Novel Agents and Strategies Under Evaluation for Patients with HER2-Positive mBC

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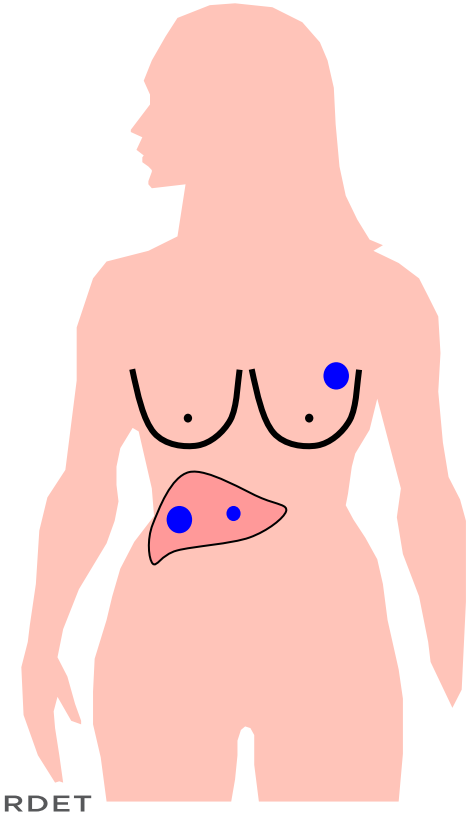
- Other: none

Case Presentation: Dr Hurvitz

- 49 y.o. woman diagnosed 17 years ago (2002) with ER+ HER2+ T2N1 breast cancer s/p neoadjuvant TCH x 4, lumpectomy with 1.6 cm residual disease (0/39 LNs!) 2 more cycles of TCH, radiation therapy → tamoxifen.
- Two years after original diagnosis, (15 years ago) diagnosed with bone metastases. Treated with fulvestrant/trastuzumab (controlled 3 years), lapatinib/trastuzumab/fulvestrant (controlled 4 years), vinorelbine/trastuzumab, T-DM1, then progression.
- Started in mid 2017 on HER2CLIMB study (trastuzumab/capecitabine +/- tucatinib). Did well 14 months then experienced progressive disease.
- Started trastuzumab deruxtecan (DS-8201) on clinical trial (phase II single arm) 9/2018, having great response with normalization of tumor markers.

Case Presentation: Prof Piccart-Gebhart

27 y old premenopausal pt (year 2006)



- **De novo metastatic HER2+ HR+ breast cancer with liver involvement**
- **Past medical HX: unremarkable**
- **Familial medical Hx: unremarkable**

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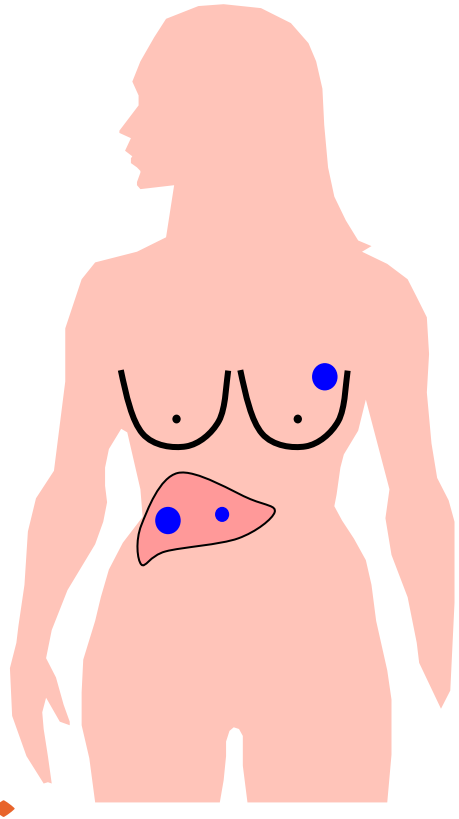
ULB iris

Case Presentation: Prof Piccart-Gebhart

27 y old premenopausal pt (year 2006)



- **Received 4 lines of chemotherapy in a peripheral hospital prior to her first consultation at I. Jules Bordet**
  Aim = control of liver disease

1.	Docetaxel Epirubicin X 6#	Trastuzumab LHRH ag/Tam	2006 - 2010
2.	Paclitaxel + Trastuzumab X 5 m	Trastuzumab LHRH ag/letrozole	2010 - 2011
3.	Radiofrequency Ablation of liver lesions	Capecitabine lapatinib X 6#	Lapatinib LHRH ag/ exemestane — 2011 - 2012
4.	Vinorelbine + lapatinib X 6 m	Lapatinib LHRH ag/ fulvestrant	End 2012 : liver SX unsuccessful Bilateral oophorectomy

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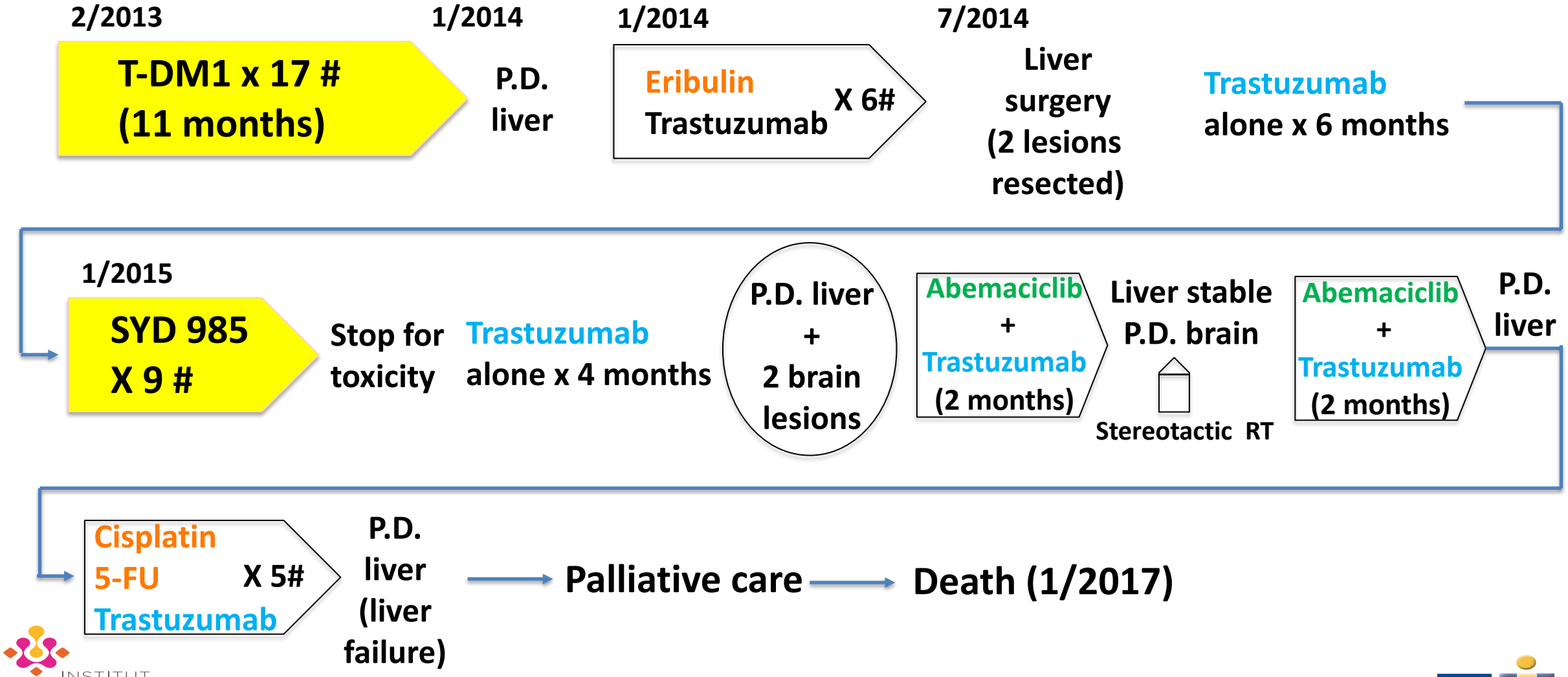
Case Presentation: Prof Piccart-Gebhart



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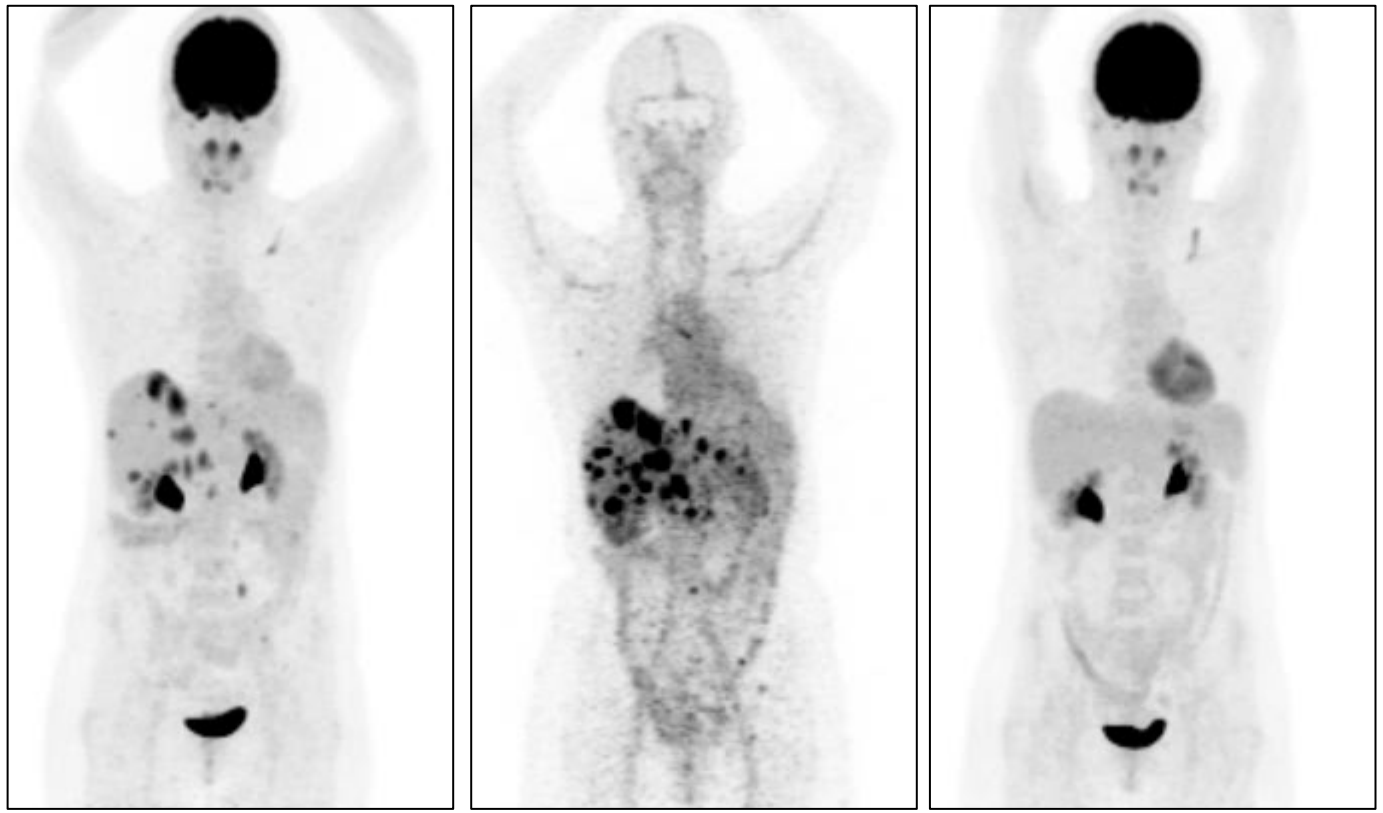
Case Presentation: Prof Piccart-Gebhart



