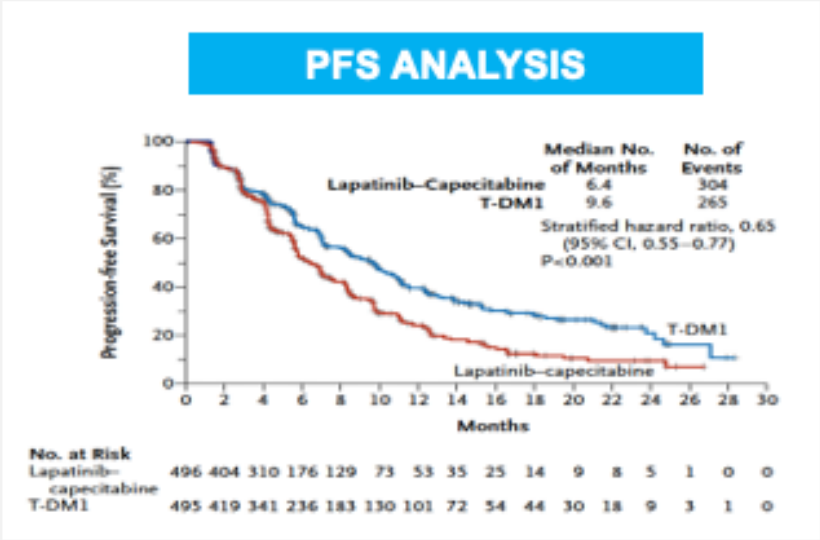


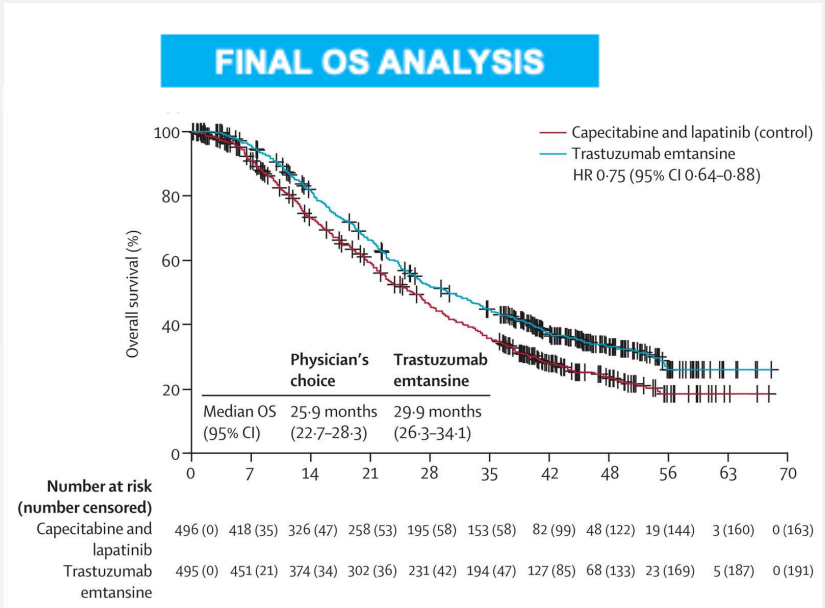
Swain S et al. N Engl J Med 2015; Swain S et al. Lancet Oncol 2020

Current standard treatment: Second Line



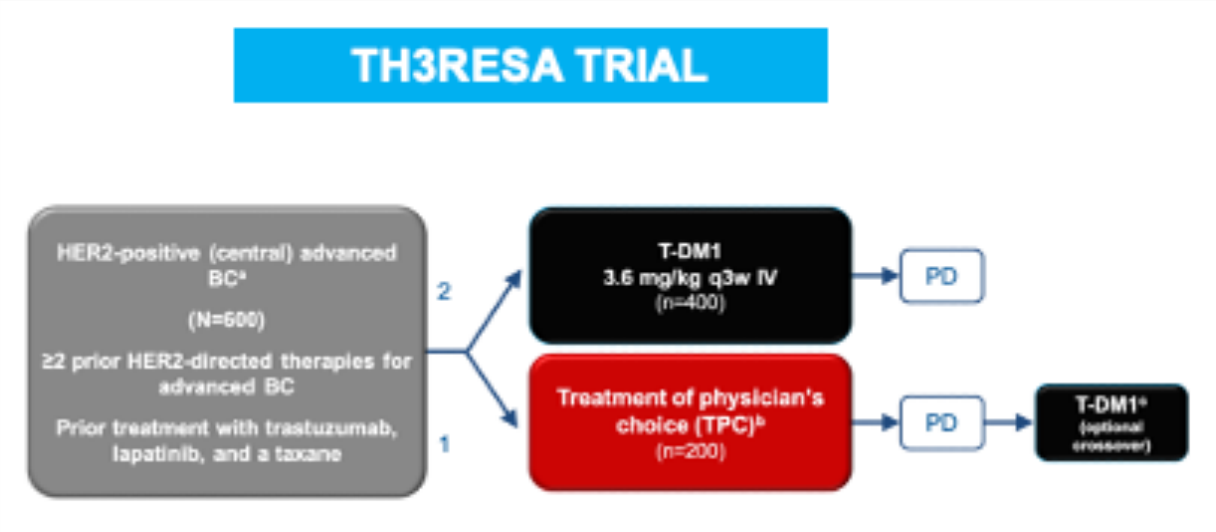
- **Stratification factors**: World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary endpoints**: PFS by independent review, OS, and safety

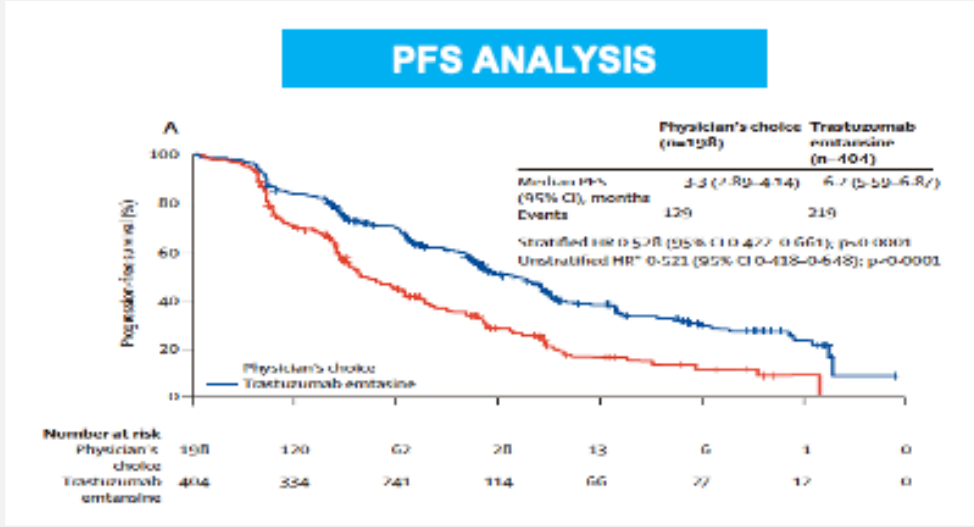




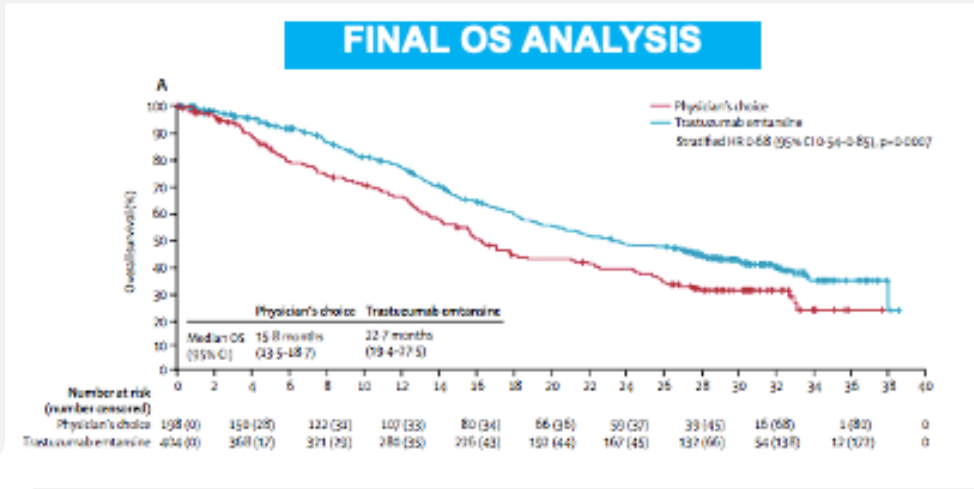
Verma S, et al. NEJM 2012; Diéras V, et al. Lancet Oncol. 2017

Third line options and beyond





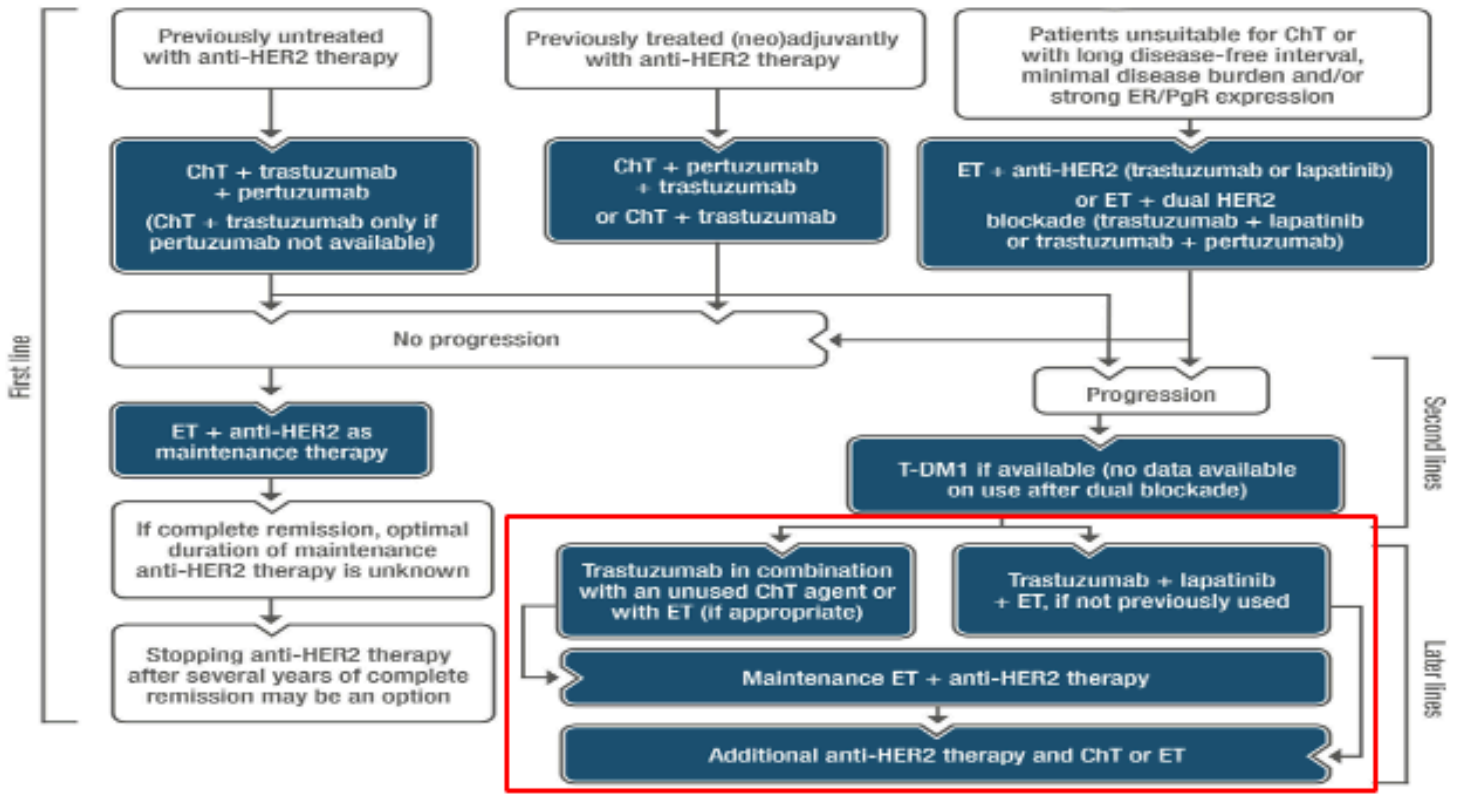
- **Stratification factors**: World region, number of prior regimens for advanced BC,d presence of visceral disease
- **Co-primary endpoints**: PFS by investigator and OS
- **Key secondary endpoints**: ORR by investigator and safety



Krop IE. Lancet Oncology 2014; Krop IE. Lancet Oncology 2017

Third line options and beyond:

There is insufficient evidence to recommend a specific regimen and in general, it is at the physician discretion what is prescribed taking into account patient's preferences and adverse events of each regimen.



