SOPHIA Primary PFS Analysis: A Phase 3 Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies

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Abstract #1000
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Persistent Unmet Need in HER2+ MBC After Anti-HER2 Therapy

- Current standard of care for HER2-positive MBC
  - First-line: trastuzumab and pertuzumab with chemotherapy[1-3]
  - Second-line: T-DM1[4,5]
- After the above therapies, there is no recognized standard of care
  - Subsequent therapies are poorly defined, including sequential chemotherapy with trastuzumab and/or lapatinib[6,7]
  - Continued anti-HER2 therapy after progression is generally preferred, in combination with chemotherapy[8-11]

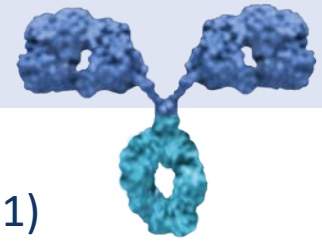
HER2=human epidermal growth factor receptor 2; MBC=metastatic breast cancer; T-DM1=ado-trastuzumab emtansine.

1. Baselga J, et al. *N Engl J Med.* 2012;366(2):109-119. 2. Swain SM, et al. *Lancet Oncol.* 2013;14(6):461-471. 3. Swain SM, et al. *N Engl J Med.* 2015;372(8):724-734. 4. Verma S, et al. *N Engl J Med.* 2012;367(19):1783-1791. 5. Diéras V, et al. *Lancet Oncol.* 2017;18(6):732-742. 6. Giordano SH, et al. *J Clin Oncol.* 2018;36(26):2736-2740. 7. Cardoso F, et al. *Ann Oncol.* 2018;29(8):1634-1657. 8. von Minckwitz G, et al. *J Clin Oncol.* 2009;27(12):1999-2006. 9. von Minckwitz G, et al. *Eur J Cancer.* 2011;47(15):2273-2281. 10. Geyer CE, et al. *N Engl J Med.* 2006;355(26):2733-2743. 11. Cameron D, et al. *Oncologist.* 2010;15(9):924-934.

Margetuximab: Fc-engineered to Activate Immune Responses

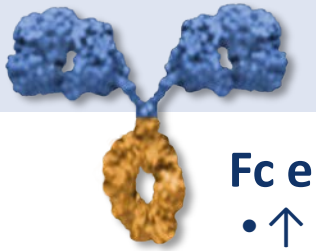
Trastuzumab

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.

CD16A Genotype May Predict Anti-HER2 Antibody Benefit

- Two retrospective studies of HER2+ MBC[1] and early breast cancer[2] suggest patients with lower affinity CD16A-158F allele have lower PFS and ORR with trastuzumab than those homozygous for higher affinity CD16A-158VV
  - Two other retrospective studies showed no association between FcγR genotypes and outcome with adjuvant trastuzumab in early breast cancer[3,4]

- **Hypothesis**: Greater margetuximab benefit in lower binding CD16A-158F carriers
  - Increased affinity of margetuximab for CD16A-158F over trastuzumab (wild-type IgG1)

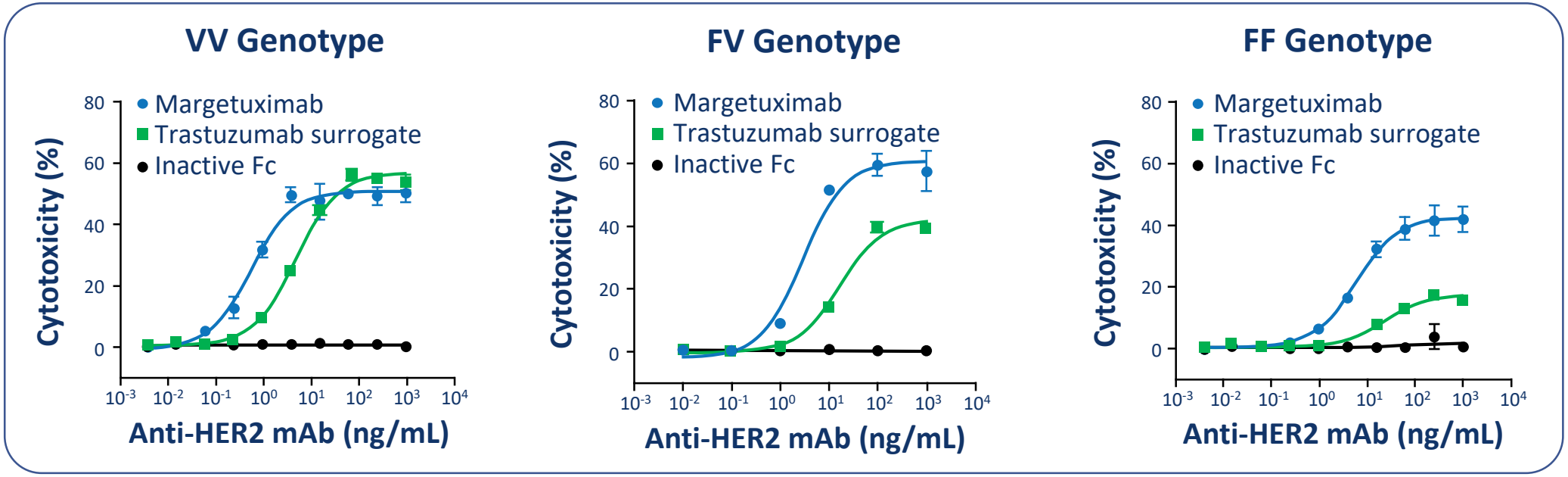
- **SOPHIA is first prospective* analysis of FcγR genotype impact on anti-HER2 antibody efficacy**

*Non-alpha allocating, exploratory analysis.
ORR=objective response rate; PFS=progression-free survival.

1. Musolino A, et al. *J Clin Oncol.* 2008;26(11):1789-1796. 2. Gavin PG, et al. *JAMA Oncol.* 2017;3(3):335-341.
3. Hurvitz SA, et al. *Clin Cancer Res.* 2012;18(12):3478-3486. 4. Norton N, et al. *Cancer Immunol Res.* 2014;2(10):962-969.