Baseline FDG PET	HER2 PET	FDG PET post 3 T-DM1

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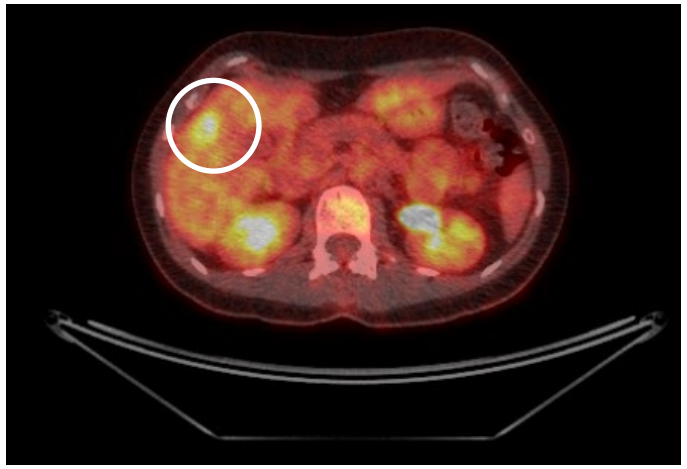
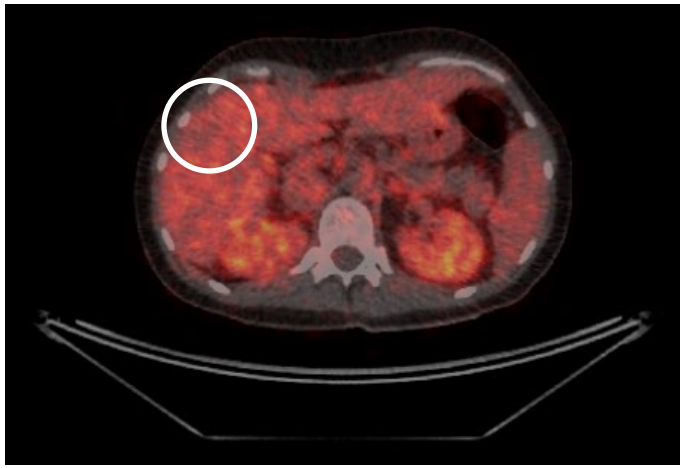
Case Presentation: Prof Piccart-Gebhart

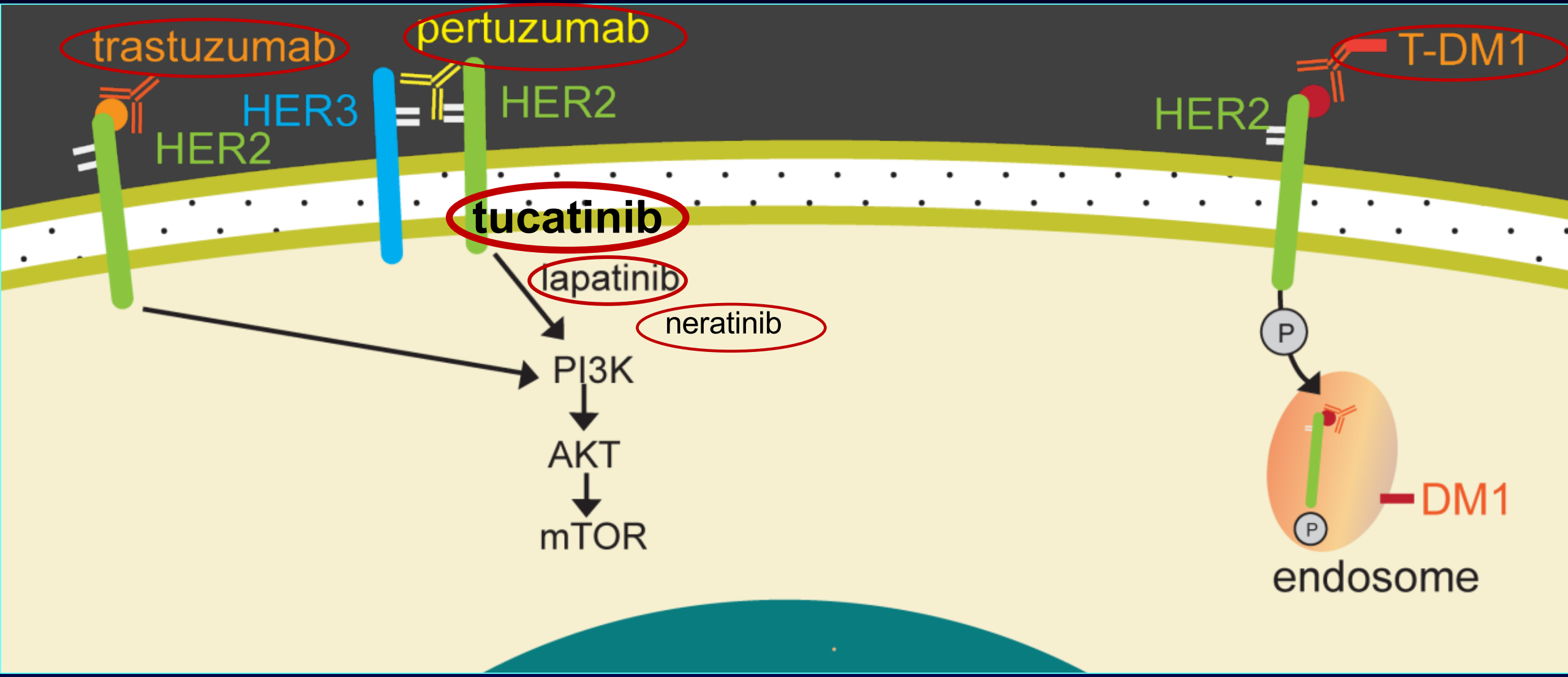


FDG PET/CT post 15 cycles of T-DM1: liver progression



HER2 PET/CT at progression showing no tracer uptake in the liver metastasis

Tucatinib: HER2 SELECTIVE TKI



T-DM1, trastuzumab emtansine

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

Murthy R, SABCS 2019 Abstract GS1-01.

HER2CLIMB Trial Design

Key Eligibility Criteria

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

R* (2:1)

N=410

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

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

N=202

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

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

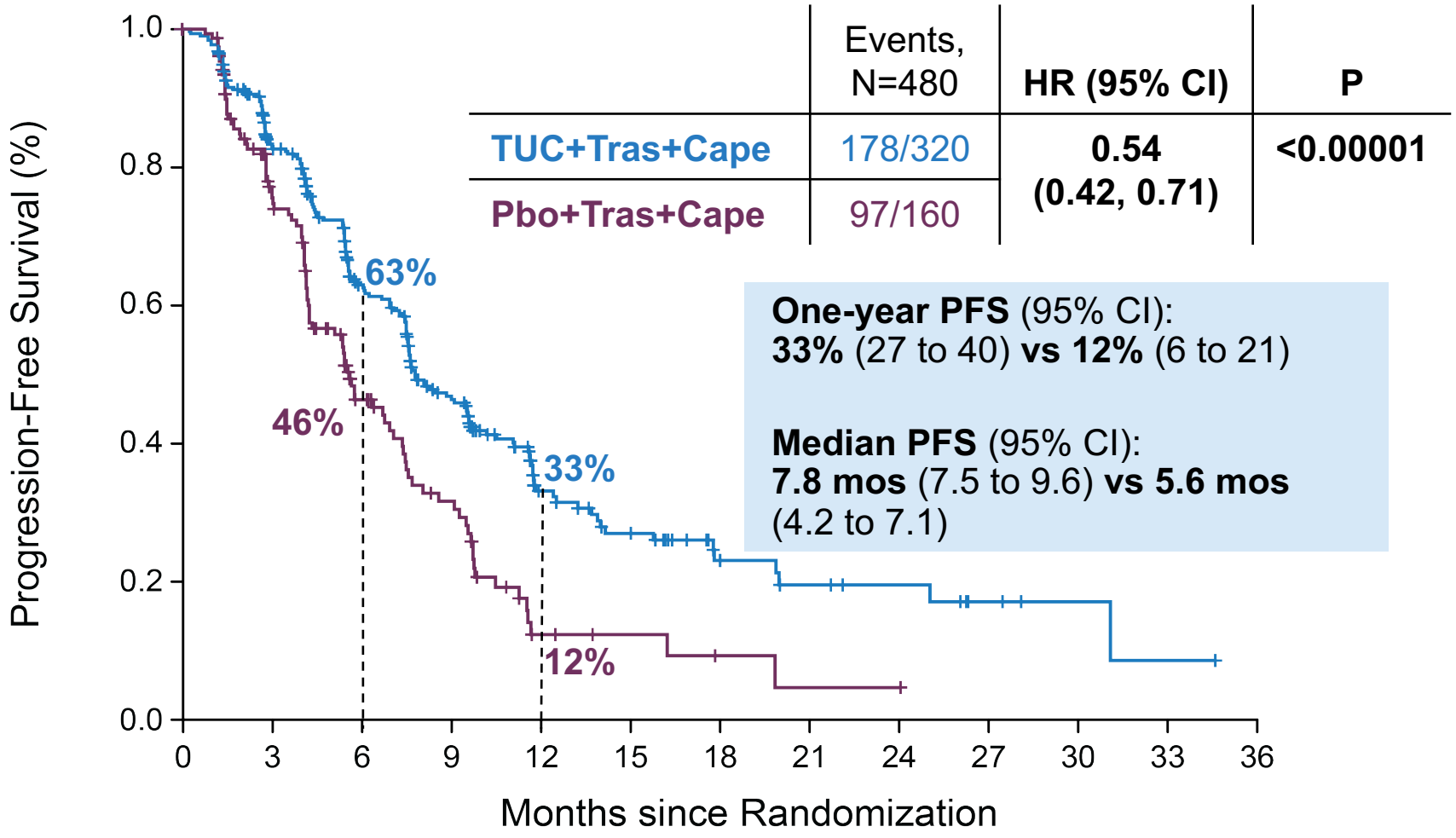
*Stratification Factors: presence of brain metastases (yes/no), ECOG status (0 or 1), and region of world (US or Canada or rest of world)