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* Include in clinical trials when available

Cardoso F. et al, Ann Oncology 2018

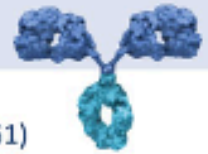
Recent efficacy and safety results in the post T-DM1 setting

- ✓ Margetuximab – SOPHIA
- ✓ Neratinib – NALA
- ✓ DS8201 – DESTINY-Breast01
- ✓ Tucatinib – HER2CLIMB

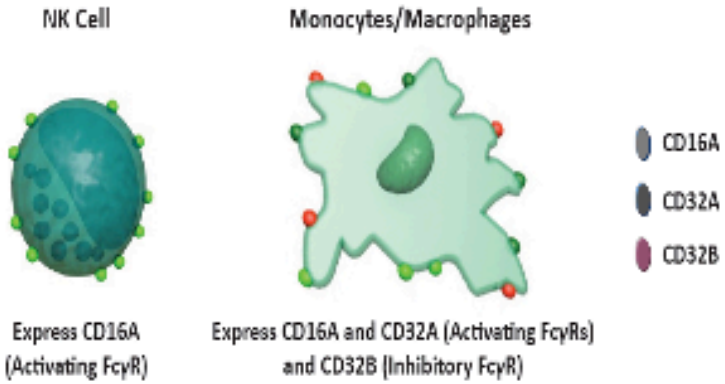
Novel Anti-HER2 Abs: Margetuximab

Trastuzumab

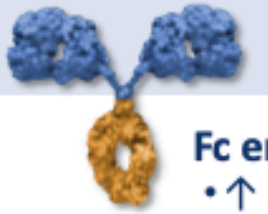
Fab:
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival



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



Margetuximab[1,2]



Fab:
- Same specificity and affinity
- Similarly disrupts signaling

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

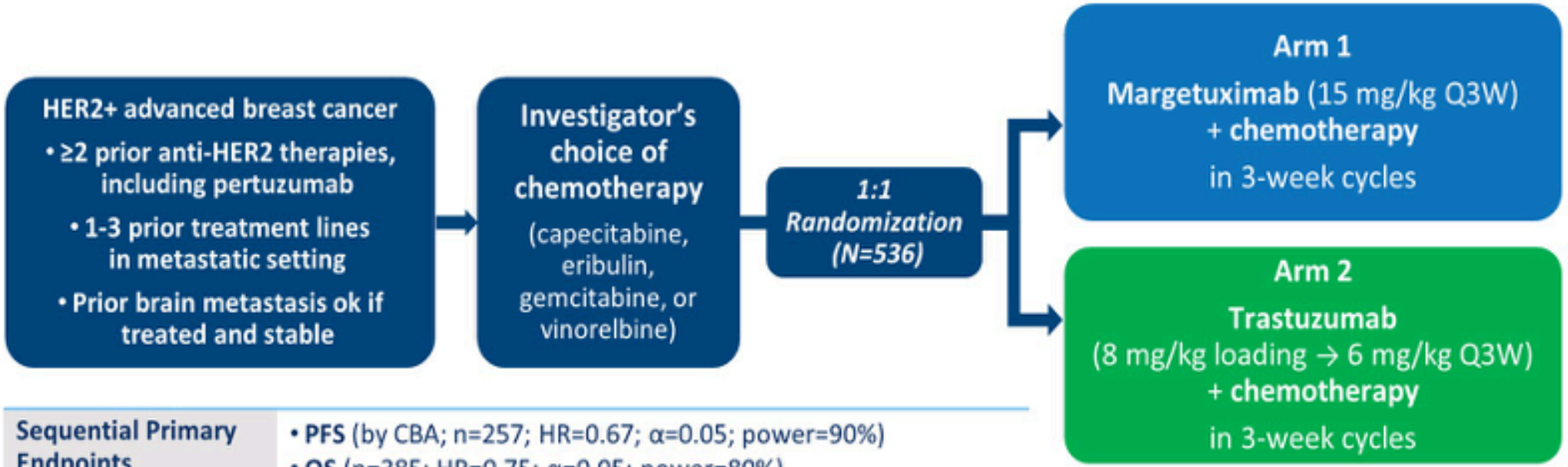
Margetuximab Binding to FcγR Variants:

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

ADCC: antibody dependent cell-mediated cytotoxicity;

1. Nordstrom JL, et al. Breast Cancer Res. 2. Stavenhagen JB, et al. Cancer Res.

Study CP-MGAH22-04 (SOPHIA) Design 1,2



HR = HAZARD RATIO; CBA = central blinded analysis.

1. Ruso HS. Et al. J Clin Oncal. 2016:34Isuppl 15):TPS630. 2. Clinicaltrials.gov.NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Acessed April 8. 2019

SOPHIA TRIAL

ITT Population: Baseline Characteristics

		Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
	Median age	55	56
	Female sex	266 (100%)	267 (98.9%)
Demographics	Europe	152 (57%)	138 (51%)
	North America	85 (32%)	102 (38%)
	Other region	29 (11%)	30 (11%)
	ECOG PS 0	149 (56%)	161 (60%)
	ECOG PS 1	117 (44%)	109 (40%)
	Metastatic	260 (98%)	264 (98%)
Disease Characteristics	Locally advanced, unresectable	6 (2%)	6 (2%)
	Measurable disease by CBA	262 (99%)	262 (97%)
	≤2 metastatic sites	138 (52%)	144 (53%)
	>2 metastatic sites	128 (48%)	126 (47%)
	Hormone receptor positive	164 (62%)	170 (63%)
	Hormone receptor negative	102 (38%)	98 (36%)
	Capecitabine	71 (27%)	72 (27%)
Backbone chemotherapy	Eribulin	66 (25%)	70 (26%)
	Gemcitabine	33 (12%)	33 (12%)
	Vinorelbine	96 (36%)	95 (35%)

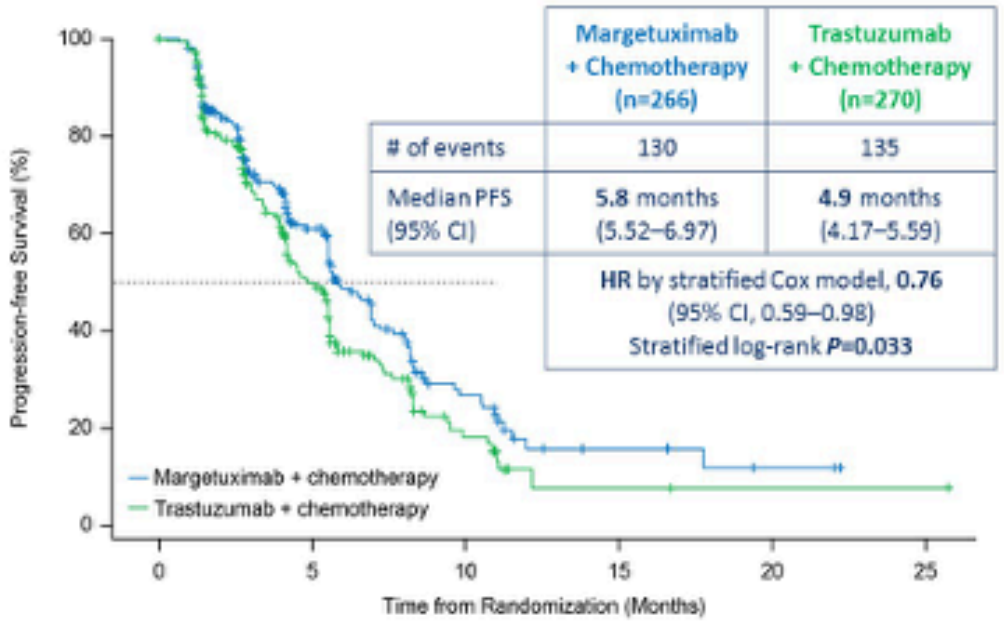
ITT Population: Prior Cancer Therapy

	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Settings of prior therapy		
Adjuvant and/or neoadjuvant	**158 (59%)**	**145 (54%)**
Metastatic only	108 (41%)	125 (46%)
Prior metastatic lines of therapy		
≤2	175 (66%)	180 (67%)
>2	91 (34%)	90 (33%)
Prior anti-HER2 therapy		
Trastuzumab	**266 (100%)**	**270 (100%)**
Pertuzumab	**266 (100%)**	**269 (100%)**
T-DM1	**242 (91%)**	**247 (92%)**
Lapatinib	41 (15%)	39 (14%)
Other HER2	6 (2%)	6 (2%)
Prior chemotherapy		
Taxane	252 (95%)	249 (92%)
Anthracycline	118 (44%)	110 (41%)
Platinum	34 (13%)	40 (15%)
Prior endocrine therapy	126 (47%)	133 (49%)

Rugo H et al, ASCO 2019

PFS Analysis in ITT Population

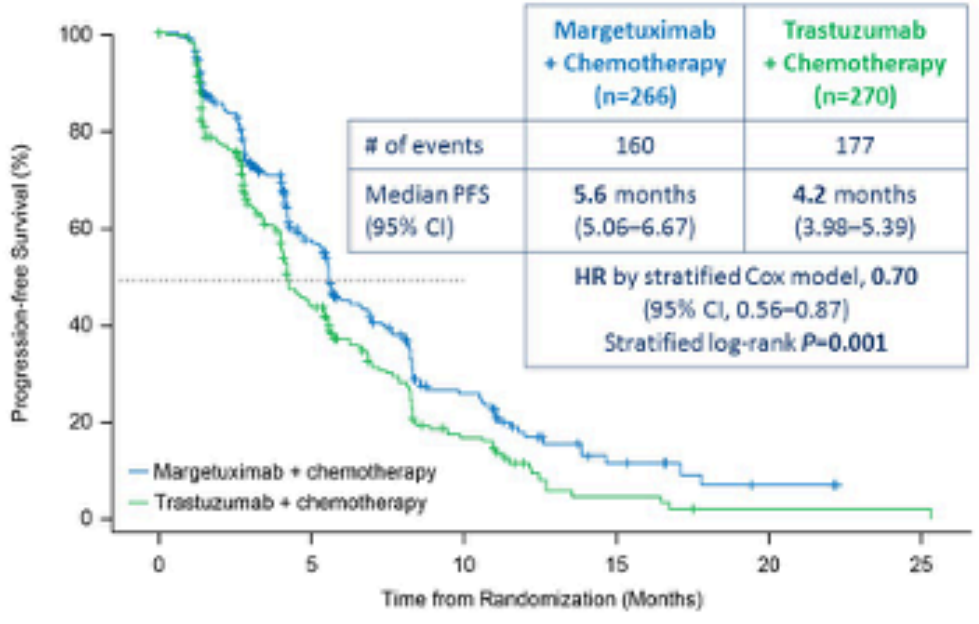
24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	5.8 months (5.52–6.97)	4.9 months (4.17–5.59)
HR by stratified Cox model, 0.76 (95% CI, 0.59–0.98) Stratified log-rank *P*=0.033		

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

30% Risk Reduction of Disease Progression
Investigator Assessed (Secondary Endpoint)



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	160	177
Median PFS (95% CI)	5.6 months (5.06–6.67)	4.2 months (3.98–5.39)
HR by stratified Cox model, 0.70 (95% CI, 0.56–0.87) Stratified log-rank *P*=0.001		

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	0

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

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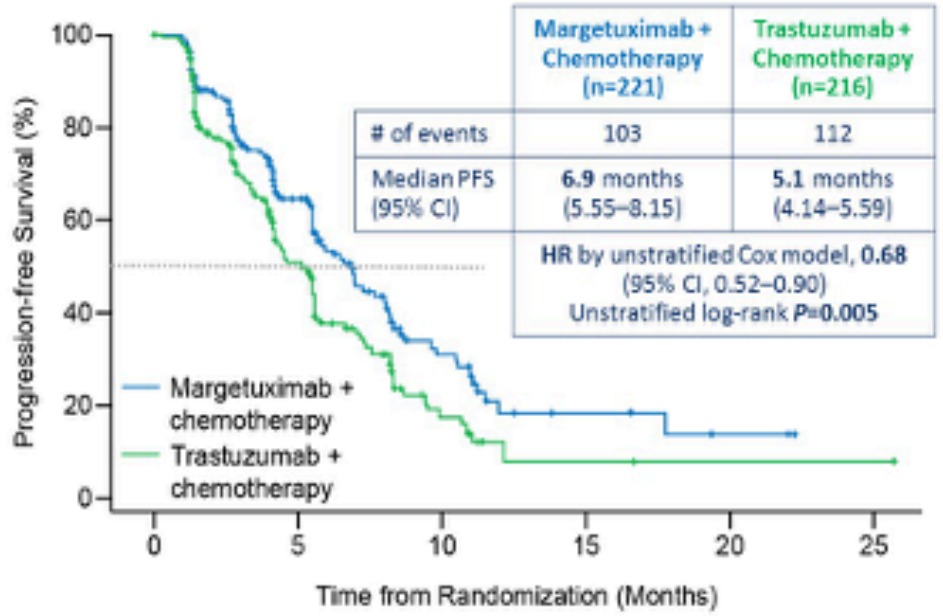
PFSPlanned Exploratory PFS Analysis by CD16A Genotype, by CBA

506 patients genotyped (94%)

FF or FV, n=437 of 506 (86%)

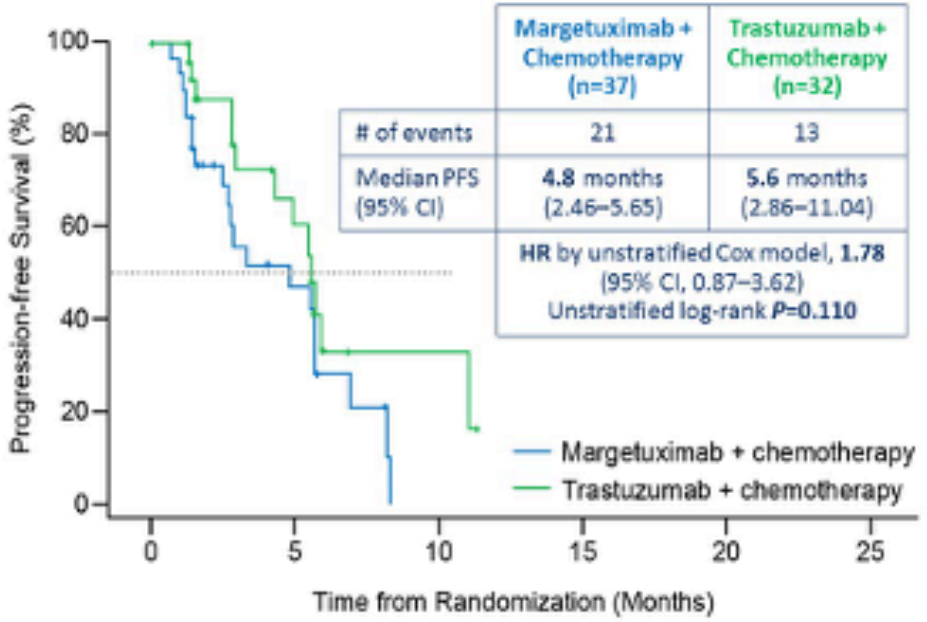


	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)

HR by unstratified Cox model, **0.68** (95% CI, 0.52–0.90)
Unstratified log-rank ***P*=0.005**

Margetuximab	221	157	84	42	21	8	6	4	2	0	
Trastuzumab	216	129	62	30	11	2	2	1	1	1	1

VV, n=69 of 506 (14%)