Margetuximab Enhances Innate Immunity *In Vitro*

Greater relative cytotoxicity of margetuximab with NK cells from CD16A-158F allele carriers



Preclinical Assay of Antibody-Dependent Cellular Cytotoxicity (ADCC)[1]

Effector Cells: Human NK cells from donors with CD16A genotypes 158VV, 158FV, and 158FF

Target Cells: JIMT-1 HER2+ breast cancer cell line resistant to trastuzumab antiproliferative activity

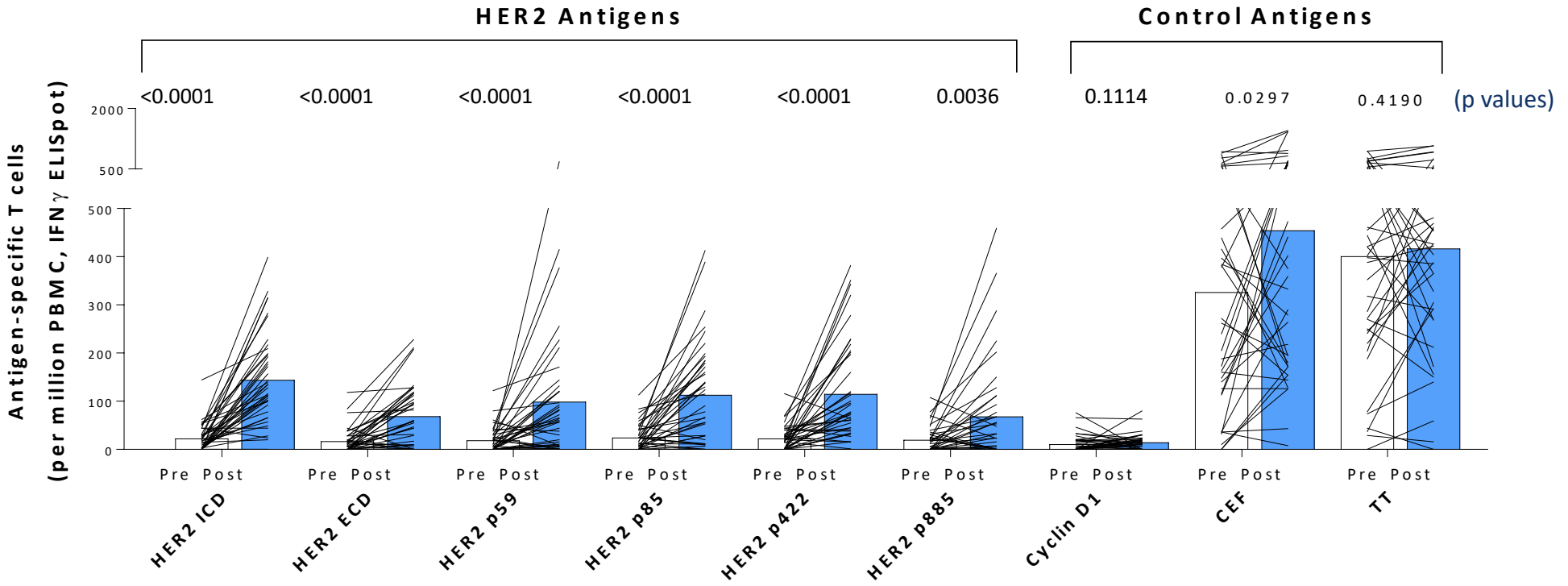
Cellular Assay: 3:1 Effector:Target ratio; 24-hour incubation time; endpoint: % lactate dehydrogenase release

mAb=monoclonal antibody; NK=natural killer.

Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123.

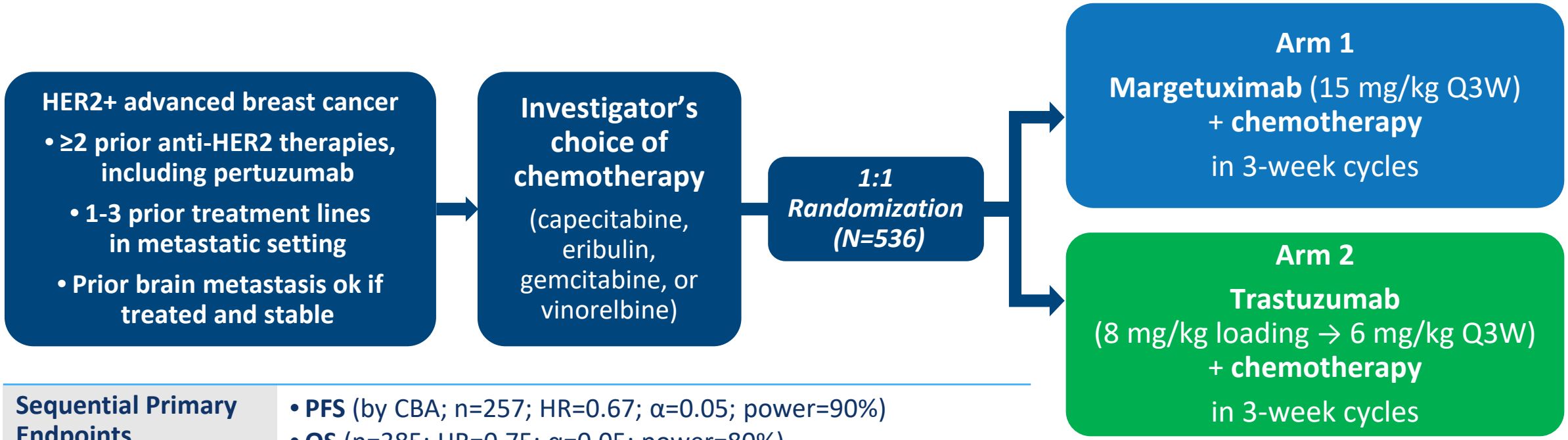
Margetuximab Enhances HER2-specific Adaptive Immunity[1,2]

- Phase 1 margetuximab monotherapy study in 66 pretreated patients with HER2+ carcinomas[3,4]:
  - Four (17%) confirmed responses in 24 evaluable patients with HER2+ MBC[3]
  - Three patients continue on margetuximab at least 4 to 6 years, as of 15-May-2019[4]
- Enhanced HER2-specific T- and B-cell responses after margetuximab monotherapy[5]



1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890. 3. Bang YJ, et al. *Ann Oncol.* 2017;28(4):855-861.
4. Im SA, et al. *Cancer Res.* 2019;79(suppl 4): Abstract P6-18-11. 5. Nordstrom JL, et al. ASCO 2019 Poster (Abstr. #1030).