Baseline Characteristics of Note

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

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

Progression-Free Survival in the Primary Endpoint Population



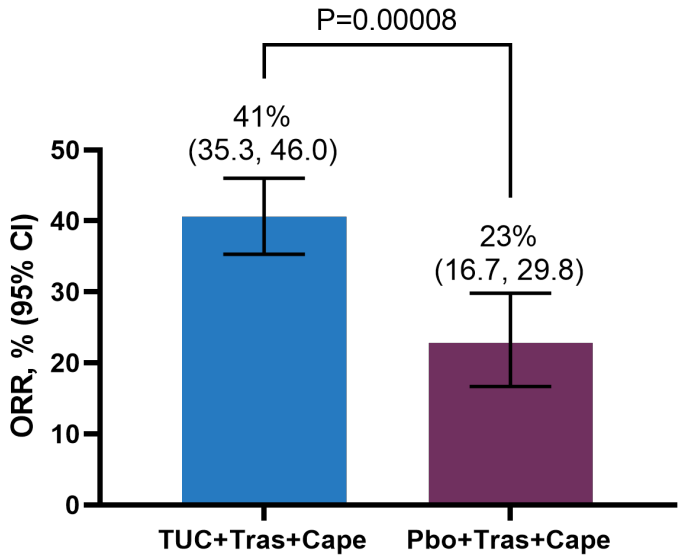
	Events, N=480	HR (95% CI)	P
TUC+Tras+Cape	178/320	0.54 (0.42, 0.71)	<0.00001
Pbo+Tras+Cape	97/160		

One-year PFS (95% CI):
33% (27 to 40) **vs 12%** (6 to 21)

Median PFS (95% CI):
7.8 mos (7.5 to 9.6) **vs 5.6 mos** (4.2 to 7.1)

No. at Risk												
TUC+Tras+Cape	320	235	152	98	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

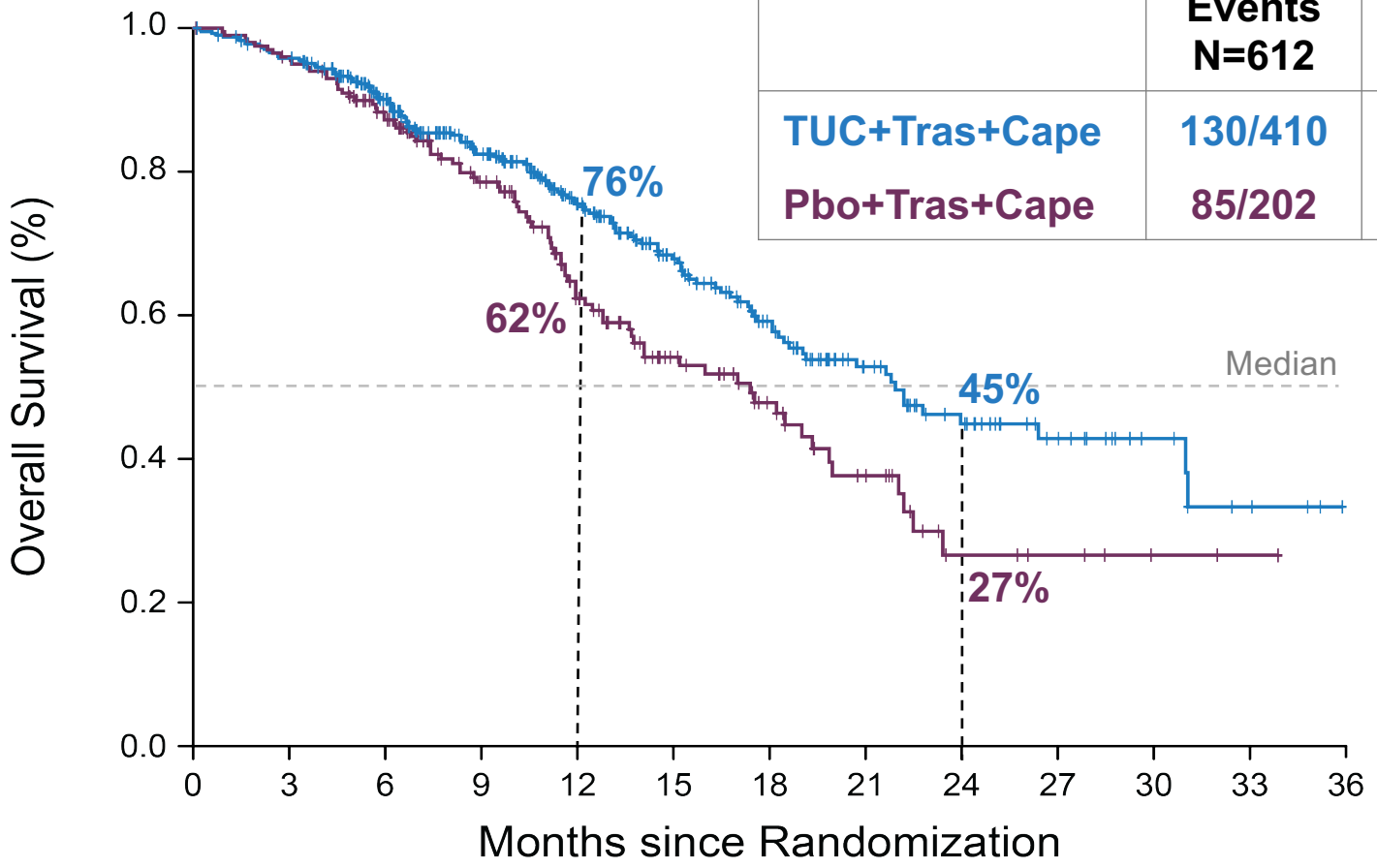
- Confirmed Objective Response Rate (RECIST 1.1, BICR)



Prespecified efficacy boundary for PFS was p=0.05

Overall Survival in the Total Study Population

	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		



No. at Risk

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

Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
45% (37, 53)	27% (16, 39)

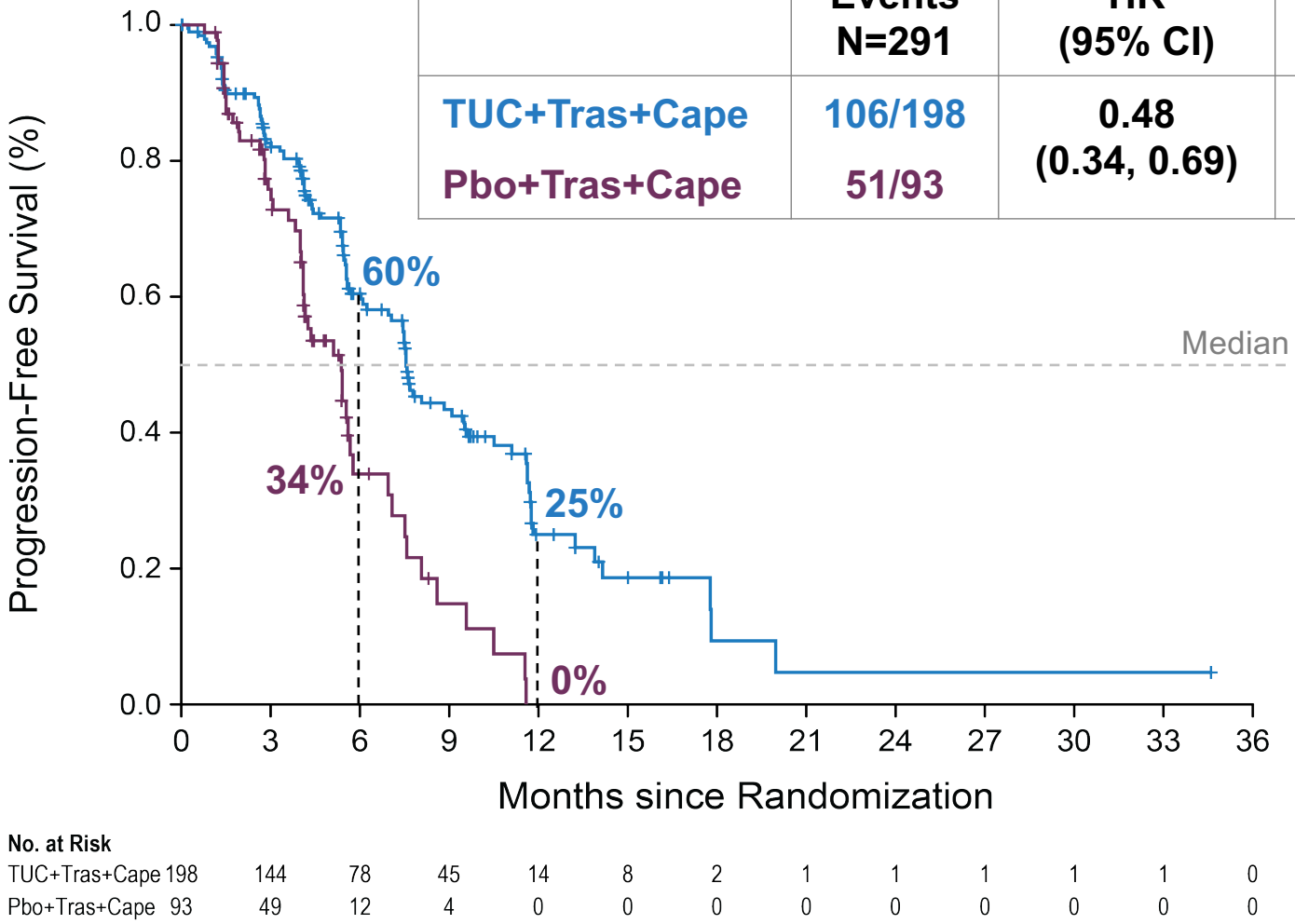
Median OS (95% CI):