	Margetuximab + Chemotherapy (n=37)	Trastuzumab + Chemotherapy (n=32)
# of events	21	13
Median PFS (95% CI)	**4.8** months (2.46–5.65)	**5.6** months (2.86–11.04)

HR by unstratified Cox model, **1.78** (95% CI, 0.87–3.62)
Unstratified log-rank ***P*=0.110**

Margetuximab	37	16	10	3	0	
Trastuzumab	32	18	10	2	2	0

Rugo H et al, ASCO 2019

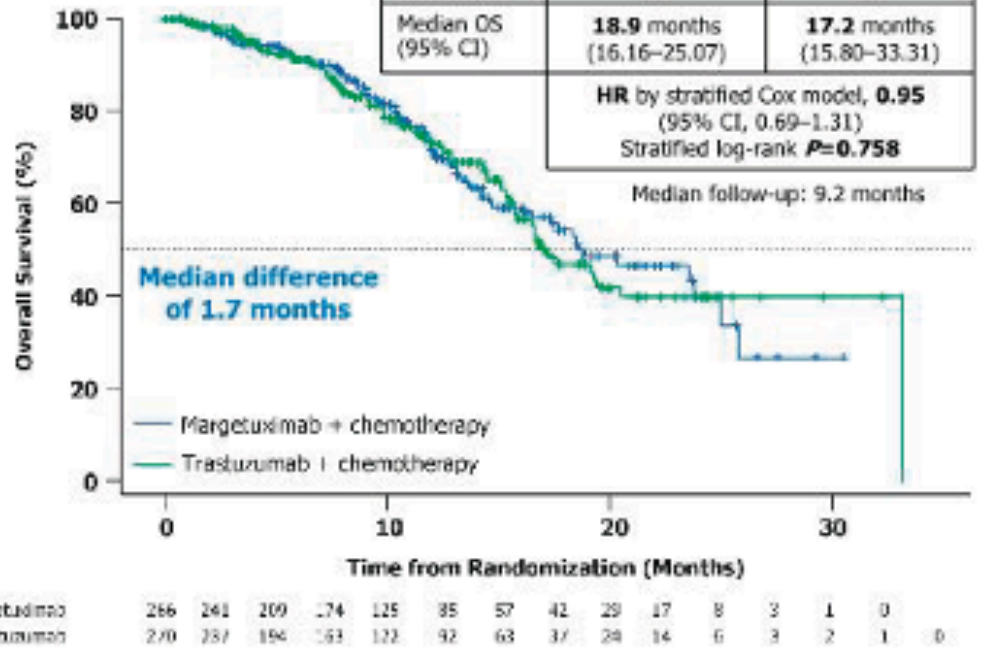
San Antonio Breast Cancer Symposium®, December 10-14, 2019

ITT Population: Interim OS Analyses (n=536)

First Interim OS Analysis (Oct-2018 Cutoff)[a]

	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	78	80
Median OS (95% CI)	**18.9** months (16.16–25.07)	**17.2** months (15.80–33.31)
	HR by stratified Cox model, **0.95** (95% CI, 0.69–1.31) Stratified log-rank ***P*=0.758**	

Median follow-up: 9.2 months

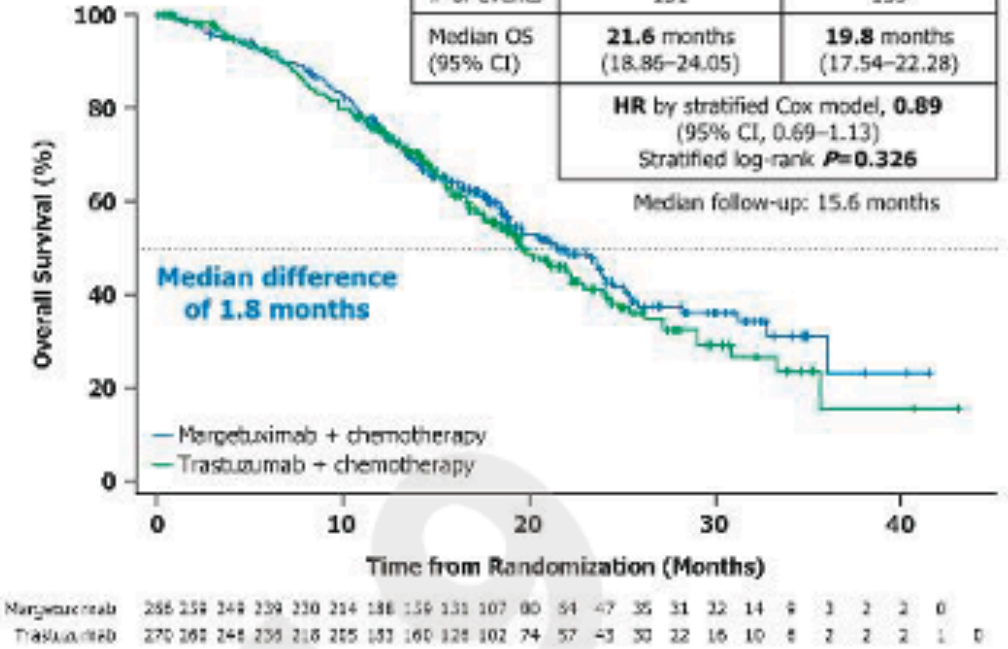


Margetuximab	266	241	209	174	125	85	57	42	29	17	8	3	1	0
Trastuzumab	270	237	194	163	122	92	63	37	28	14	6	3	2	1	0

Second Interim OS Analysis (Sep-2019 Cutoff)[b]

	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	131	139
Median OS (95% CI)	**21.6** months (18.86–24.05)	**19.8** months (17.54–22.28)
	HR by stratified Cox model, **0.89** (95% CI, 0.69–1.13) Stratified log-rank ***P*=0.326**	

Median follow-up: 15.6 months



Margetuximab	266	259	248	239	230	214	188	159	131	107	80	54	47	35	31	22	14	6	3	2	2	0
Trastuzumab	270	262	248	236	218	205	183	160	128	102	74	57	43	30	22	16	10	6	2	2	2	1	0

[a]OS analysis performed as of October 10, 2018 data cutoff, after 158 (41%) of 385 events needed for final OS analysis had occurred.
[b]OS analysis performed as of September 10, 2019 data cutoff, after 270 (70%) of 385 events needed for final OS analysis had occurred.

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Aes Regardless of Causality:

	Margetuximab + Chemotherapy (n=264)		Trastuzumab + Chemotherapy (n=265)	
Most common AEs, n (%)	**All Grade***	**Grade ≥3†**	**All Grade***	**Grade ≥3†**
Fatigue	103 (39.0)	12 (4.5)	92 (34.7)	7 (2.6)
Nausea	81 (30.7)	3 (1.1)	84 (31.7)	1 (0.4)
Neutropenia	73 (27.7)	51 (19.3)	51 (19.2)	30 (11.3)
Diarrhea	59 (22.3)	6 (2.3)	62 (23.4)	5 (1.9)
Febrile neutropenia	8 (3.0)	8 (3.0)	12 (4.5)	12 (4.5)
AEs of special interest, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Infusion-related reaction (IRR)‡	**34 (12.9)**	**4 (1.5)**	**10 (3.8)**	**0**
Left ventricular dysfunction	6 (2.3)	3 (1.1)	7 (2.6)	1 (0.4)
Discontinuation due to IRRs, n (%)	3 (1.1)	2 (0.8)	0	0

File under review by FDA

Safety Population: N=529.
*Incidence ≥20% in either treatment group.
†Incidence ≥5% in either treatment group.
‡All patients received prior trastuzumab. In pivotal trials of trastuzumab, IRRs occurred in 21% to 40% of patients (US package insert).

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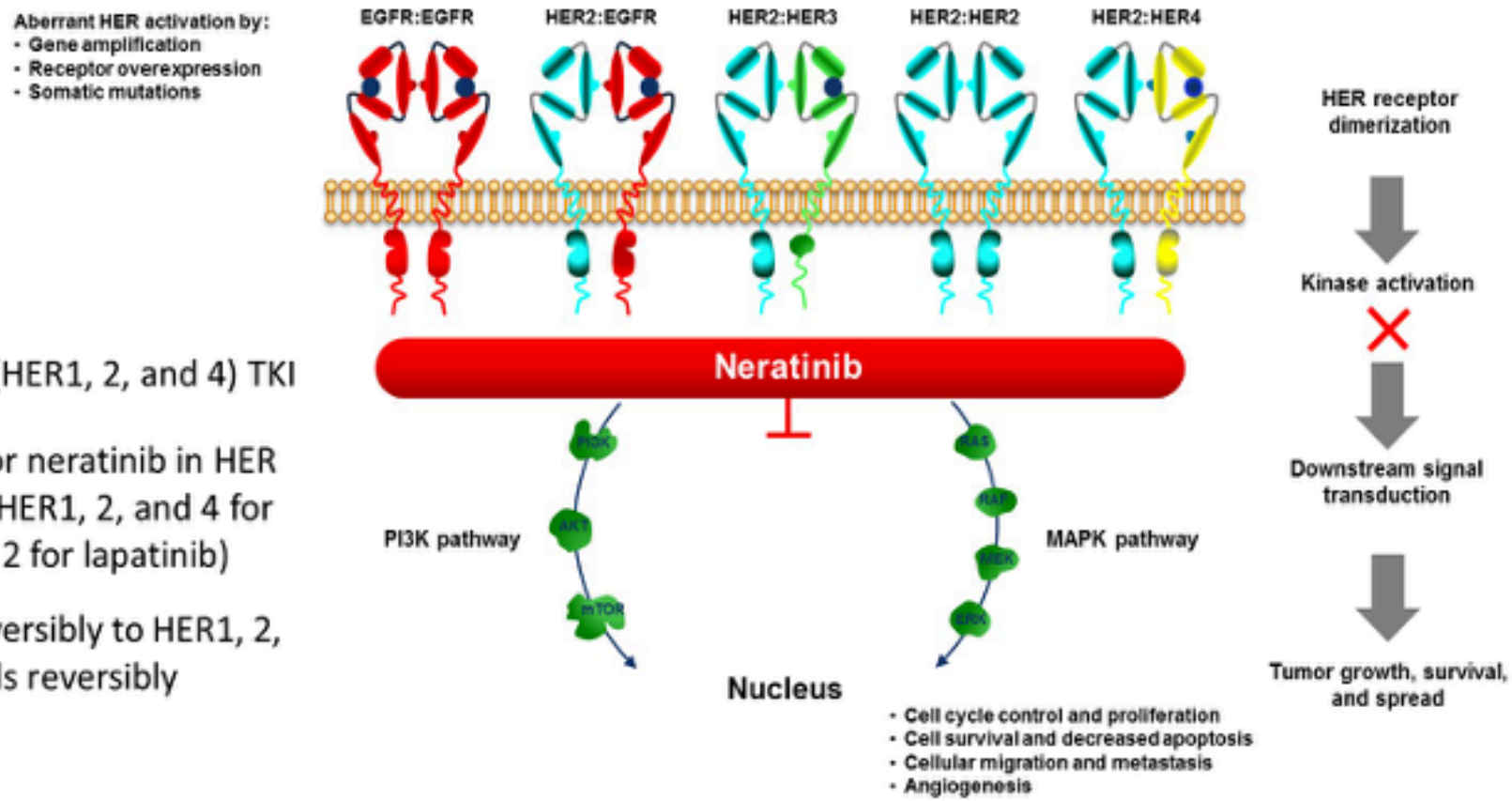
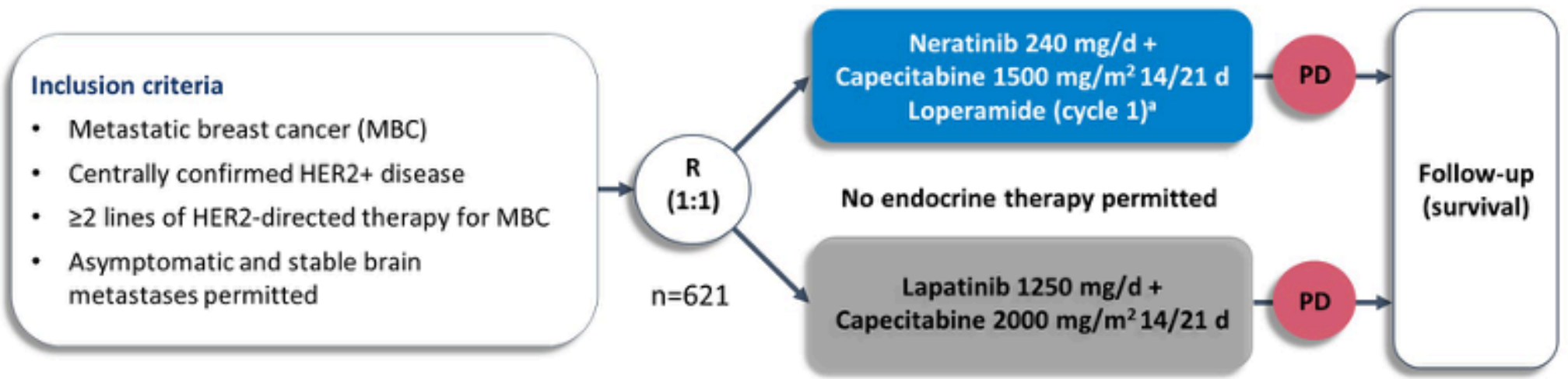
Neratinib: An irreversible pan HER TKI

- Neratinib: pan-HER (HER1, 2, and 4) TKI
- Breadth of targets for neratinib in HER family of receptors (HER1, 2, and 4 for neratinib; HER1 and 2 for lapatinib)
- Neratinib binds irreversibly to HER1, 2, and 4; lapatinib binds reversibly