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



Sequential Primary Endpoints	• **PFS** (by CBA; n=257; HR=0.67; α=0.05; power=90%) • **OS** (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (Investigator assessed) • Objective response rate (by CBA)
Tertiary/Exploratory Endpoints	• Clinical benefit rate (CBR), duration of response (DoR) • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

Stratification:
- Chemotherapy choice
- Prior therapies (≤2 *vs* >2)
- Metastatic sites (≤2 *vs* >2)

HR=hazard ratio; CBA=central blinded analysis.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. www.clinicaltrials.gov/ct2/show/NCT02492711. Accessed April 8, 2019.

ITT Population: Baseline Characteristics

		Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Demographics	Median age	55	56
	Female sex	266 (100%)	267 (98.9%)
	Europe	152 (57%)	138 (51%)
	North America	85 (32%)	102 (38%)
	Other region	29 (11%)	30 (11%)
Disease Characteristics	ECOG PS 0	149 (56%)	161 (60%)
	ECOG PS 1	117 (44%)	109 (40%)
	Metastatic	260 (98%)	264 (98%)
	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%)
Backbone chemotherapy	Capecitabine	71 (27%)	72 (27%)
	Eribulin	66 (25%)	70 (26%)
	Gemcitabine	33 (12%)	33 (12%)
	Vinorelbine	96 (36%)	95 (35%)

Treatment arms overall balanced

ITT population (all randomized patients): N=536.

ECOG=Eastern Cooperative Oncology Group; hormone receptor positive=ER+ and/or PgR+; hormone receptor negative=ER- and PgR-; ITT=intention to treat; PS=performance status.

ITT Population: Prior Cancer Therapy

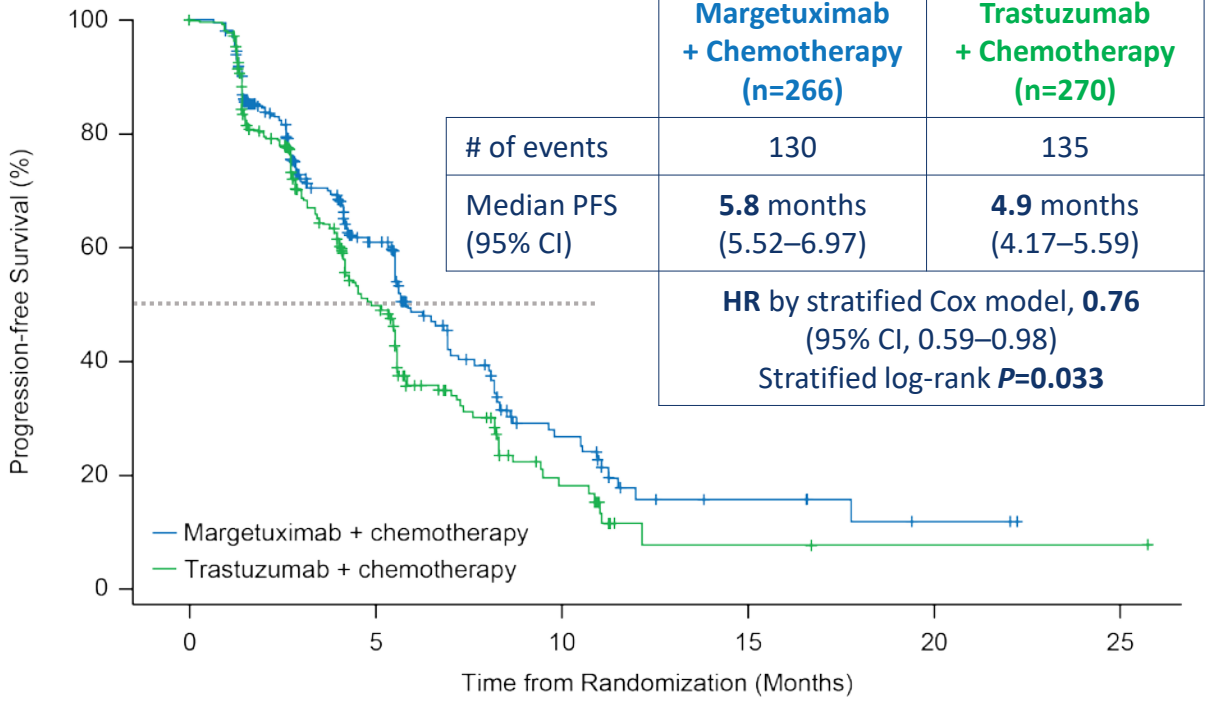
	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
Settings of prior therapy		
Adjuvant and/or neoadjuvant	**158 (59%)**	**145 (54%)**
Metastatic only	108 (41%)	125 (46%)
Prior metastatic lines of therapy		
≤2	175 (66%)	180 (67%)
>2	91 (34%)	90 (33%)
Prior anti-HER2 therapy		
Trastuzumab	**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%)

Treatment arms overall balanced

ITT population: N=536.