TUC+Tras+Cape	Pbo+Tras+Cape
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

Progression-Free Survival for Patients with Brain Metastases

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

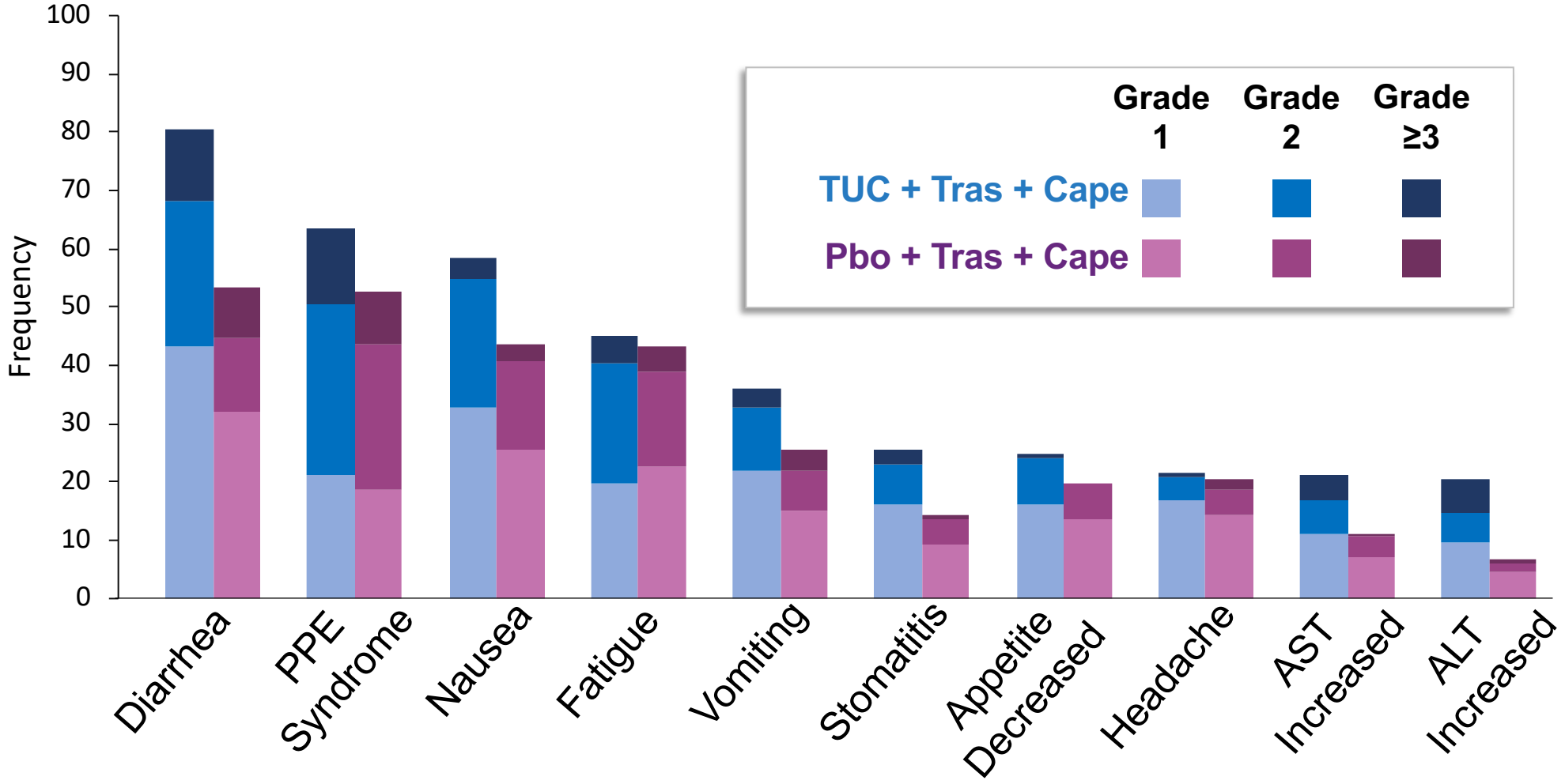


Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

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

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

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



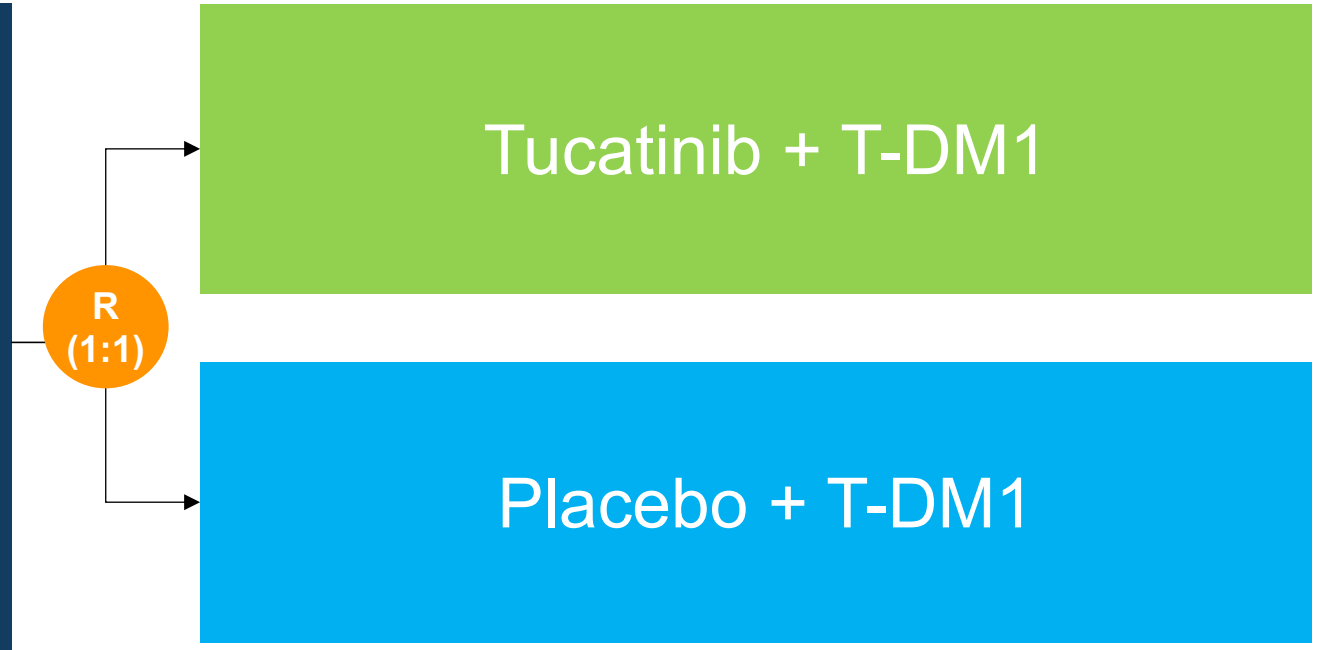
PPE: palmar-plantar erythrodysesthesia, AST: aspartate transaminase, ALT: alanine transaminase

HER2CLIMB-02: A Phase III Trial of Tucatinib or Placebo in Combination with T-DM1

Target accrual (n = 460)

Key Eligibility Criteria

- HER2-positive unresectable locally advanced or metastatic breast cancer
- Prior treatment with a taxane and trastuzumab in any setting
- ECOG PS 0-1