TKI, tyrosine kinase inhibitor

NALA study design



Stratification variables

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

Endpoints

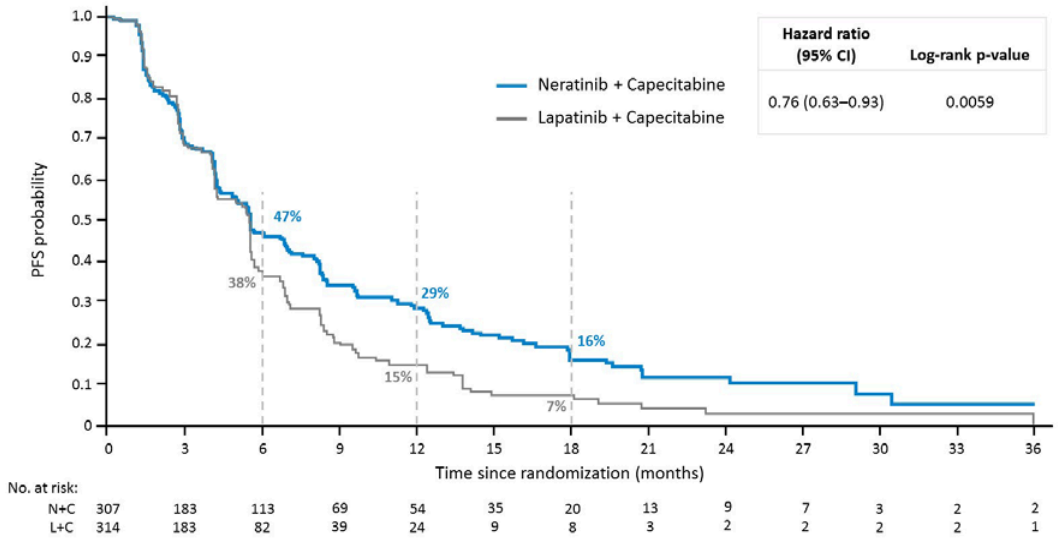
- Co-primary: PFS (centrally confirmed) and OS
- Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

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

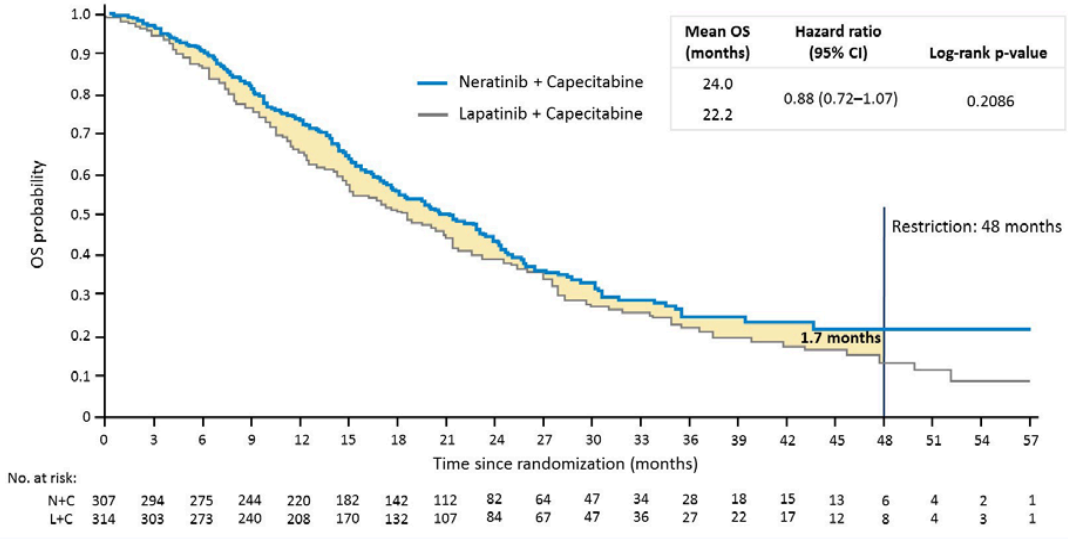
Saura et al, ASCO 2019

NALA study design

Centrally confirmed PFS (co-primary endpoint)



OS (co-primary endpoint)



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NALA TRIAL

	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)

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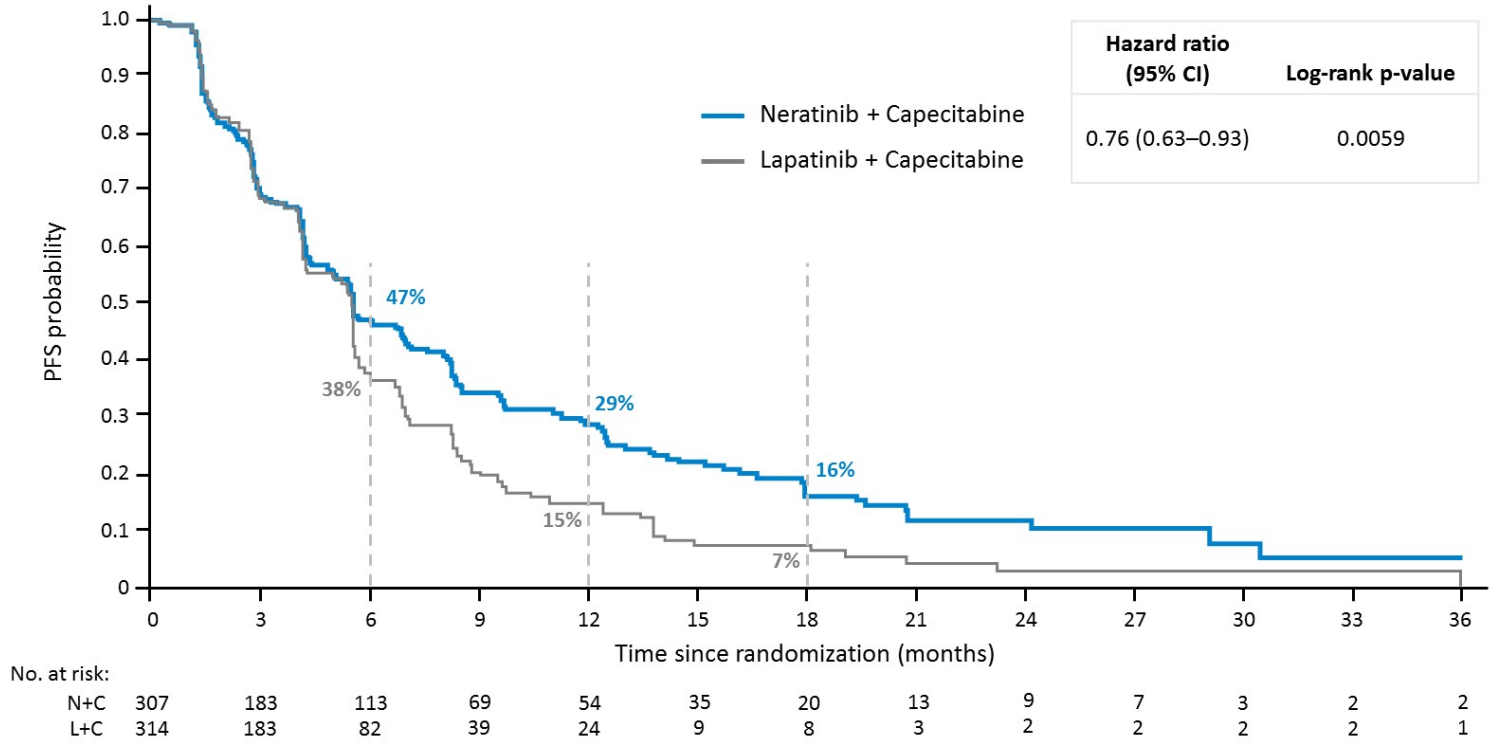
NALA

Centrally confirmed PFS (co-primary endpoint)



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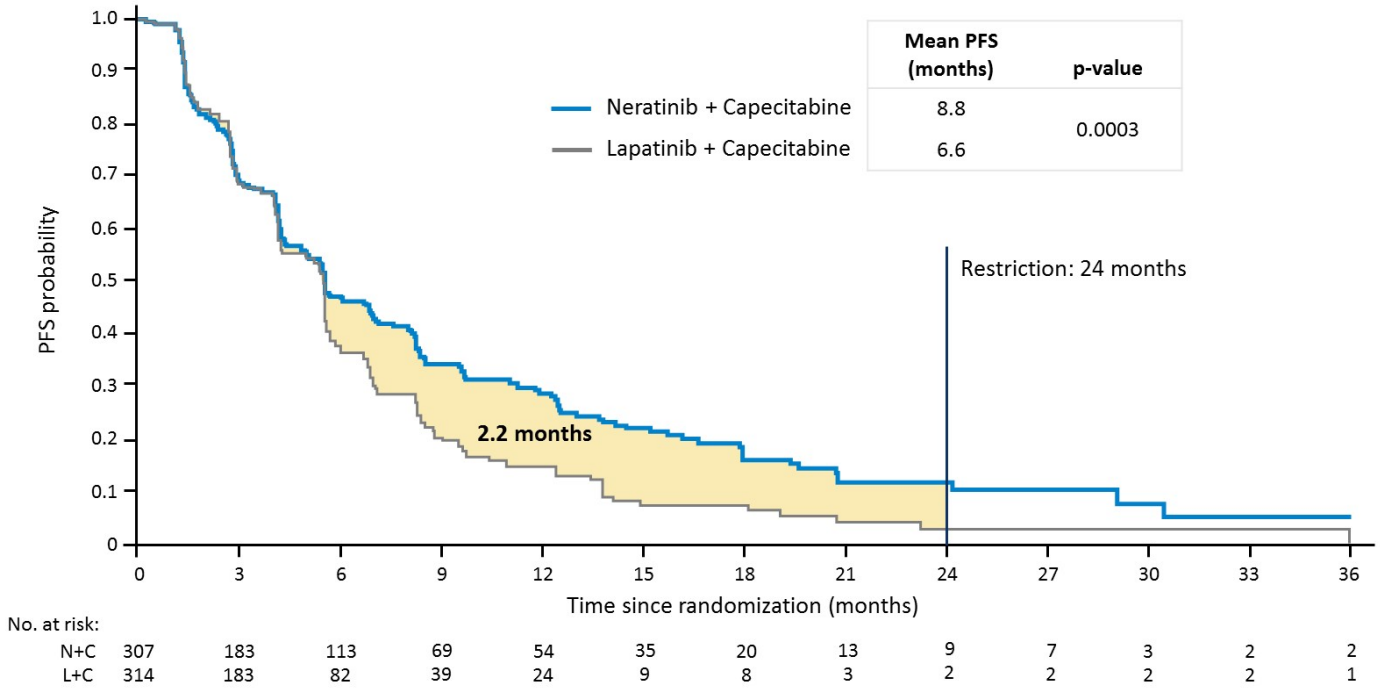
Prespecified restricted means analysis – PFS



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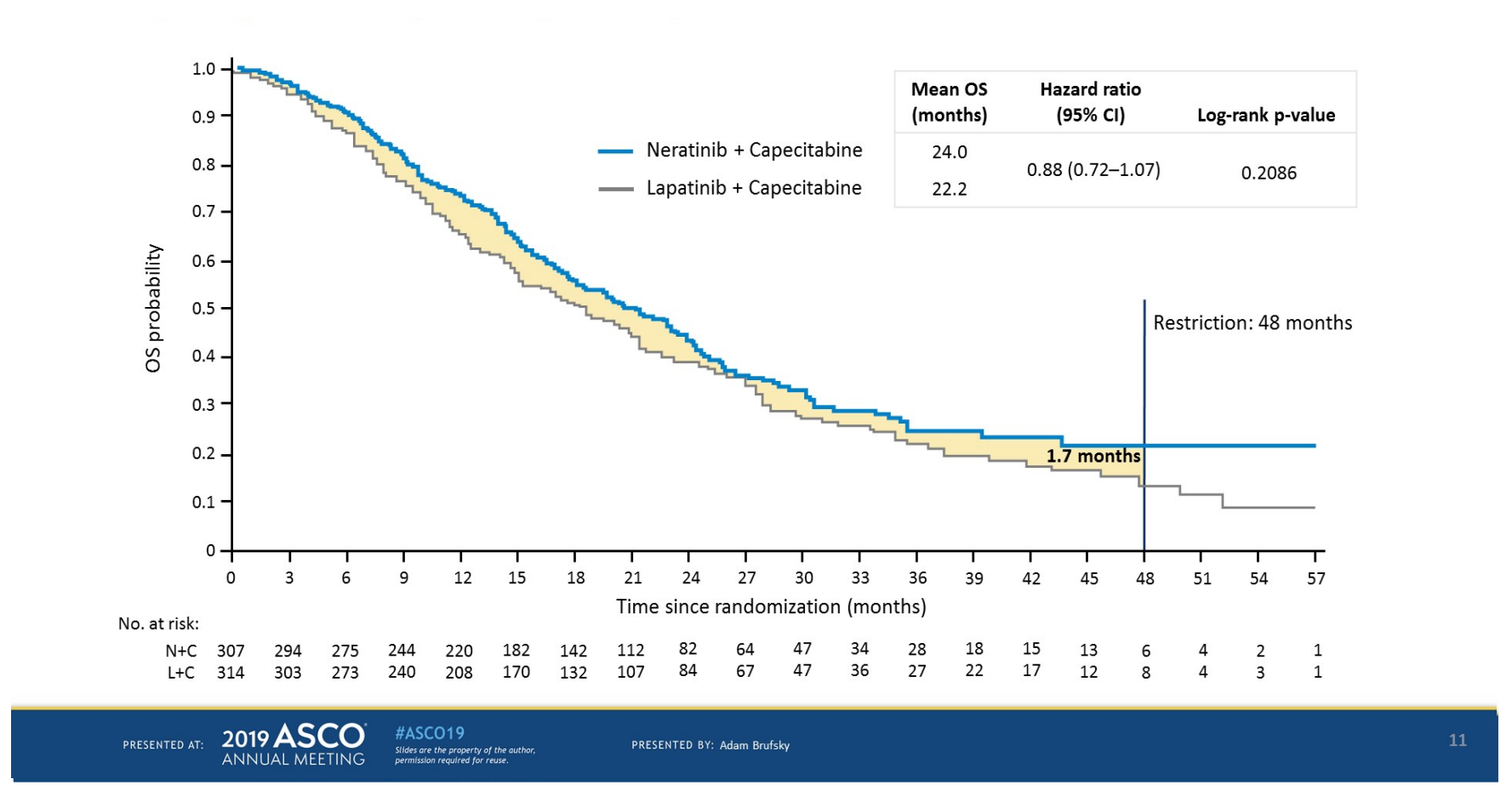
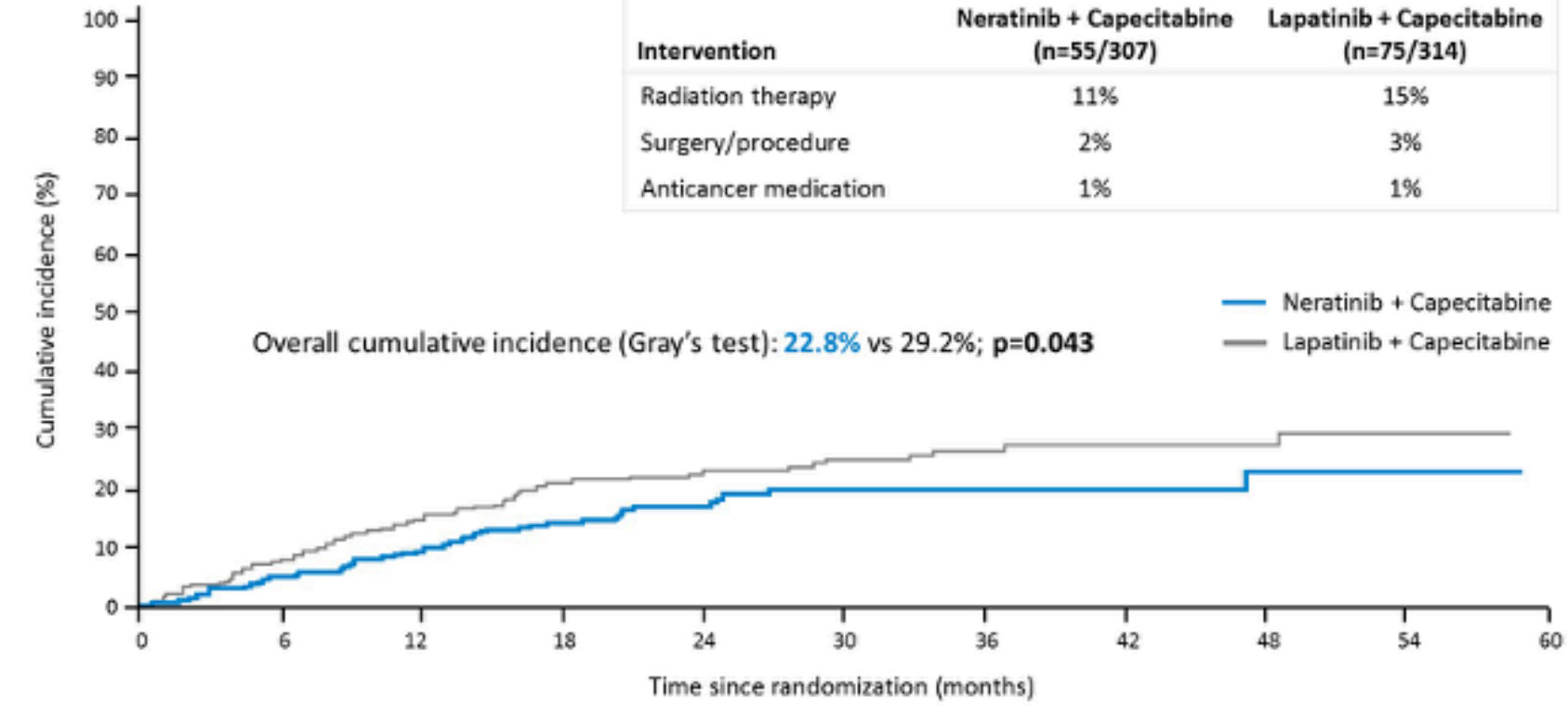
OS (co-primary endpoint)