PFS Analysis in ITT Population

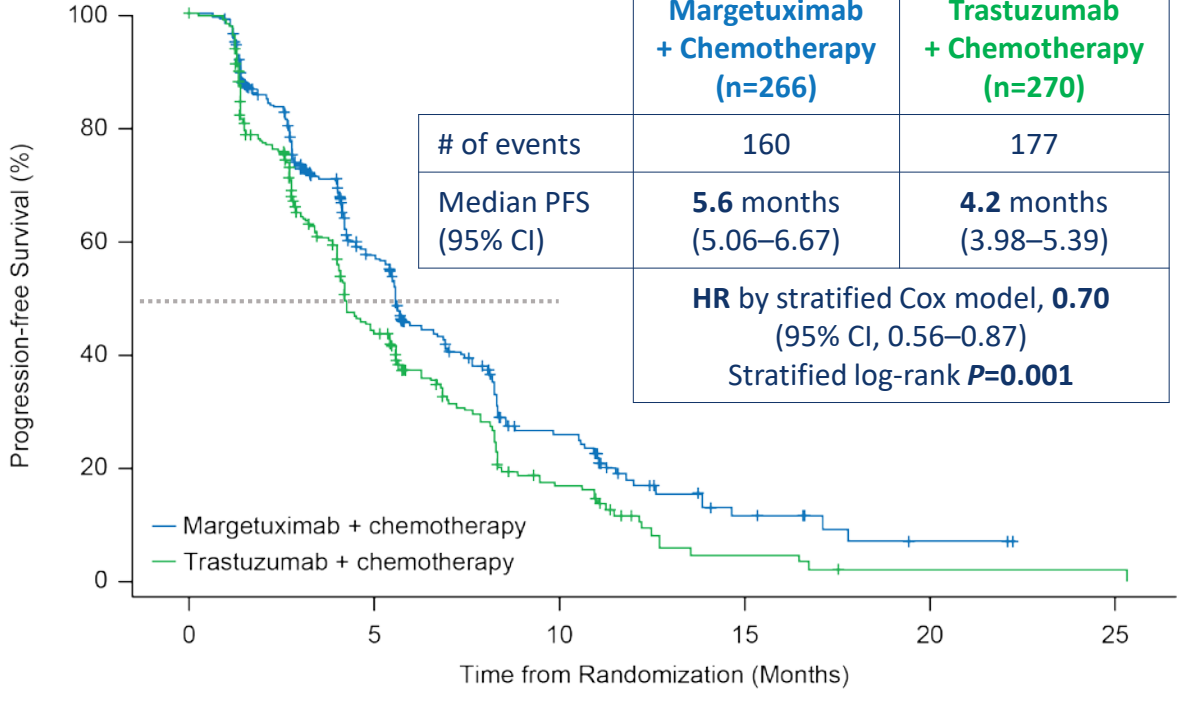
24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)



	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**	

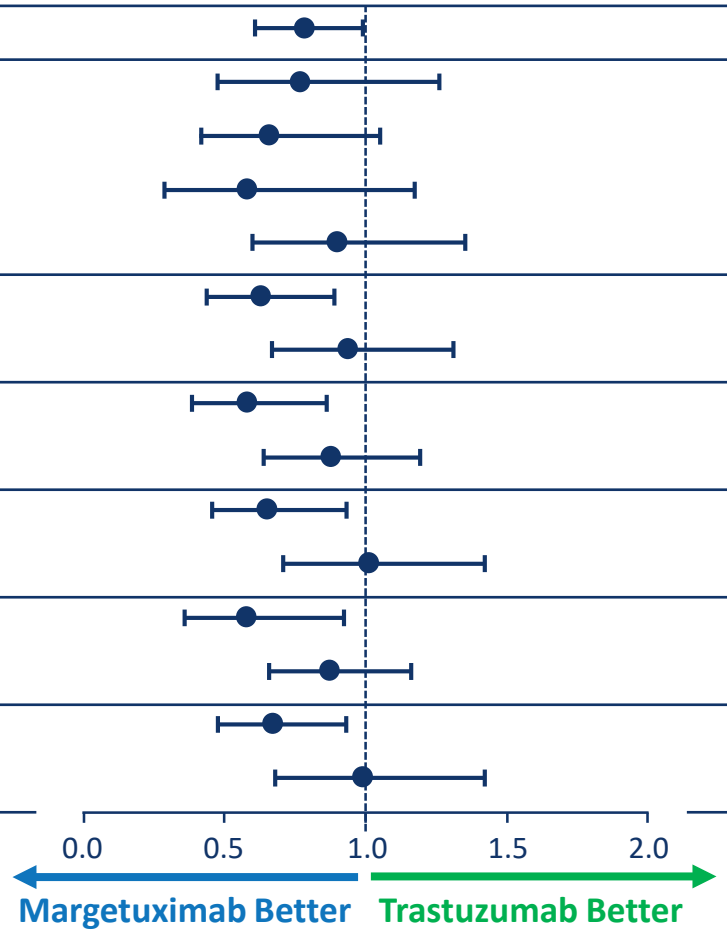
Margetuximab	266	206	155	112	72	61	33	32	16	13	8	7	3	2	2	0		
Trastuzumab	270	184	130	87	59	45	25	21	10	5	4	3	1	1	1	1	1	0