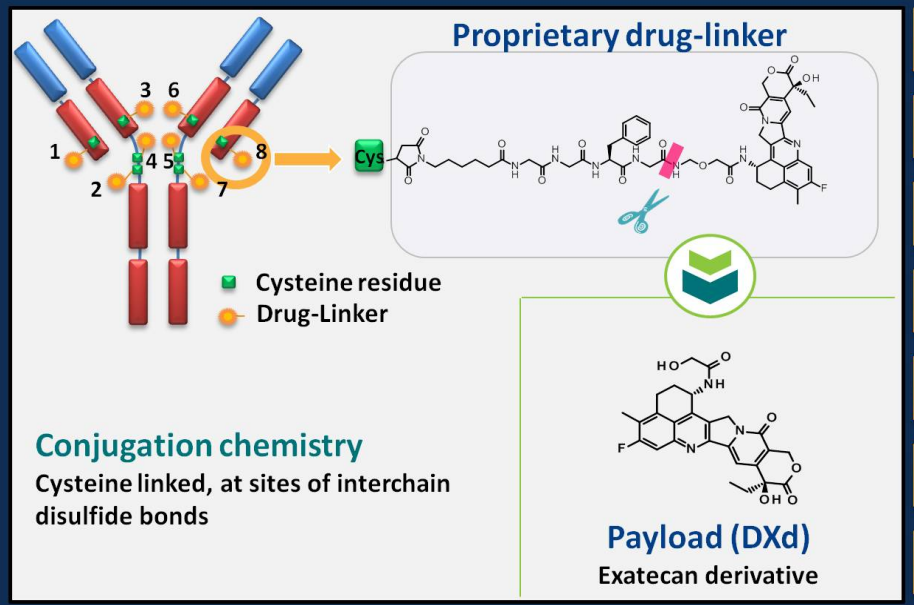


- **Primary endpoint:** PFS by investigator assessment per RECIST v1.1

www.clinicaltrials.gov;Accessed December 2019

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

DS-8201a



- Novel payload
- High potency
- Bystander effect
- Short systemic half-life payload
- Stable linker-payload
- Tumor selective cleavable-linker
- High drug-to-antibody ratio

Drug Design Attributes

	DS-8201	T-DM1	Clinical Implications
Payload	Topoisomerase-1 inhibitor	Tubulin inhibitor	Validated topo-1 mechanism
Drug antibody ratio	High: 7-8	Low: 3-4	More drug delivery, greater tumor cell killing
Payload Membrane permeability	Highly membrane permeable → "bystander effect"	Membrane impermeable → no bystander effect	Kills neighboring heterogenous non-HER2 tumor cells (pH dependent topo-1 potency)

Designed with the goal of improving clinical attributes of an ADC

FDA granted breakthrough therapy designation 8/2017

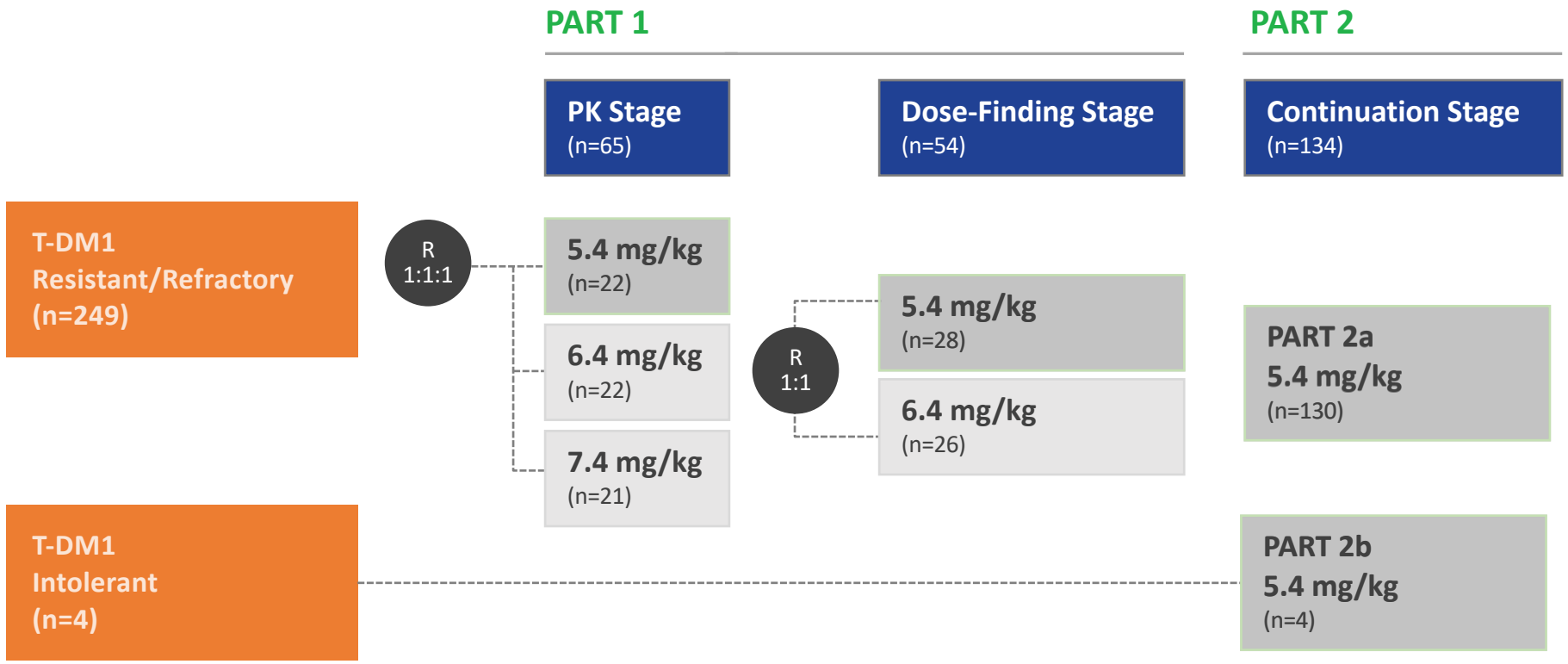
Doi et al. *J Clin Oncol*. 2017;35. DOI: 10.1200/JCO.2017.35.15_suppl.108

DESTINY-Breast01 Study Design:

An Open-Label, Multicenter, Phase II Study

Population

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

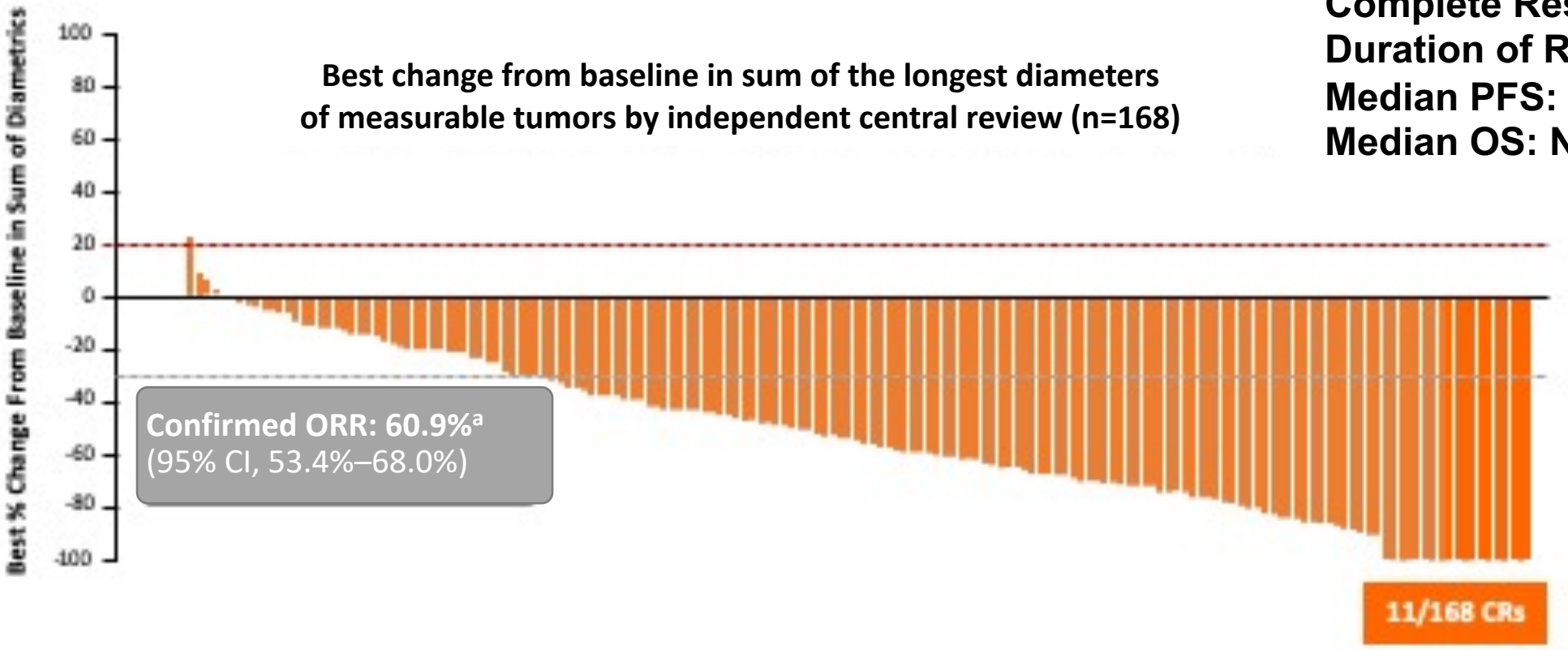


Baseline Characteristics of Note

- **53% HR positive**
- **HER2 IHC 3+ 84%; 1+/2+ (FISH+) 16%**
- **92% visceral disease; 13% h/o brain metastases**
- **Median 6 prior lines of therapy (range 2-27)**

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

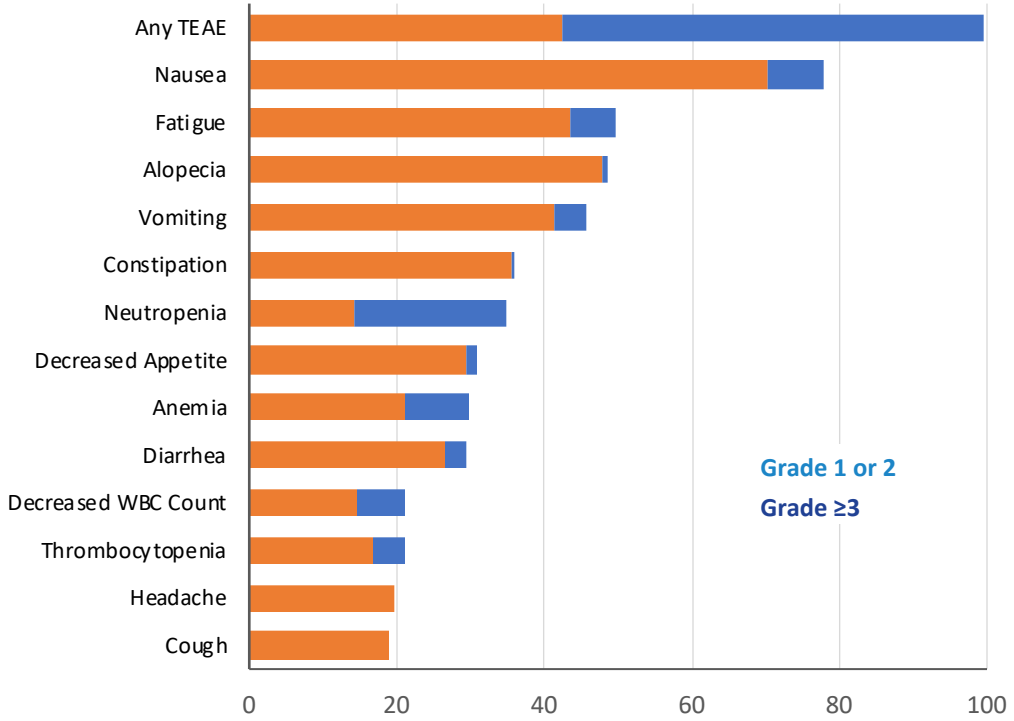
Objective Response Rate at 5.4 mg/kg: 60.9% (112/184)



Complete Response Rate: 6%
Duration of Response: 14.8 mos
Median PFS: 16.4 mos
Median OS: Not reached

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).