Saura et al, ASCO 2019

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 et al, ASCO 2019

Most frequent grade 3/4 adverse events

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (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

i adverse events

FDA approved. EMA file in Q3 2020

	Neratinib + Capecitabine (n=303)	Lapatinib + Capecitabine (n=311)
Maximum toxicity, n (%)		
Grade 1	91 (30)	111 (36)
Grade 2	87 (29)	56 (18)
Grade 3	74 (24)	39 (13)
Time to first onset of diarrhea, days		
Grade 2 or 3	9	18
Grade 3	11	38
Median cumulative duration per patient, days		
Grade 2 or 3	7	9
Grade 3	4	4

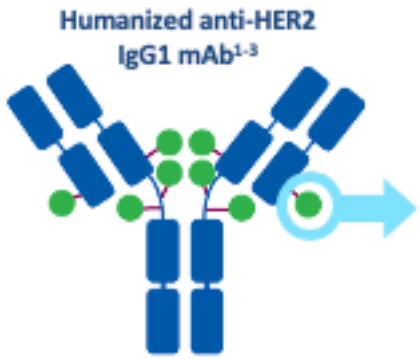
Treatment discontinuation due to diarrhea: N+C: 2.6% L+C: 2.3%

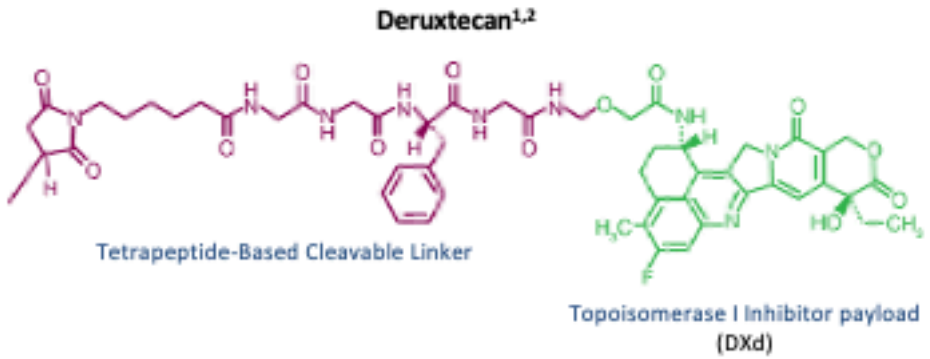
Saura et al, ASCO 2019

Trastuzumab Deruxtecan (DS-8201) is a Novel ADC Designed to Deliver an Optimal Antitumor Effect1-4

Trastuzumab deruxtecan is an ADC composed of 3 components:

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





1. Payload MOA: topoisomerase I inhibitor
2. High potency of payload
3. High drug to antibody ratio ≈ 8
4. Payload with short systemic half-life
5. Stable linker-payload
6. Tumor-selective cleavable linker
7. Membrane-permeable payload

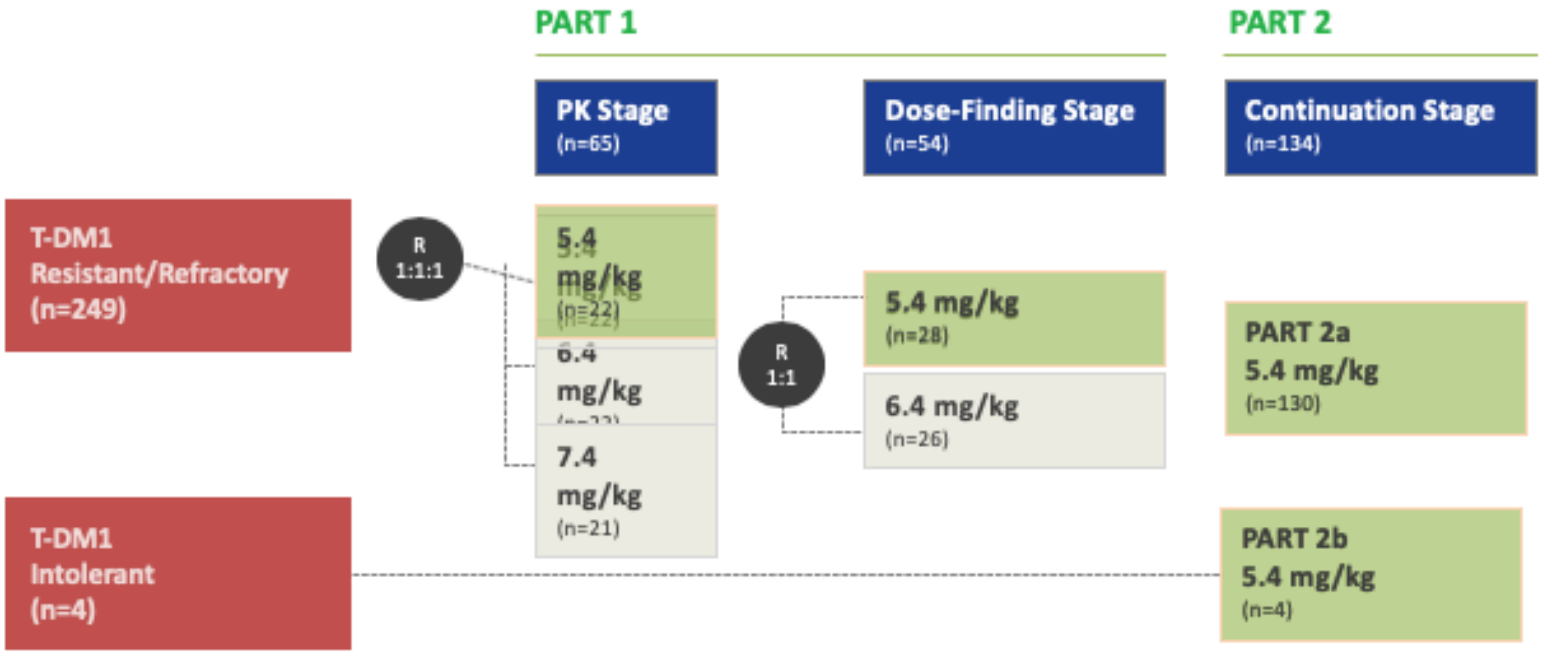
The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate; MOA, mechanism of action.

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.

DESTINY-Breast01 Study Design: An Open-Label, Multicenter, Phase 2 Study

Population

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2-positive (centrally confirmed on archival tissue)
- Prior T-DM1
- Stable, treated brain metastases were allowed



184 patients enrolled at 5.4 mg/kg

Endpoints

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

Data Cutoff: August 1, 2019

- **79 patients** (42.9%) are ongoing
- **105 patients** (57.1%) discontinued, primarily for progressive disease (28.8%)

Krop I al, SABCS 2019 & NEJM 2019

Patient Baseline Characteristics

	Patients T-DXd 5.4 mg/kg (N=184)[a]
Age, median (range), years	55.0 (28-96)
Female, %	100
Region, % Asia / North America / Europe	34.2 / 28.8 / 37.0
ECOG performance status 0 / 1 / 2, %	55.4 / 44.0 / 0.5
Hormone receptor positive / negative / unknown, %	52.7 / 45.1 / 2.2
HER2 expression, %[b] IHC 3+ IHC 2+; ISH+ /IHC 1+; ISH+	 83.7 15.2 / 1.1
Presence of visceral disease, %	91.8
History of brain metastases, %	13.0

[a]All 184 patients received ≥1 dose of T-DXd. [b]HER2 status was centrally assessed on archival tissue according to guidelines of the American Society of Clinical Oncology–College of American Pathologists.

ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; ISH, in situ hybridization.

Krop I al, SABCS 2019 & NEJM 2019

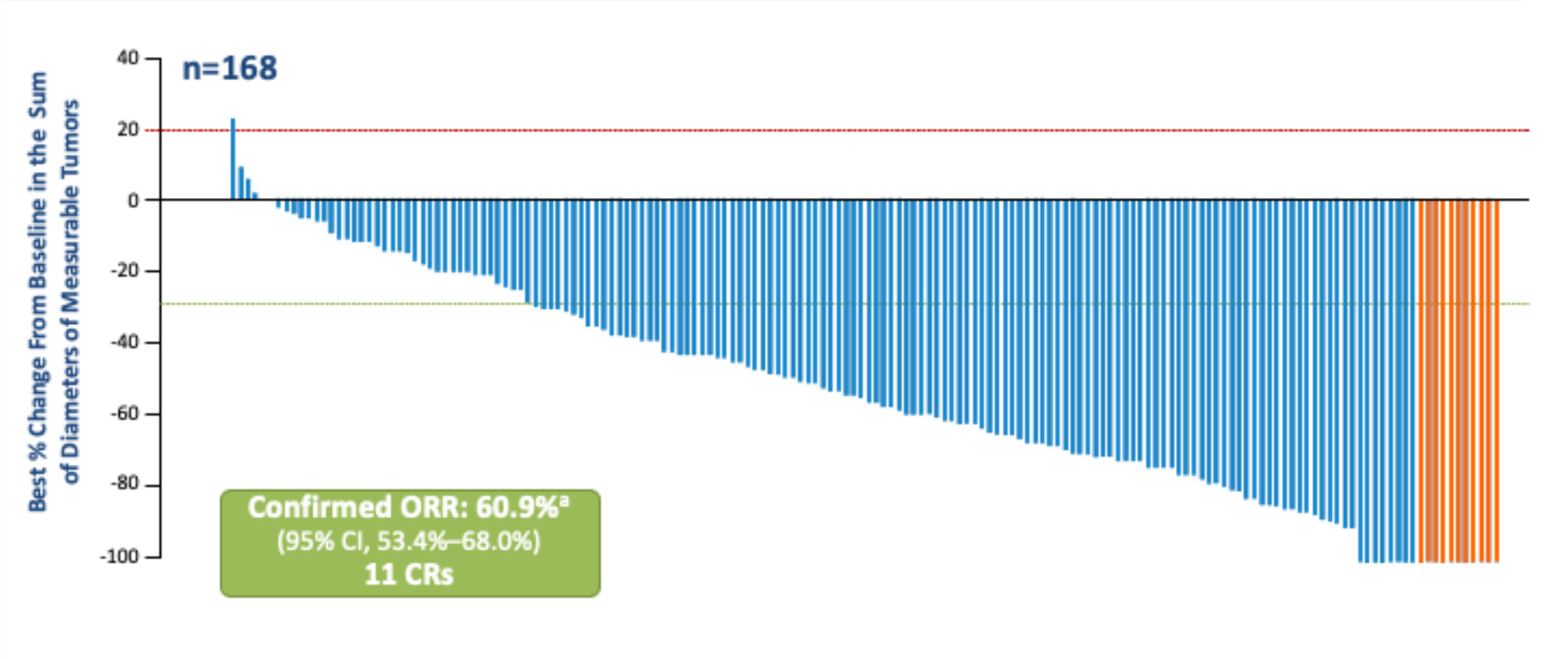
Patient Baseline Characteristics *(cont'd)*

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

Prior Treatment[a]	Patients, % T-DXd 5.4 mg/kg (N=184)
Trastuzumab	100
T-DM1	100
Pertuzumab	65.8
Other anti-HER2 therapies	54.3
Hormone therapy	48.9
Other systemic therapy	99.5

[a]Therapies for locally advanced or metastatic breast cancer, including hormone therapy.