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

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

PFS Subgroup Analyses

	Median PFS (95% CI), Months		HR by Unstratified Cox Model	95% CI	Unstratified Log-Rank *P* Value
	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy			
All patients, n=536	**5.8** (5.52–6.97)	**4.9** (4.17–5.59)	0.78	(0.61–0.99)	0.044
Capecitabine, n=143	8.3 (5.55–11.50)	5.5 (4.17–8.28)	0.77	(0.47–1.26)	0.302
Eribulin, n=136	6.0 (3.81–8.05)	4.2 (3.38–5.55)	0.66	(0.42–1.05)	0.080
Gemcitabine, n=66	5.4 (4.07–11.01)	3.5 (1.45–7.16)	0.58	(0.29–1.18)	0.128
Vinorelbine, n=191	5.6 (4.24–6.97)	5.1 (3.42–6.67)	0.90	(0.60–1.35)	0.606
>2 metastatic sites, n=254	6.3 (5.42, 8.08)	4.2 (3.38, 5.55)	0.63	(0.44–0.89)	0.009
≤2 metastatic sites, n=282	5.7 (4.47, 6.97)	5.5 (4.24, 5.85)	0.94	(0.67–1.31)	0.702
Hormone Receptor-, n=200	5.8 (4.80, 7.23)	4.2 (2.83, 5.55)	0.58	(0.39–0.86)	0.007
Hormone Receptor+, n=334	5.7 (5.52, 8.18)	5.5 (4.24, 7.03)	0.88	(0.64–1.19)	0.393
HER2 IHC 3+, n=291	6.9 (5.55, 8.31)	5.6 (3.98, 5.85)	0.64	(0.46–0.90)	0.011
HER2 ISH amplified, n=245	5.5 (4.01, 6.60)	4.6 (4.07, 5.55)	1.01	(0.71–1.42)	0.972
Age >60 years, n=170	6.9 (5.52, 10.51)	5.6 (4.14, 5.85)	0.58	(0.36–0.92)	0.020
Age ≤60 years, n=366	5.6 (4.24, 6.97)	4.6 (4.01, 5.59)	0.87	(0.66–1.16)	0.337
Prior (neo)adjuvant Tx: yes, n=303	6.3 (5.55–8.05)	5.4 (4.01–5.59)	0.67	(0.48–0.93)	0.014
Prior (neo)adjuvant Tx: no, n=233	5.6 (3.71–6.97)	4.9 (4.07–7.16)	0.99	(0.68–1.42)	0.935

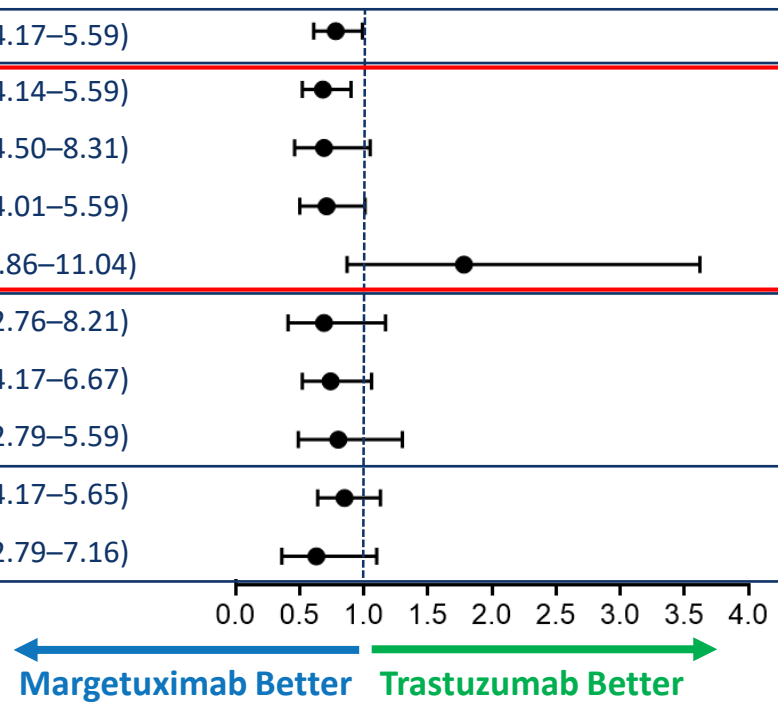


Hormone receptor positive=ER+ and/or PgR+; hormone receptor negative=ER- and PgR-; IHC=immunohistochemistry; ISH=in situ hybridization; Tx=treatment.

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



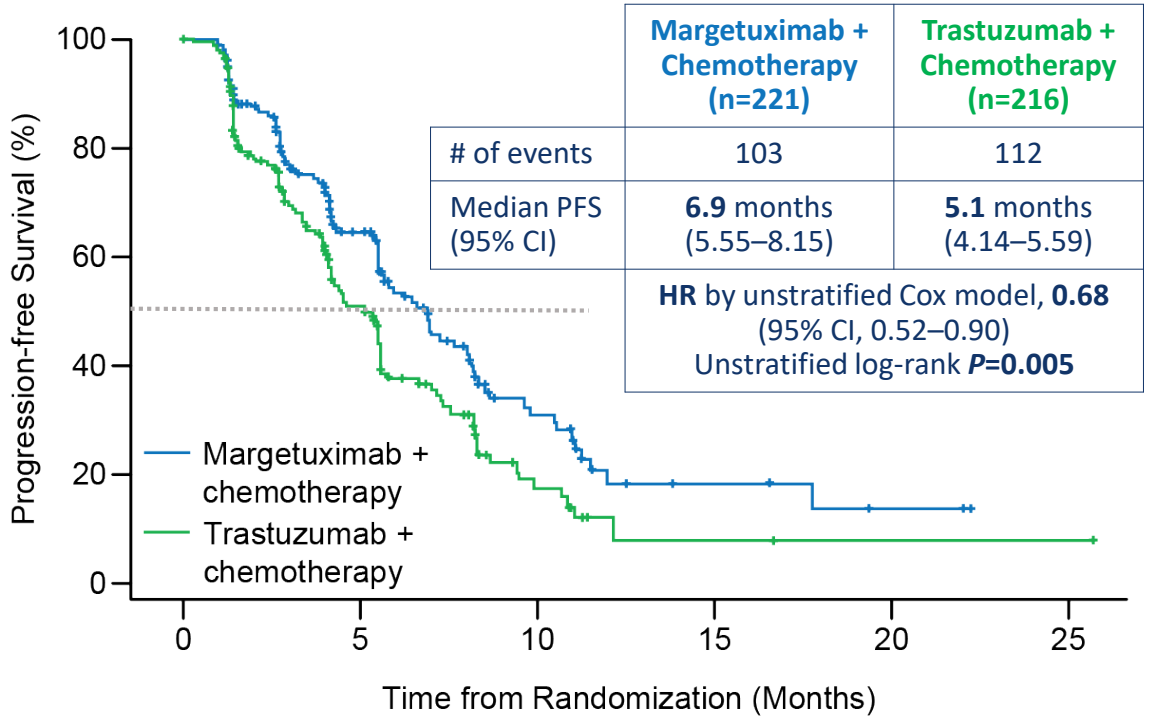
*Non-alpha allocating, exploratory analysis.