Treatment-emergent Adverse Events in >15% of Patients[a]



Interstitial Lung Disease

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

Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial lung disease[a]	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**

- Serious TEAEs, 22.8% (drug related, 12.5%)
- TEAEs associated with discontinuation, 15.2% (drug related, 14.7%); **the majority were due to pneumonitis/ILD (8.7%)**
- 9 (4.9%) TEAE-associated deaths[b]

[a]Patients who received T-DXd 5.4 mg/kg.

[b]Each of the following TEAE was associated with a fatal outcome: respiratory failure, acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, shock hemorrhagic; 1 patient had two TEAEs associated with death: acute kidney injury and acute hepatic failure.

Pneumonitis associated with DS-8201a

ILD in Phase 1/2 studies[1]

	All-grade	Grade 5
All subjects N=665	9.9%	0.8%
Breast cancer, any dose N=510	10.6%	0.8%
Breast cancer, 5.4 mg/kg N=269	5.6%	0.4%

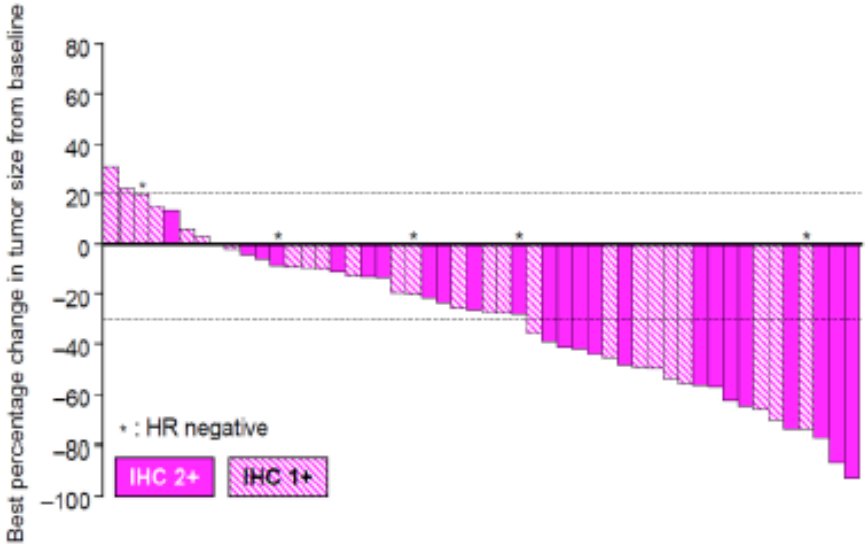
Source: [1]Powell et al, SABCS 2018; Poster #P6-17-06, Abstract #979

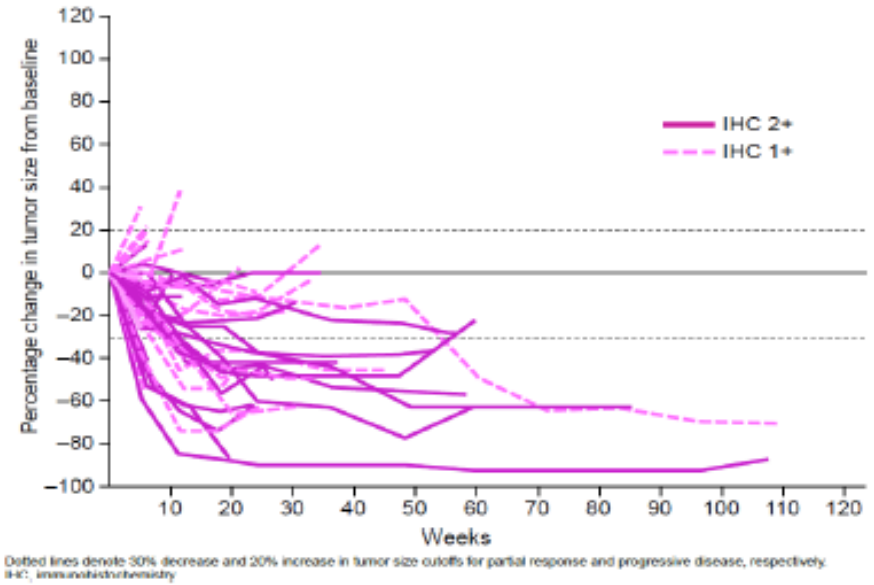
Conclusions

- **Higher likelihood of developing ILD associated with[1]:**
  - **Higher dose (≥6.4 mg/kg)**
  - **Japanese origin:** *Japanese patients 49% of N=665 sample*
  - **Number of prior therapies:** *Many patients in Phase1/2 have multiple prior lines of therapy*
- **Median 149 days (~6 months) to onset[1] allows for monitoring & intervention**
- **Education and guidelines implementation underway**

ILD, interstitial lung disease.

DS-8201: Breakthrough efficacy in HER2 low breast cancer





	Confirmed ORR	mDoR	mPFS
All (N = 51)	44.2% (N=43)	9.4m	7.6m
IHC 2+ (n = 24)	54.5% (N=22)	11.0m	13.6m
IHC 1+ (n = 27)	33.3% (N=21)	7.9m	5.7m
HR+ (n = 45)	47.4% (N=38)	11.0m	7.9m
Prior CDK4/6 inhibitor (n = 15)	33.3% (N=12)	NR	7.1m

Source: SABCS Dec 2018, Modi et al; Poster # p6-17-02, Abstract #486. October 12th, 2018 data cut off

DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mPFS, median progression-free survival; ORR, overall response rate

Ongoing Phase III Trials with DS-8201a

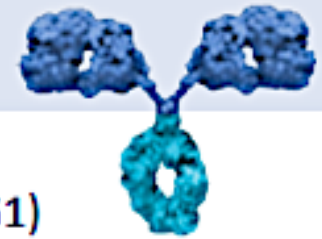
Clinical Trial	Setting	Treatment Arms
DESTINY-Breast-02 (U301)	HER2+ unresectable and/or metastatic breast cancer previously treated with T-DM1	• DS-8201a • Investigator's choice (trastuzumab + capecitabine or lapatinib + capecitabine)
DESTINY-Breast-03 (U302)	HER2+ unresectable and/or metastatic breast cancer previously treated with trastuzumab + taxane	• DS-8201a • T-DM1
DESTINY-Breast-04 (U303)	HER2-low (IHC 1+ or 2+/ISH-), unresectable and/or metastatic breast cancer	• DS-8201a • Treatment of physician's choice (single-agent capecitabine, eribulin, gemcitabine, paclitaxel or *nab*-paclitaxel)

Clinicaltrials.gov. Accessed December 2019.

Margetuximab: Fc-engineered to Activate Immune Responses

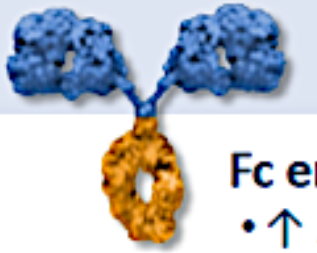
Trastuzumab

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



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

Margetuximab[1,2]