Best Change in Tumor Size



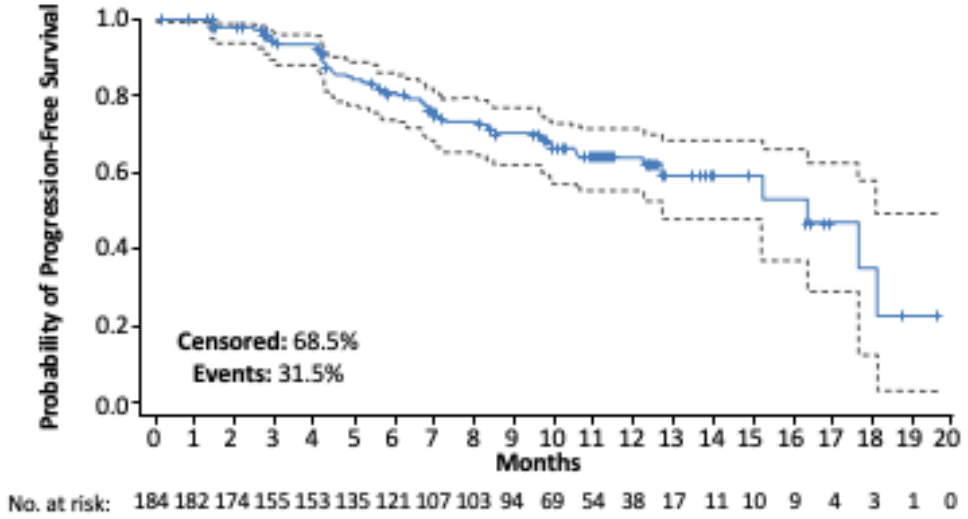
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
a Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Krop I al, SABCS 2019 & NEJM 2019

Results

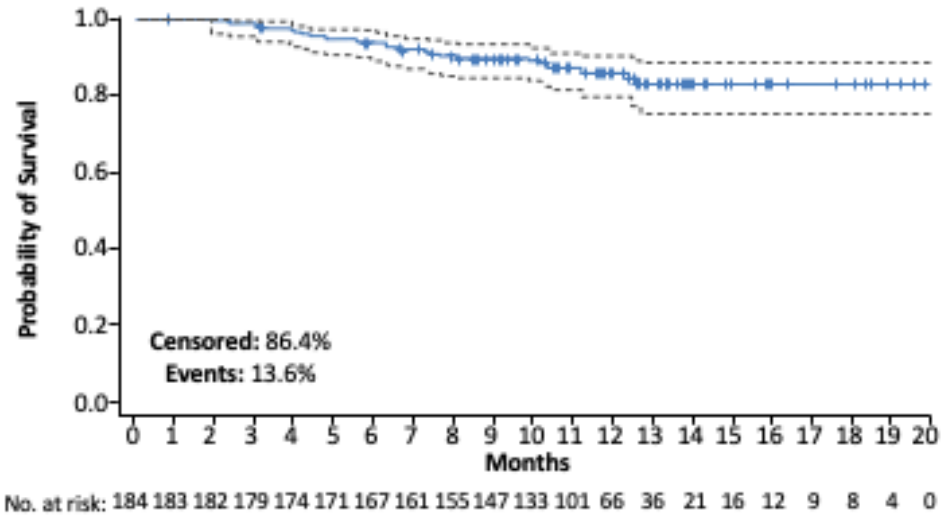
Progression-Free Survival

Median: 16.4 months (95% CI, 12.7-NE)



Overall Survival

Median: Not reached (95% CI, NE-NE)



- Median follow-up, 11.1 months (range, 0.7-19.9 months)
- Median PFS in the 24 patients with brain metastases was 18.1 months (95% CI, 6.7-18.1 months)[a]

Patients who received T-DXd 5.4 mg/kg.
CI, confidence interval; NE, not estimable.

Krop I al, SABCS 2019 & NEJM 2019

Overall Safety Summary (>15%)

Adverse Events	Any Grade	Grade 3	Grade 4
	number of patients (percent)		
Any adverse event†	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count‡	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia§	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased white-cell count¶	39 (21.2)	11 (6.0)	1 (0.5)
Decreased platelet count‖	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain**	31 (16.8)	2 (1.1)	0
Decreased lymphocyte count††	26 (14.1)	11 (6.0)	1 (0.5)
Adverse events of special interest			
Interstitial lung disease‡‡	25 (13.6)	1 (0.5)	0
Prolonged QT interval	9 (4.9)	2 (1.1)	0
Infusion-related reaction	4 (2.2)	0	0
Decreased left ventricular ejection fraction§§	3 (1.6)	1 (0.5)¶¶	0

‡‡ The presence of interstitial lung disease was determined by an independent adjudication committee, since the condition has been associated with trastuzumab deruxtecan. Four patients who had grade 5 events are included in the category of any grade.

Krop I al, SABCS 2019 & NEJM 2019

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**

FDA approved. EMA file in Q3 2020

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

Median time from the first infusion of T-DXd to onset of ILD was 27.6 weeks (range, 6-76 weeks)

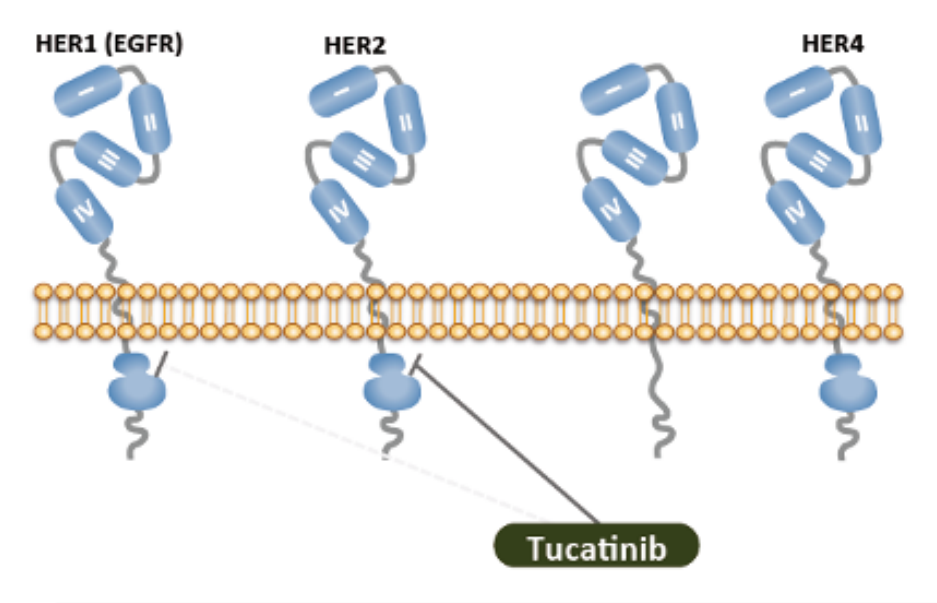
ILD, interstitial lung disease.

Krop I al, SABCS 2019 & NEJM 2019

Mechanism of Action

Orally bioavailable, potent HER2 selective TKI

HER2 IC50 8 nM > EGFR IC50 > 10,000 nM: Decreased potential for EGFR-related toxicities



HER2CLIMB Trial Design

Key Eligibility Criteria

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

R* (2:1)

N=410

Tucatinib + Trastuzumab + Capecitabine
(21-day cycle)

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

N=202

Placebo + Trastuzumab + Capecitabine
(21-day cycle)

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

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

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

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R.K. Murthy et al, SABCS 2019 & NEJM 2019

HER2CLIMB: Baseline demographic and disease characteristics

Characteristic, n (%)		Total Population, N=612 TUC+Tras+Cape n=410	Pbo+Tras+Cape n=202
Female		407 (99)	200 (99)
Age (years), median (range)		55.0 (22, 80)	54.0 (25, 82)
ECOG performance status	0	204 (50)	94 (47)
	1	206 (50)	108 (54)
Stage IV at initial diagnosis		143 (35)	77 (39)
Hormone receptor status	ER and/or PR-positive	243 (60)	127 (63)
	ER and PR-negative	161 (40)	75 (37)
Prior lines of therapy, median (range)	Overall	4.0 (2, 14)	4.0 (2,17)
	Metastatic setting	3.0 (1, 14)	3.0 (1, 13)
Presence/history of brain metastases		198 (48)	93 (46)
Treated, stable		118 (59.6)	55 (59.1)
Untreated		44 (22.2)	22 (23.7)
Treated, progressing		36 (18.2)	16 (17.2)

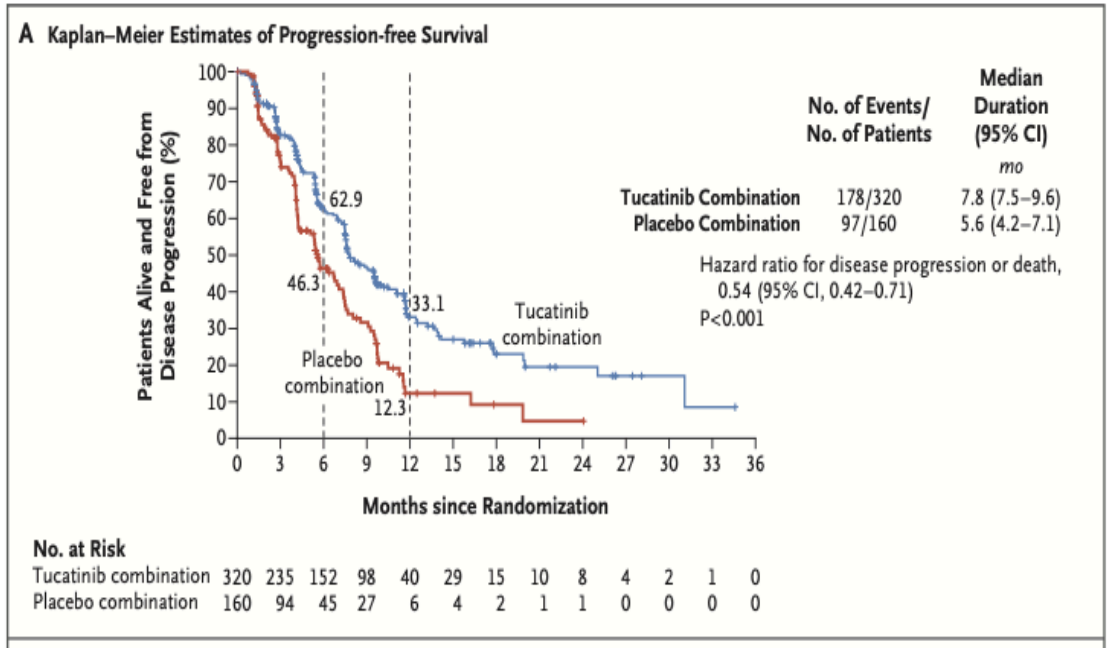
R.K. Murthy et al, SABCS 2019 &NEJM 2019

HER2CLIMB: Baseline demographic and disease characteristics

Presence or history of brain metastases — no. (%)	148 (46.2)	71 (44.4)	198 (48.3)	93 (46.0)
Location of other metastases — no. (%)				
Lung	160 (50.0)	82 (51.2)	200 (48.8)	100 (49.5)
Liver	108 (33.8)	64 (40.0)	137 (33.4)	78 (38.6)
Bone	178 (55.6)	85 (53.1)	223 (54.4)	111 (55.0)
Previous lines of therapy, median no. (range)	4 (2–14)	4 (2–17)	4 (2–14)	4 (2–17)
Previous lines of therapy for metastatic cancer, median no. (range)	3 (1–14)	3 (1–13)	3 (1–14)	3 (1–13)
Previous therapies — no. (%)				
Trastuzumab	320 (100)	160 (100)	410 (100)	202 (100)
Pertuzumab	320 (100)	159 (99.4)	409 (99.8)	201 (99.5)
Trastuzumab emtansine	320 (100)	160 (100)	410 (100)	202 (100)
Lapatinib	22 (6.9)	10 (6.2)	24 (5.9)	10 (5.0)