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

Planned Exploratory PFS Analysis by CD16A Genotype, by CBA

506 patients genotyped (94%)

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

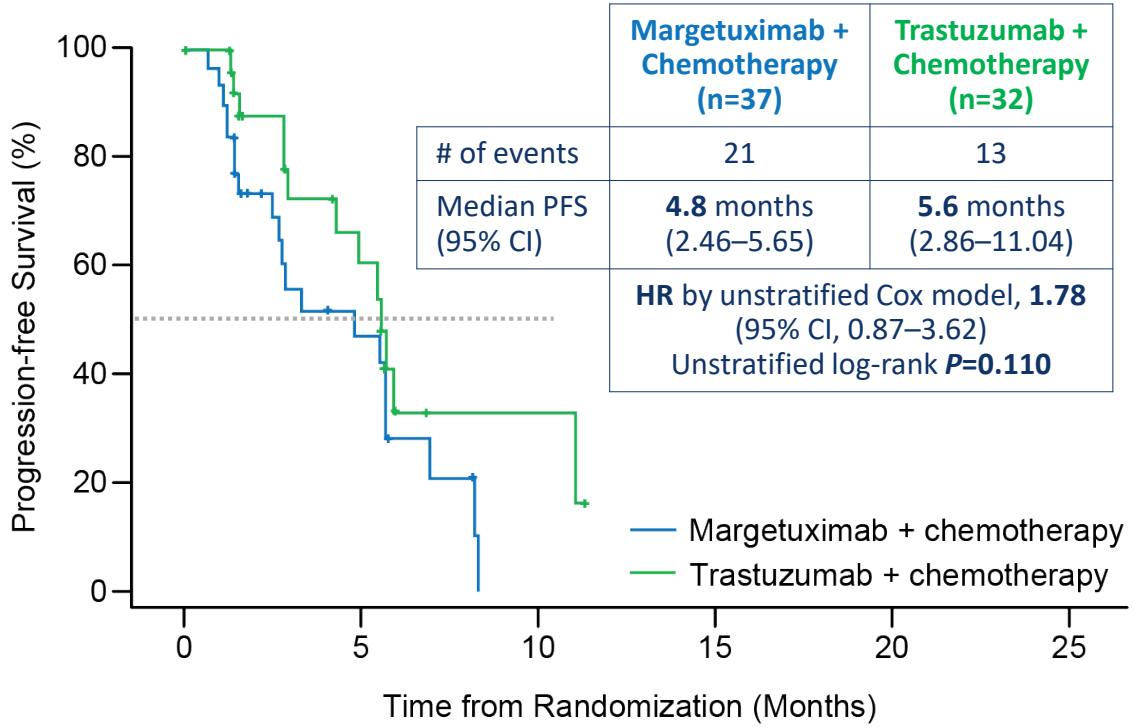


	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	103	112
Median PFS (95% CI)	**6.9** months (5.55–8.15)	**5.1** months (4.14–5.59)

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)

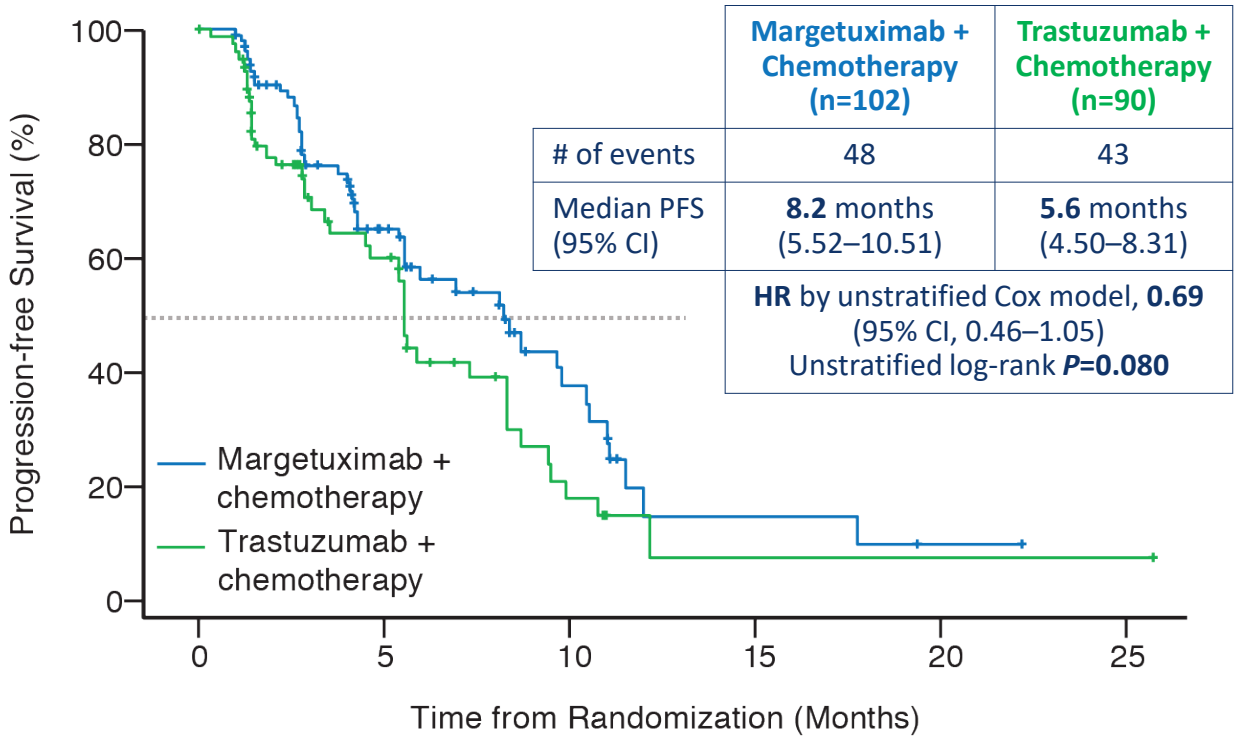
HR by unstratified Cox model, **1.78** (95% CI, 0.87–3.62)
Unstratified log-rank ***P*=0.110**