Fab:
- Same specificity and affinity
- Similarly disrupts signaling

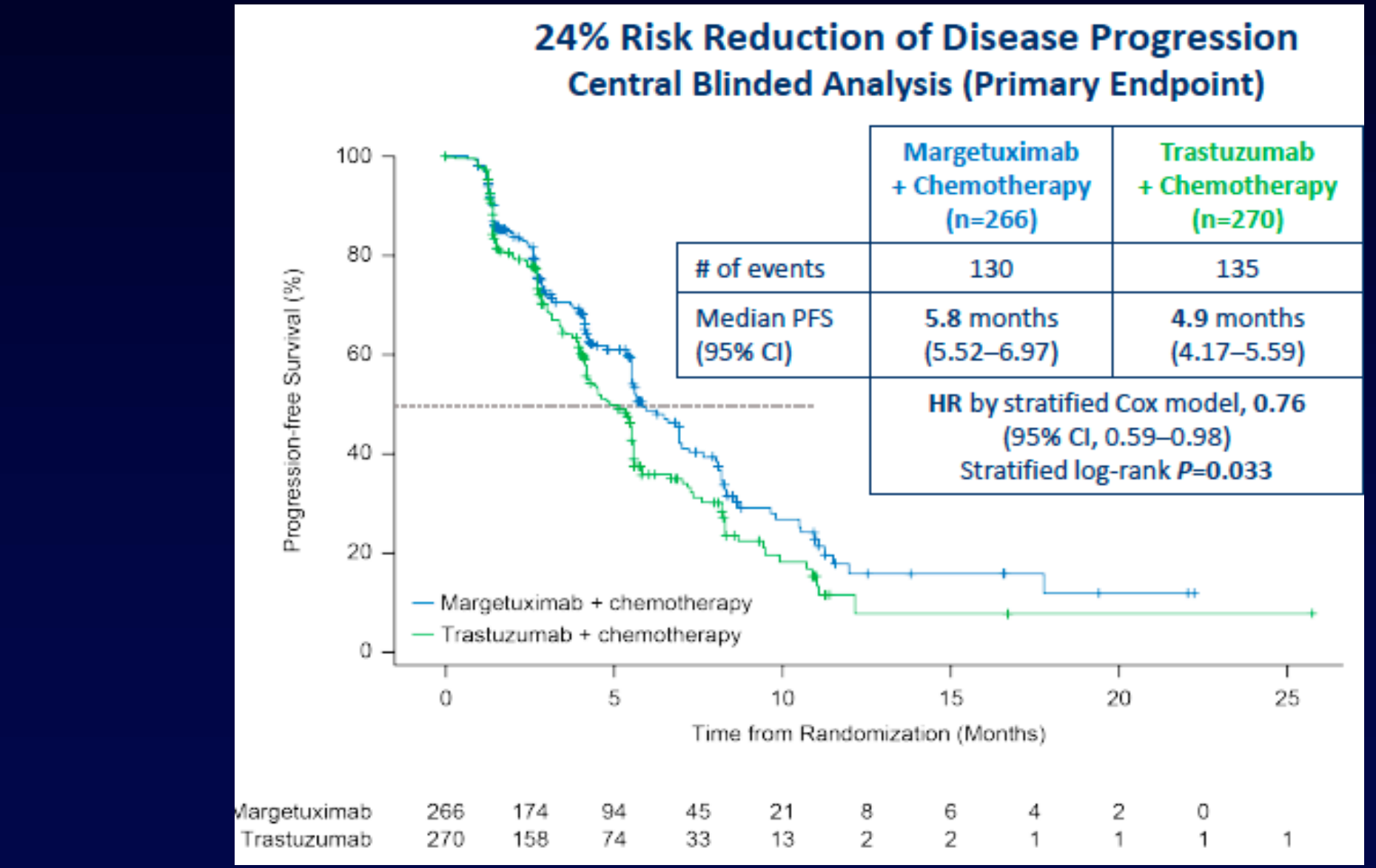
Fc engineering:
- ↑ Affinity for activating FcγRIIIA (**CD16A**)
- ↓ Affinity for inhibitory FcγRIIB (**CD32B**)

Margetuximab Binding to FcγR Variants:

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

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

Phase III SOPHIA Trial: PFS Analysis of Margetuximab in ITT Population

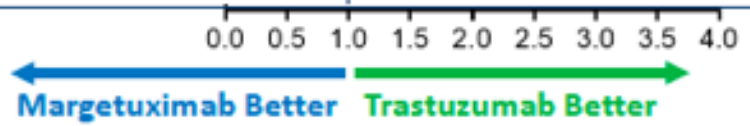


Rugo HS et al. ASCO 2019;Abstract 1000.

Planned* Exploratory PFS Analyses by FcγR Genotypes (CBA)

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

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



Rugo HS et al. ASCO 2019;Abstract 1000.

*Non-alpha allocating, exploratory analysis.

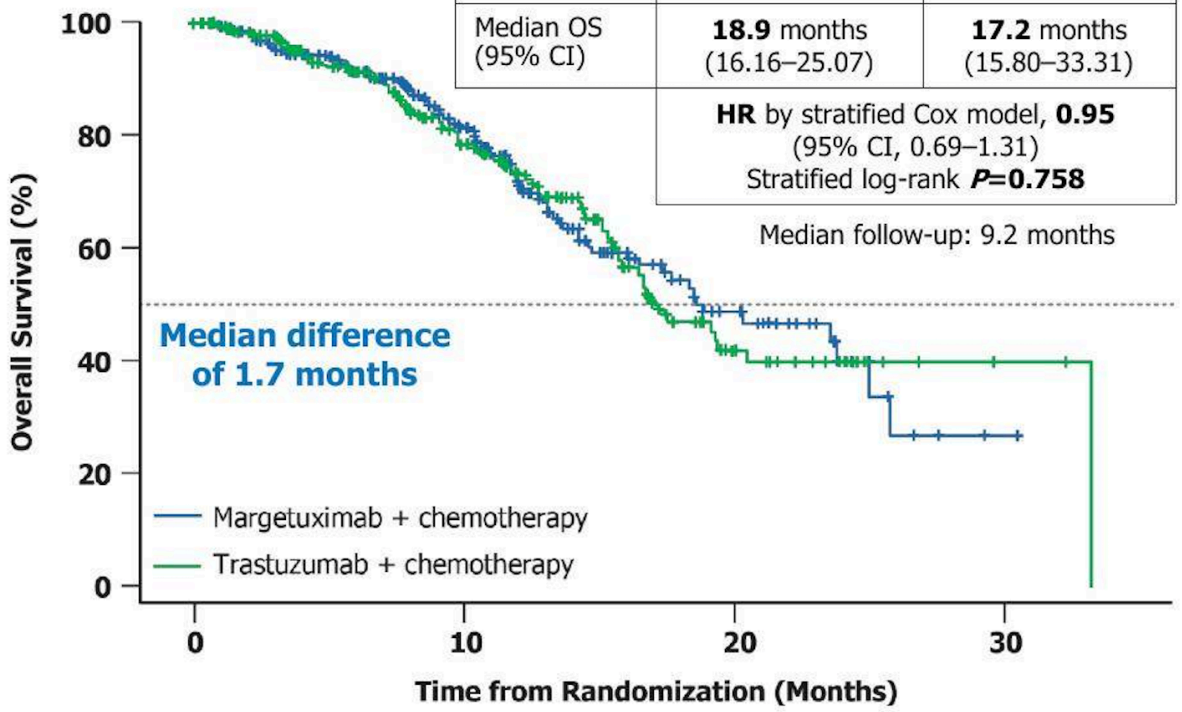
†CD32B/TT not included on forest plot because n=9 is too small (5 on margetuximab, 4 on trastuzumab) to make analysis meaningful.

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

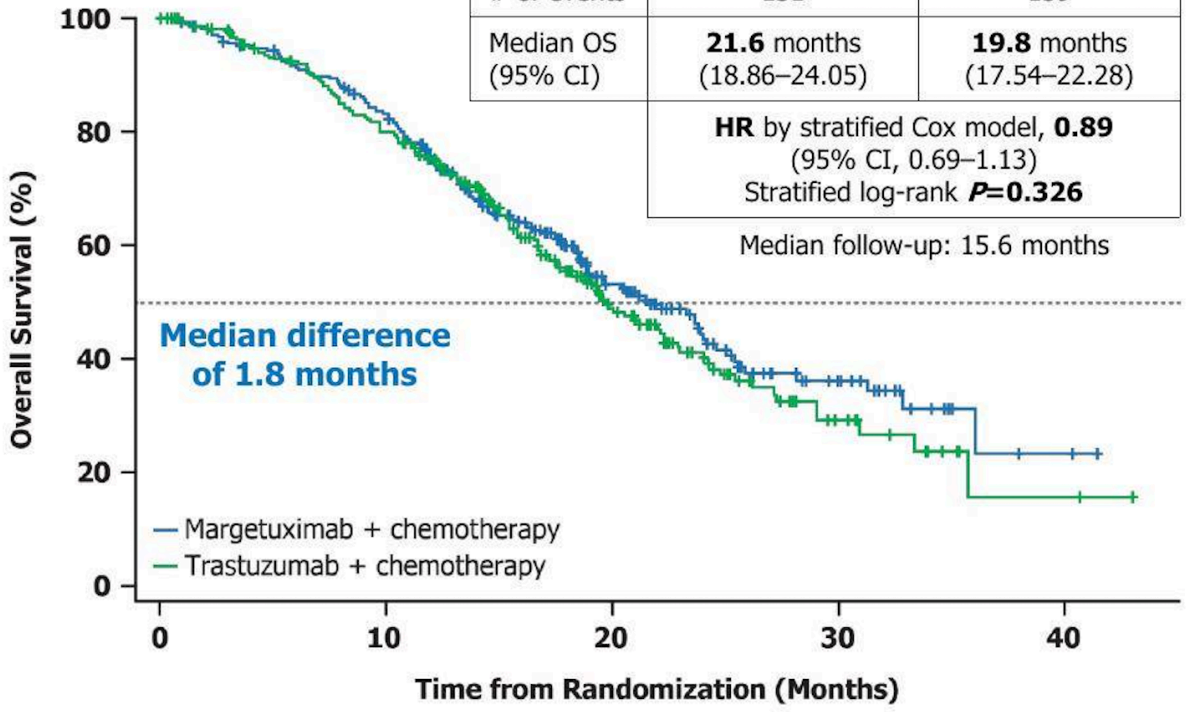


Margetuximab	266	241	209	174	125	85	57	42	29	17	8	3	1	0
Trastuzumab	270	237	194	163	122	92	63	37	24	14	6	3	2	1	0

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	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