R.K. Murthy et al, SABCS 2019 &NEJM 2019

Primary Endpoint: PFS

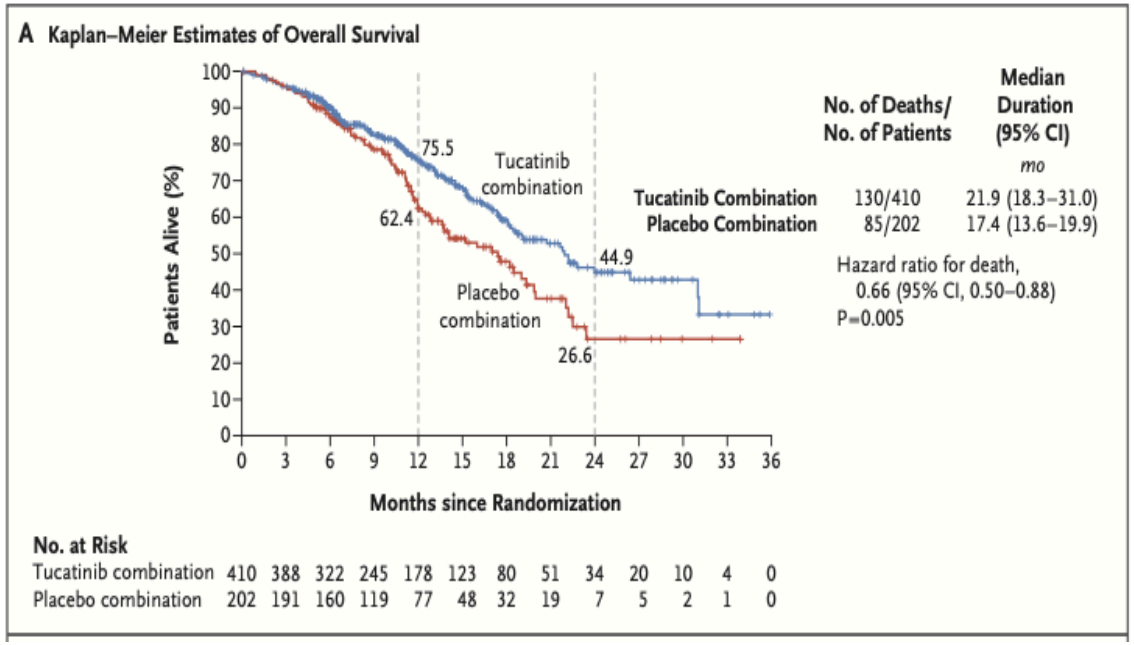


	Projected PFS rates	
	TUC/TRAS/CPC	PLAC/TRAS/CPC
1 year (95% CI)	33%	12%

46% reduction in risk of disease progression

R.K. Murthy et al, SABCS 2019 &NEJM 2019

Secondary Endpoint:OS



Projected OS rates		
	TUC/TRAS/CPC	PLAC/TRAS/CPC
2 year (95% CI)	45%	27%

34% reduction in risk of death

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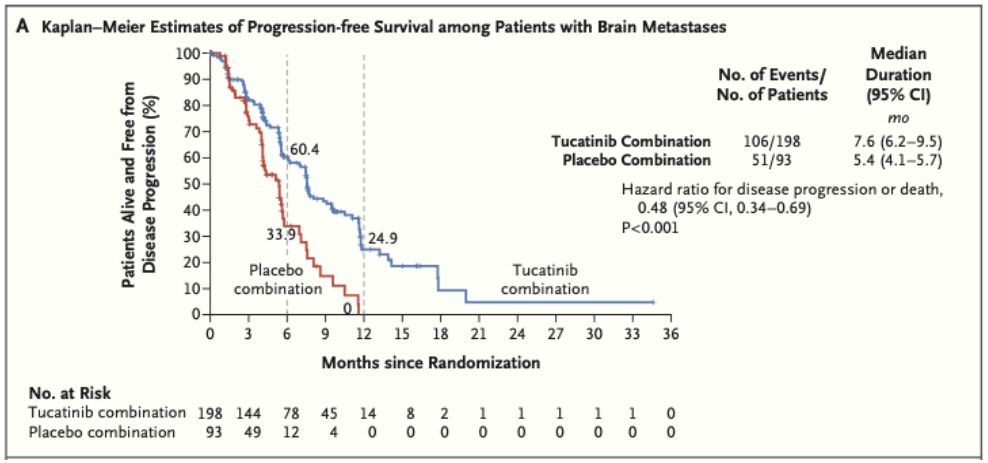
HER2CLIMB: Results

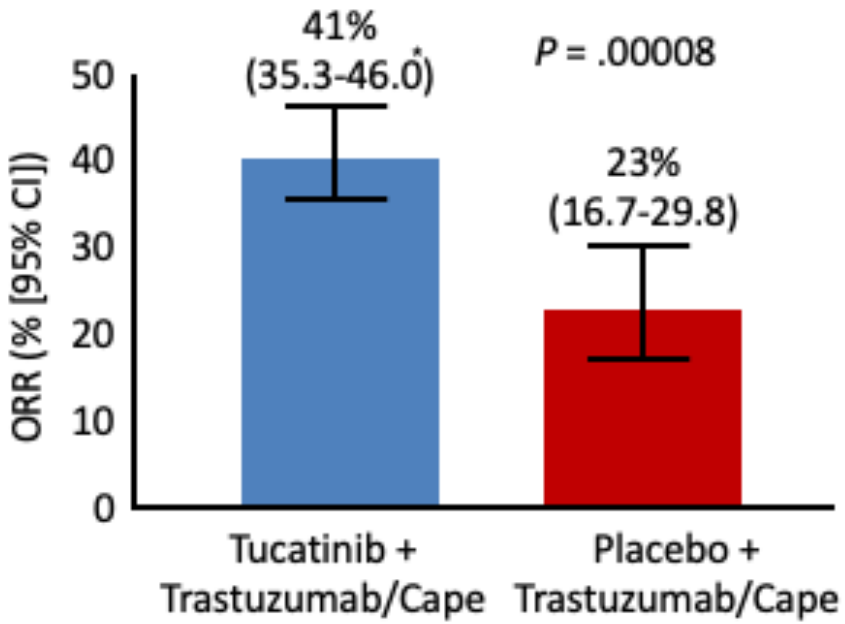
Secondary Endpoint: PFS in Brain



Projected PFS rates BM		
	TUC/TRAS/CPC	PLAC/TRAS/CPC
1 year (95% CI)	25%	0%

52% reduction in risk of disease progression

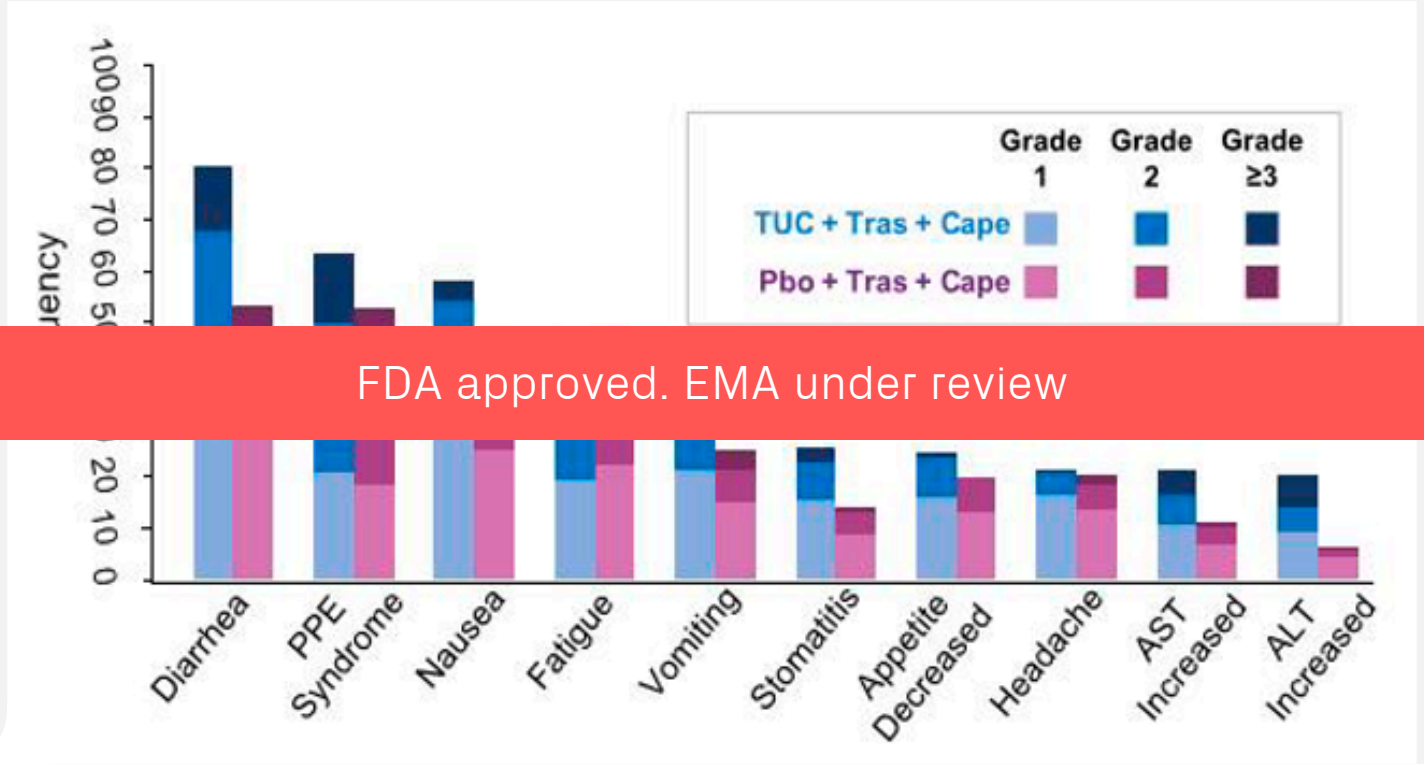
Secondary Endpoint: ORR *



*Per RECIST v1.1.

R.K. Murthy et al, SABCS 2019 &NEJM 2019

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



FDA approved. EMA under review

R.K. Murthy et al, SABCS 2019 &NEJM 2019

Outline:

- HER2:
  Current standard treatment landscape in HER2+ mBC
  Third line options and beyond:

  -Guidelines recommendations:
  -Recent efficacy and safety results in the post T-DM1 setting

  Margetuximab – SOPHIA
  Neratinib – NALA
  DS8201 – DESTINY-Breast01
  Tucatinib – HER2CLIMB

- HER3:
  Signaling and targeted therapy in BC

Table 1 Mono- and bi-specific anti-HER3 Abs under clinical studies in cancer patients

Abs	Target	Most advanced clinical phase	Clinicaltrials.gov identifier	Current Results on clinicaltrials.gov	Sponsor
mAbs:					
U3–1287/Patritumab	HER3	Phase III	NCT02134015	Terminated (Pre-defined criteria Not reached)	Daiichi Sankyo
MM-121/Seribantumab	HER3	Phase II	NCT00994123	MM-121+ erlotinib ineffective to prolong PFS in EGFR WT NSCLC	Merrimack Pharmaceuticals
RG7116/Lumretuzumab	HER3	Phase I	NCT01482377	No results posted	Roche
LJM716/Elgemtumab	HER3	Phase I/II	NCT01822613	No results posted	Novartis
U3–1402	HER3	Phase I/II	NCT02980341	Ongoing	Daiichi Sankyo
AV-203	HER3	Phase I	NCT01603979	No results posted	Aveo Oncologyo
KTN3379/CDX-3379	HER3	Phase I	NCT02014909	No results posted	Celldex Therapeutics
GSK2849330	HER3	Phase I	NCT01966445	Results submitted, But not posted	GlaxoSmithKline
Bispecific Abs:					
MM-111	HER2/HER3	Phase II	NCT01774851	Terminated (Lack of efficacy)	Merrimack Pharmaceuticals
MCLA-128	HER2/HER3	Phase II	NCT03321981	Ongoing	Merus NV
MM-141/Istiratumab	HER3/IGF-1R	Phase II	NCT02399137	No results posted	Merrimack Pharmaceuticals
MEHD7945A/Duligotumab	HER3/EGFR	Phase II	NCT01652482	No results posted	Genentech

MCLA-128: bispecific humanized full-length IgG1 antibody

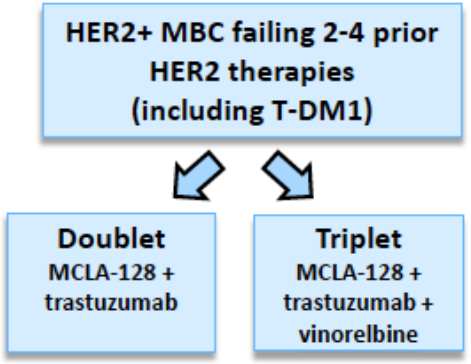


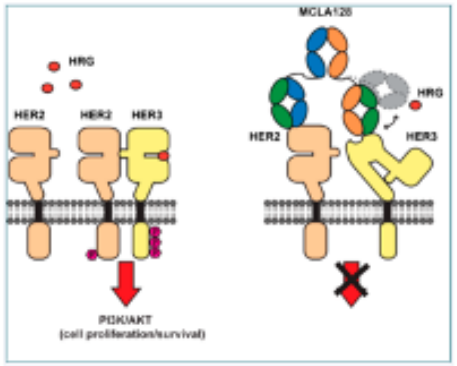
Table 1. Demographics and disease characteristics

	N=39
Age (years), median [range]	57 [29-84]
ECOG PS (0/1), N (%)	21 (54%) / 18 (46%)
Prior therapies	
N therapies (chemotherapy, anti-HER2, hormonal), median [range]	5 [2-8]
N anti-HER2 lines (metastatic setting), median [range]	3 [1-5]
Prior pertuzumab, N (%)	39 (100%)
Prior T-DM1, N (%)	39 (100%)
N metastatic sites*, median [range]	3 [1-5]
Lymph nodes	22 (56%)
Bone	21 (54%)
Lung	20 (51%)
Liver	13 (33%)
Breast	12 (31%)
Brain	8 (21%)

* Sites present in >20% of the cohort.