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

Planned Exploratory PFS Analysis by CD16A Genotype, by CBA

506 patients genotyped (94%)

FF, n=192 of 506 (38%)

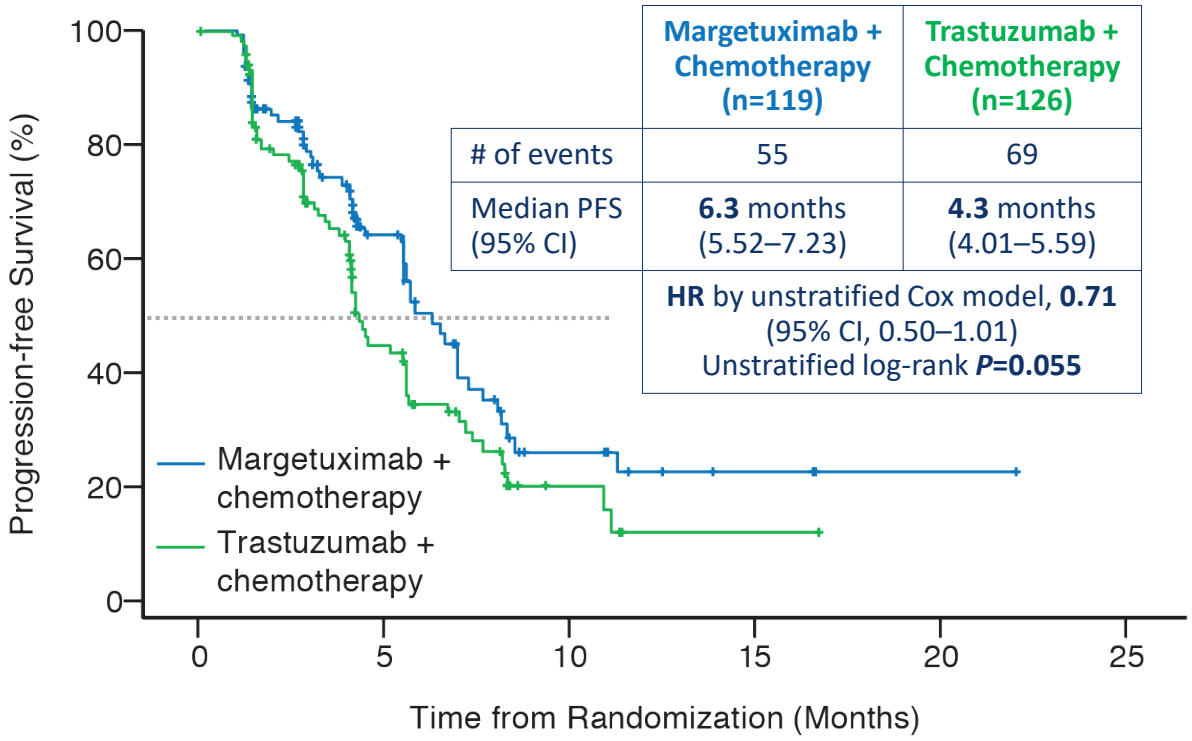


	Margetuximab + Chemotherapy (n=102)	Trastuzumab + Chemotherapy (n=90)
# of events	48	43
Median PFS (95% CI)	**8.2** months (5.52–10.51)	**5.6** months (4.50–8.31)

HR by unstratified Cox model, **0.69** (95% CI, 0.46–1.05)
Unstratified log-rank ***P*=0.080**

Margetuximab	102	75	41	23	12	3	3	3	1	0	
Trastuzumab	90	49	29	14	6	1	1	1	1	1	1

FV, n=245 of 506 (48%)



	Margetuximab + Chemotherapy (n=119)	Trastuzumab + Chemotherapy (n=126)
# of events	55	69
Median PFS (95% CI)	**6.3** months (5.52–7.23)	**4.3** months (4.01–5.59)

HR by unstratified Cox model, **0.71** (95% CI, 0.50–1.01)
Unstratified log-rank ***P*=0.055**

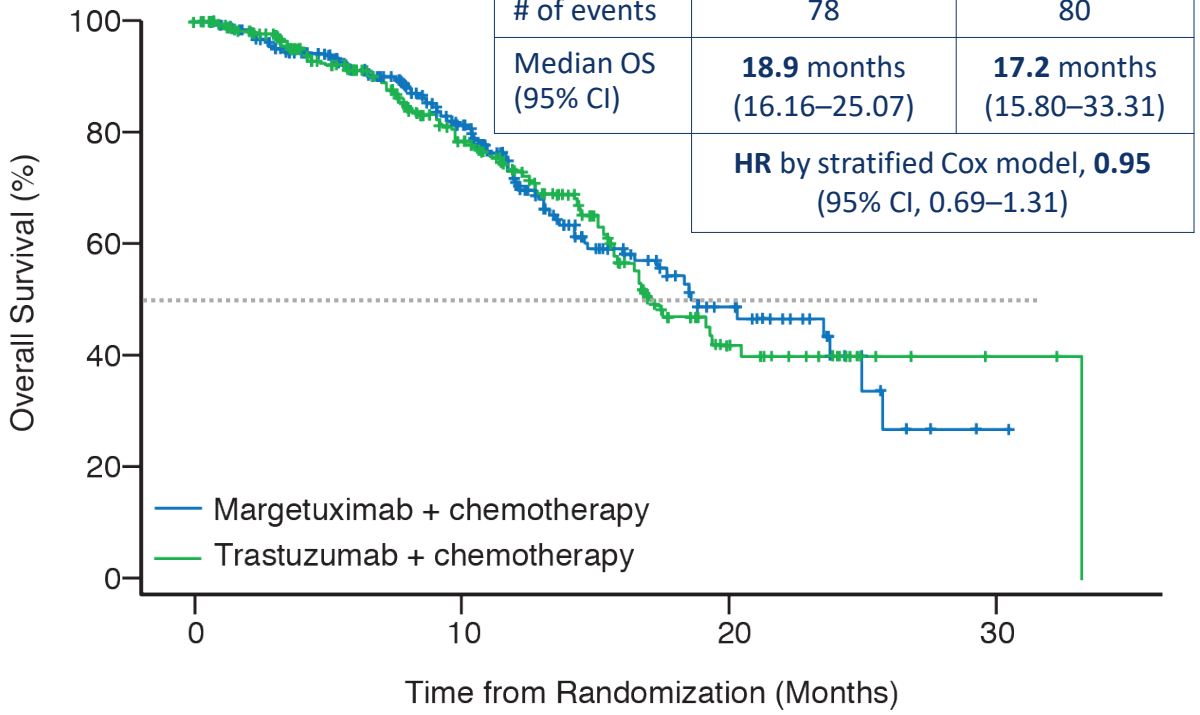
Margetuximab	119	82	42	19	9	5	3	1	1	0	
Trastuzumab	126	80	33	16	5	1	1	0			