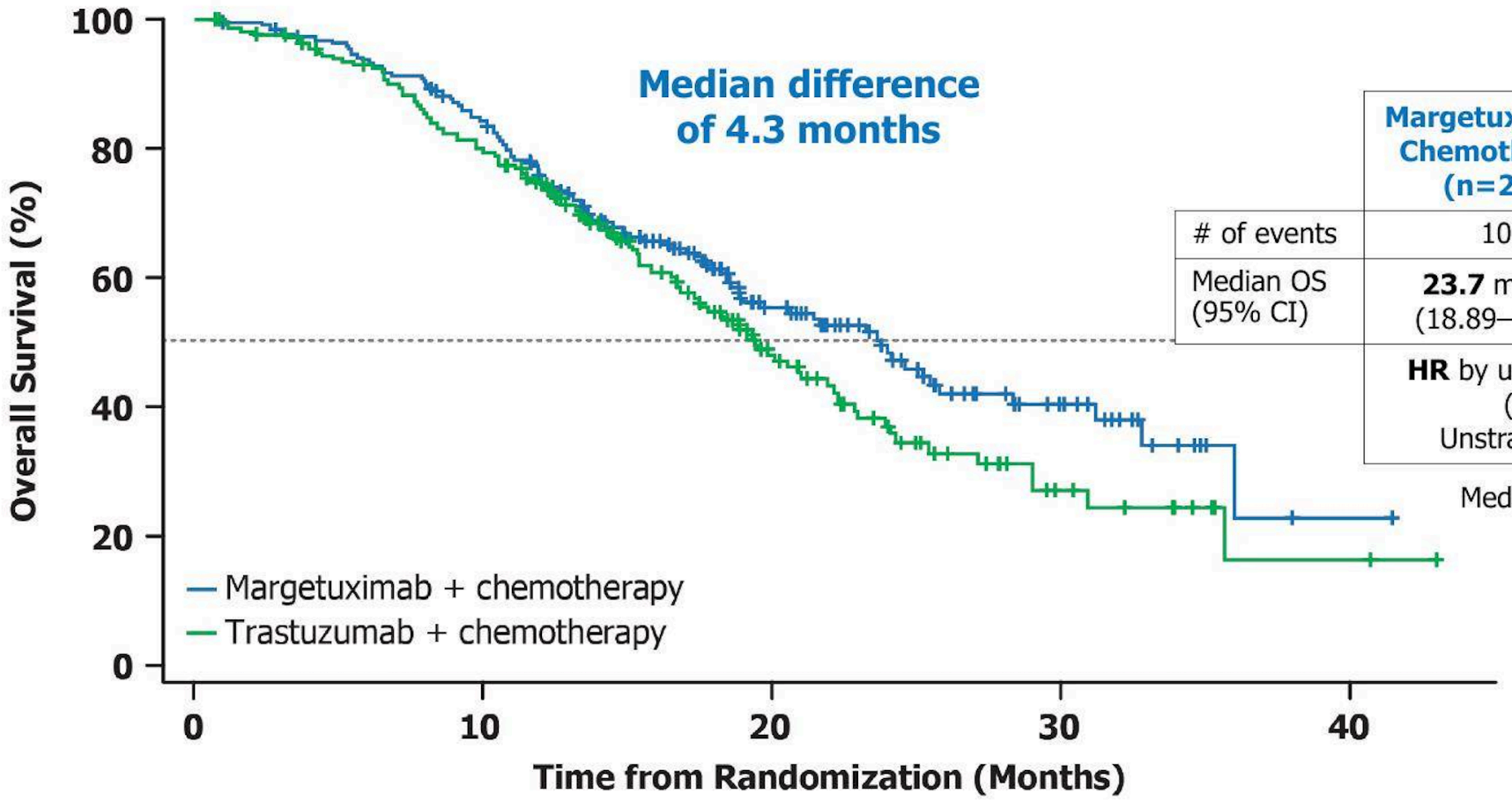
[a]OS analysis performed as of October 10, 2018 data cutoff, after 158 (41%) of 385 events needed for final OS analysis had occurred.
[b]OS analysis performed as of September 10, 2019 data cutoff, after 270 (70%) of 385 events needed for final OS analysis had occurred.

Rugo HS et al. SABCS 2019;Abstract GS1-02.

Prespecified OS in CD16A-185 F carriers

Sep-2019 Cutoff

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



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

Median follow-up: 15.6 months

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

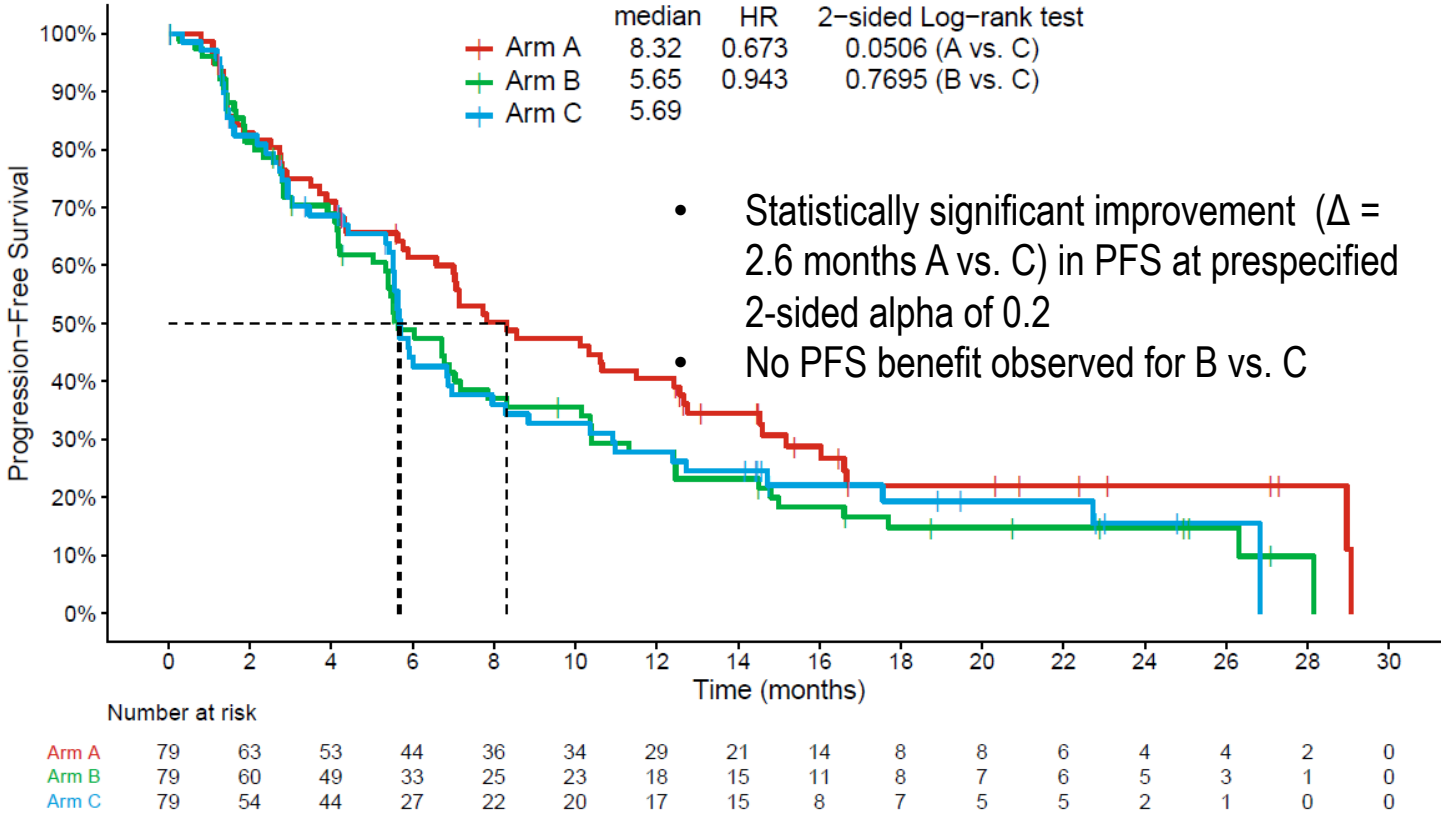
Additional HER2 Targeting ADCs in Breast Cancer

Drug Name	Clinical Trials	Setting
A166	Phase 1/2: NCT03602079	HER2+ locally advanced/metastatic solid tumors that did not respond or stopped responding to approved therapies
ALT-P7 (HM2-MMAE)	Phase 2: NCT03281824	HER2+ metastatic breast cancer patients who have progressed on previous trastuzumab-based therapy
ARX788	Phase 1: NCT02512237 Phase 1: NCT03255070	HER2+ advanced cancers
DHES0815A (anti-HER2/PBD-MA)	Phase 1: NCT03451162	HER2+ breast cancer
MEDI4276	Phase 1: NCT02576548	HER2+ advanced solid tumors
RC48	Phase 1b/2: NCT03052634 Phase 2: NCT03500380	HER2+ advanced breast cancer
SYD985 ([vic-]trastuzumab duocarmazine)	Phase 3: TULIP; NCT03262935	HER2+ unresectable locally advanced or metastatic breast cancer vs. physician's choice
XMT-1522 (TAK-522)	Phase 1: NCT02952729	HER2+ advanced breast cancer and other advanced tumors

Phase II monarcHER Study Results

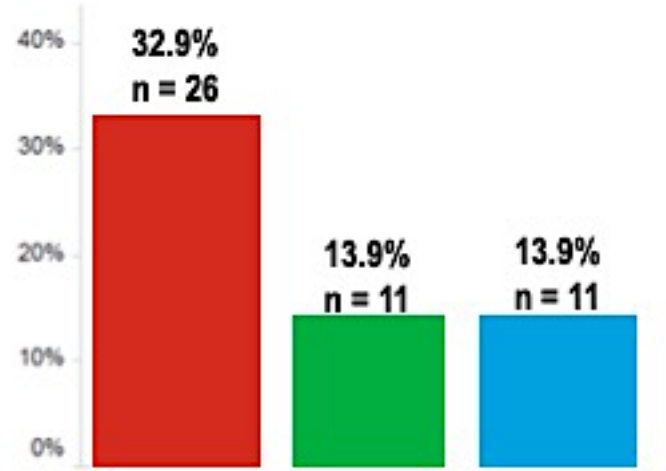
Progression-free survival

Arm A = abemaciclib + trastuzumab + fulvestrant
Arm B = abemaciclib + trastuzumab
Arm C = trastuzumab + chemotherapy



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

Objective response rate



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached

BARCELONA 2019 ESMO congress

Tolaney S et al. 2019

Summary

- VERY exciting time for novel therapies to treat HER2+ metastatic breast cancer
- Likely approval of tucatinib, trastuzumab deruxtecan, neratinib in 2020 for metastatic disease
- Many novel agents being evaluated:
  - Other ADCs
  - Novel antibodies
  - CDK4/6 inhibitors
  - Immune therapy