Table 3. CBR, ORR, and BOR, Investigator assessed (RECIST v1.1)

	N=37
Clinical benefit rate at 24 weeks, N (%) [90%CI]	13 (35.1%) [22.2-50.0]
Overall response rate, N (%) [90%CI]	7 (18.9%) [9.2-32.6]
Best overall response (confirmed)	
Complete response	1 (2.7%)
Partial response	6 (16.2%)
Stable disease	22 (59.5%)
Disease progression	8 (21.6%)



Phase 2 RP2D expansion (enrolled)	mBC (N=10)	Other[1] (N=9)	Total (N=19)
Age (years), Median (Min;Max)	52 (37;70)	57 (33;74)	54 (33;74)
Gender (male), N (%)	0	6 (67%)	6 (32%)
ECOG PS (0/1), N	2 / 8	1 / 8	3 / 16
N Metastatic Sites, Median (Min;Max)	3 (1;3)	2 (1;4)	2.5 (1;4)
N Prior Therapies, Median (Min;Max)	6 (4;18)	3 (2;8)	5.5 (2;18)
N Prior HER Therapies, Median (Min;Max)	3 (3;4)	1 (0;2)	3 (0;4)

1. Metastatic gastric/gastroesophageal (6 patients), ovarian (2 patients), and colorectal (1 patient; cohort closed prematurely)

Patient ID	Metastatic sites	N prior lines	N HER2 therapies	Dose (mg)	N cycles	Best response	Response duration (weeks)[1]
#1	Bone, lung	4	4	750	14	PR	34.4+
#2	Bone, lymph nodes	6	3	750	12	SD	37.0
#3	Skin, lymph nodes	5	3	750	11	SD	34.0
#4	Bone, brain	5	3	750	8	SD	23.3+
#5	Lung	6	5	480	7	SD	21.4
#6	Bone, skin	8	3	750	5	SD	14.9
#7	Brain, liver, peritoneum	6	2	480	4	SD	12.0
#8	Skin	18	4	750	4	SD	11.7
#9	Bone, lymph nodes, skin	5	3	750	2	PD	-
#10	Lung, lymph nodes, skin	8	2	750	2	PD	-
#11	Pleura, lymph nodes, skin	5	3	750	2	PD	-

Alsina, M et al, ASCO 2017, Hamilton et al, #3093, ASCO 2020

MCLA-128: bispecific humanized full-length IgG1 antibody

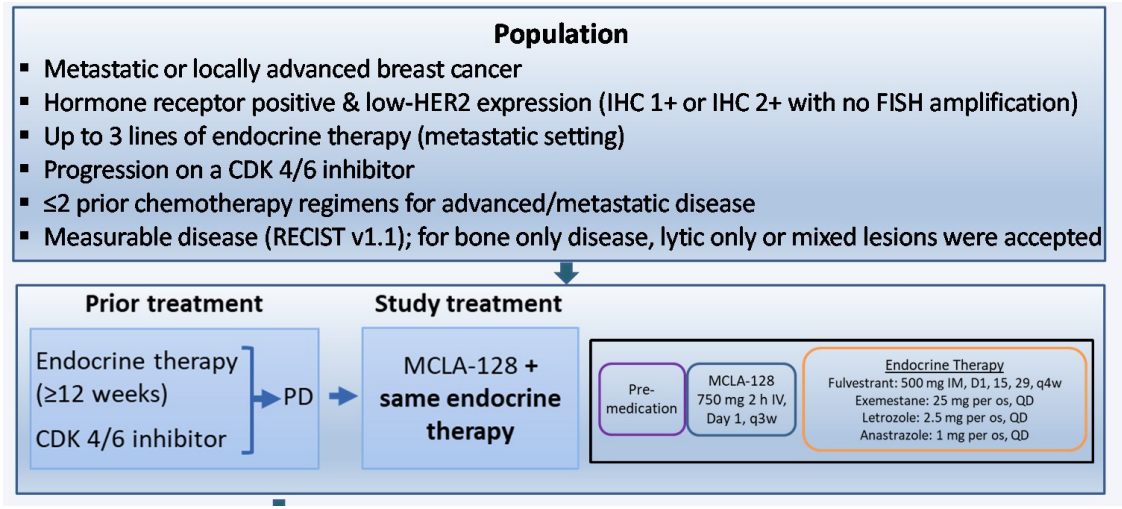


Table 1. Demographics and disease characteristics

	N=50
Age (years), median [range]	56 [27-82]
ECOG PS (0/1), N (%)	35 (70%) / 15 (35%)
ER-positive, N (%)	50 (100%)
HER2 IHC 1+ / IHC 2+, N (%)	26 (52%) / 24 (48%)
Prior therapies	
N hormone therapy lines, median [range]	2 [1-5]
N chemotherapy lines (all settings), median [range]	1 [1-3]
Prior CDK4/6 inhibitor, N (%)	50 (100%)
N metastatic sites*, median [range]	**3 [1-6]**
Bone	37 (74%)
Liver	33 (66%)
Lymph nodes	27 (54%)
Lung	14 (28%)

* Sites present in >20% of the cohort.

Table 3. CBR, ORR, and BOR, Investigator assessed (RECIST v1.1)

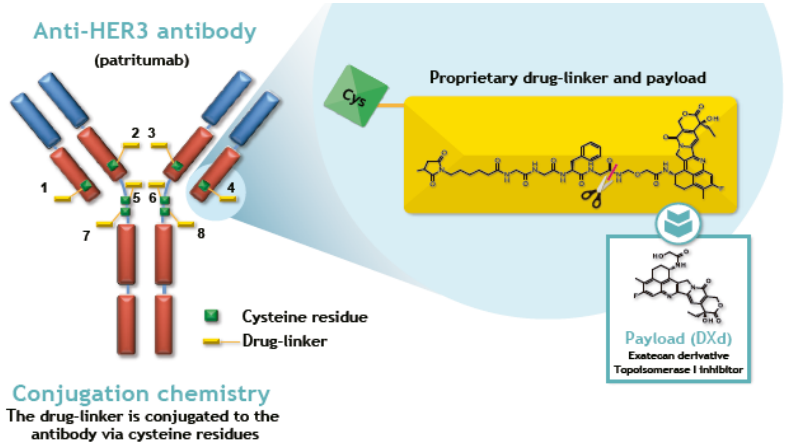
	N=48
Clinical benefit rate at 24 weeks, N (%) [90%CI]	8 (16.7%) [8.6-28.1]
Overall response rate, N (%) [90%CI]	1 (2.1%)[0.1-9.5]
Best overall response (confirmed)	
Complete response	0
Partial response	1 (2.1%)
Stable disease	20 (41.7%)
Disease progression	26 (54.2%)
Unknown*	1 (2.1%)

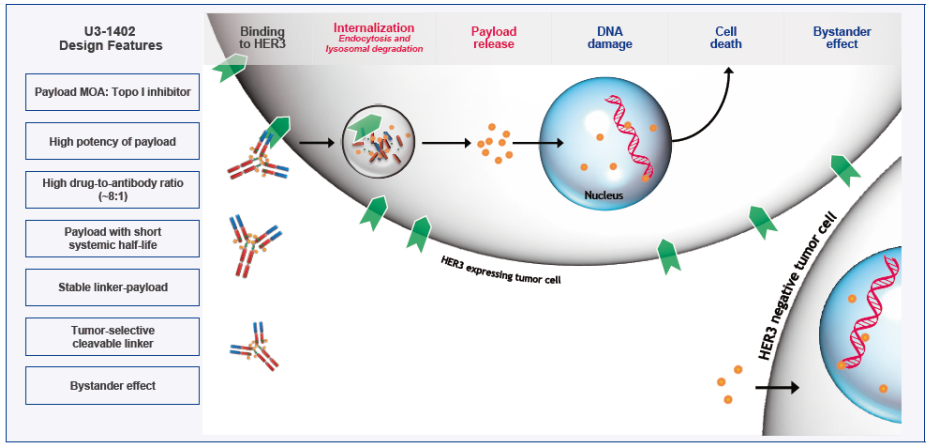
* 1st assessment was SD at week 5; 2nd assessment was PD at week 15

Pistilli B et al, #1037, ASCO 2020

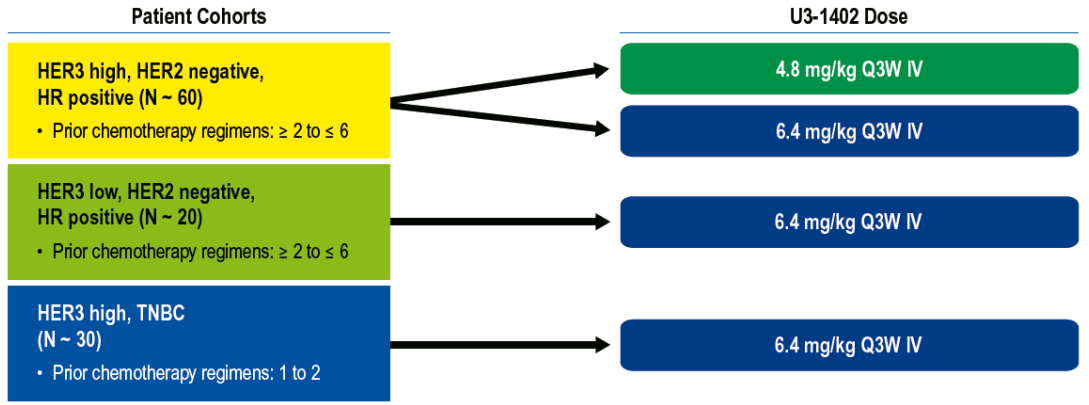
U3-1402: HER3-targeting-ADC

Phase 1/2, HER3 positive tumors (IHC +2,+3), mediana de 5 (1-12) lineas de tratamiento para CM metastasico





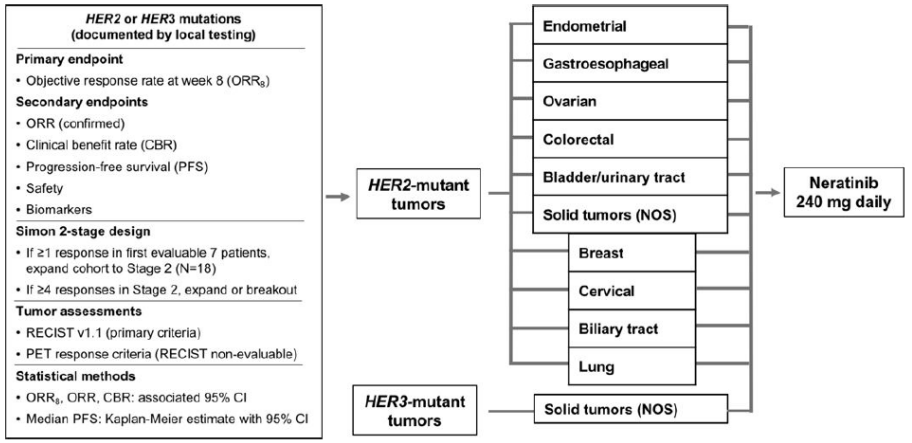
Efficacy Measures	Dose Escalation + Dose Finding		
	4.8 mg/kg (N = 15)	6.4 mg/kg (N = 15)	All dose levels (N = 42)
ORR, n/N (%)	6/15 (40.0)	9/15 (60.0)	18/42 (42.9)
DoR, median (range), months	NR (2.8, 9.8+)	NR (2.9+, 9.8+)	NR (2.8, 13.8+)
TTR, median (95% CI), months	2.1 (1.3, 4.1)	2.7 (1.4, 2.8)	2.6 (1.4, 2.8)
DCR, n/N (%)	13/15 (86.7)	15/15 (100.0)	38/42 (90.5)
PFS, median (range), months[a]	8.0 (1.2, 12.3+)	NR (5.0, 11.1+)	8.3 (1.2, 16.8+)

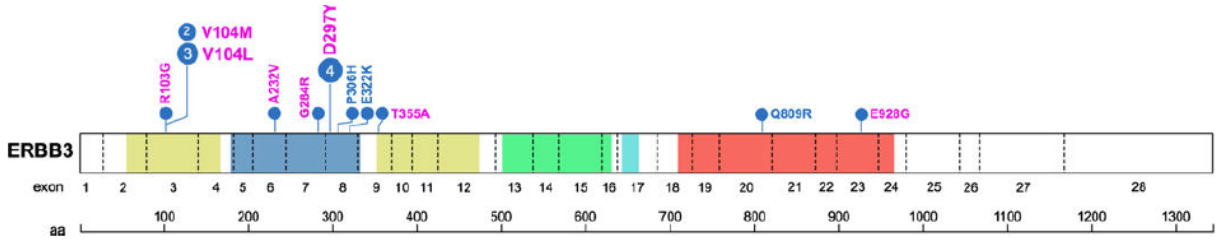


Yonemori K et al, ESMO breast 2019, Krop I et al, SABCS 2019

HER Kinase inhibition in patients with HER2- and HER3-mutant cancers

Extended Data





Outcome	HER2										HER3
	Breast (n=25)	Lung (n=26)	Bladder (n=16)	Colorectal (n=12)	Biliary tract (n=9)	Cervical (n=5)	Endometrial (n=7)	Gastroesophageal (n=5)	Ovarian (n=4)	NOS (n=16)	NOS (n=16)
ORR at week 8, n (%) [95% CI]	8 (32.0) [14.9–53.5]	1 (3.8) [0.1–19.6]	0 (0.0) [0.0–20.6]	0 (0.0) [0.0–26.5]	2 (22.2) [2.8–60.0]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–41.0]	0 (0.0) [0.0–52.2]	0 (0.0) [0.0–60.2]	1 (6.3) [0.2–30.2]	0 (0.0) [0.0–20.6]
ORR, n (%) [95% CI]	6 (24.0) [9.4–45.1]	1 (3.8) [0.1–19.6]	0 (0.0) [0.0–20.6]	0 (0.0) [0.0–26.5]	0 (0.0) [0.0–33.6]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–41.0]	0 (0.0) [0.0–52.2]	0 (0.0) [0.0–60.2]	0 (0.0) [0.0–20.6]	0 (0.0) [0.0–20.6]
Clinical benefit rate, n (%) [95% CI]	10 (40.0) [21.1–61.3]	11 (42.3) [23.4–63.1]	3 (18.8) [4.0–45.6]	1 (8.3) [0.2–38.5]	3 (33.3) [7.5–70.1]	3 (60.0) [14.7–94.7]	2 (28.6) [3.7–71.0]	1 (20.0) [0.5–71.6]	0 (0.0) [0.0–60.2]	3 (18.8) [4.0–45.6]	2 (12.5) [1.6–38.3]
Median PFS, months	3.5	5.5	1.8	1.8	2.8	20.1	2.6	1.7	2.1	1.9	1.7

Hyman et al, Nature 2018

Conclusions

- Patients with HER2+ MBC have substantially improved outcomes with the introduction of the double blockage with trastuzumab and pertuzumab in the first line setting and T-DM1 beyond first line progression.

- Despite these important therapeutic advances, most patients will eventually relapse and get somehow resistant. Novel therapeutic options with efficacy in third line and beyond showed great benefits to improve patients outcomes

  - FDA approval for neratinib, DS-8201 and tucatinib. Margetuximab under review
  - Eagerly awaited EMA approval for these drugs: tucatinib under review

- In order to decide on the best strategy following progression beyond second line, we may consider:

  - Efficacy and toxicity profile of each drug
  - Clinical characteristics of patients
  - Previous treatments received and responses achieved
  - Biomarker analysis from each trial that may identify patients that could benefit differently from each treatment

- Some promising anti HER3+ therapies under development. Stay tuned to this topic as potential new opportunities for a new HER3+ population and anti-HER3 treatments

Gracias!

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by SOLTI