October 2018 Interim OS* for ITT vs CD16A-158F Carriers

158 (41%) of 385 events needed for final OS analysis

ITT population, n=536

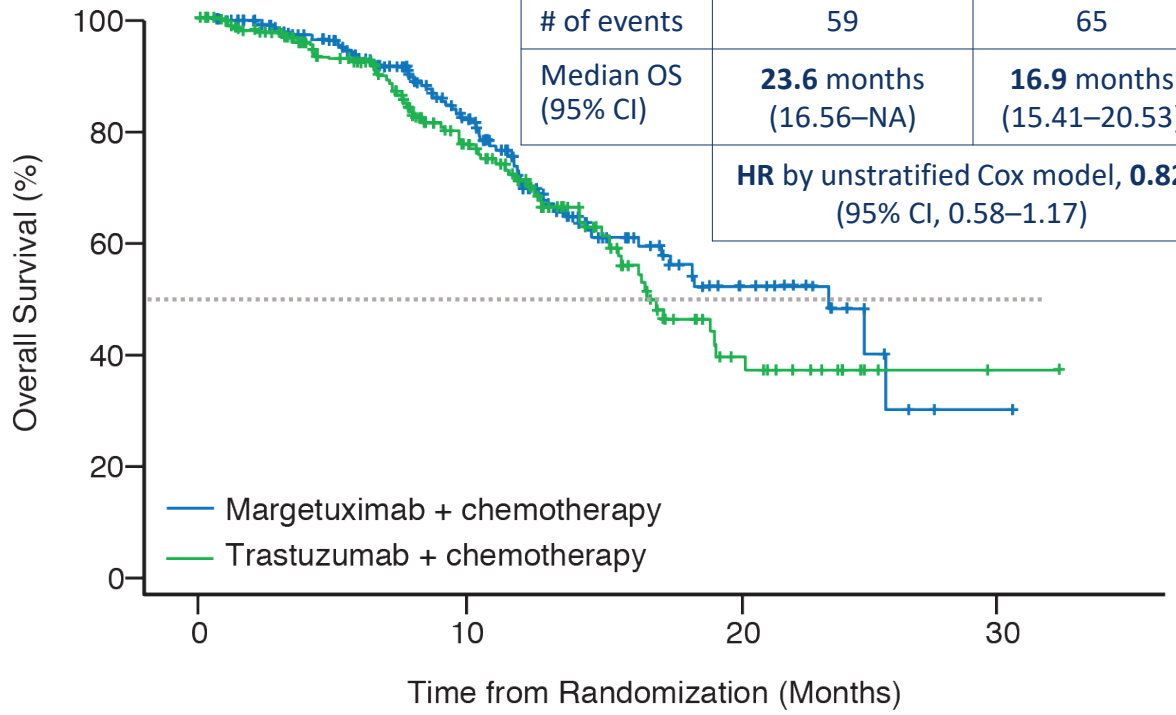
	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	78	80
Median OS (95% CI)	**18.9** months (16.16–25.07)	**17.2** months (15.80–33.31)
	HR by stratified Cox model, **0.95** (95% CI, 0.69–1.31)	



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

CD16A/FF or FV, n=437 of 506 (86%)

	Margetuximab + Chemotherapy (n=221)	Trastuzumab + Chemotherapy (n=216)
# of events	59	65
Median OS (95% CI)	**23.6** months (16.56–NA)	**16.9** months (15.41–20.53)
	HR by unstratified Cox model, **0.82** (95% CI, 0.58–1.17)	



Margetuximab	221	207	179	147	104	69	46	34	24	15	7	2	1	0	
Trastuzumab	216	189	153	130	95	71	48	26	17	10	4	2	1	0	

*First interim overall OS analysis at time of PFS analysis (Oct 10, 2018) was immature with 41% of 385 deaths needed for final OS analysis; stopping boundary was not crossed. Second interim OS analysis will occur after 270 deaths. Final OS analysis will occur after 385 deaths. NA=not achieved.

Overall Response and Clinical Benefit Rates Complement PFS

	Margetuximab + Chemotherapy (n=262)	Trastuzumab + Chemotherapy (n=262)	*P* Value
Objective Response Rate (CR+PR), n (%) [95% CI]	58 (**22.1%**) [17.3–27.7]	42 (**16.0%**) [11.8–21.0]	0.060*
Clinical Benefit Rate (CR+PR+SD>6 months), n (%) [95% CI]	96 (**36.6%**) [30.8–42.8]	65 (**24.8%**) [19.7–30.5]	0.003*
Best Overall Response, n (%)			
Complete Response	7 (2.7%)	4 (1.5%)	
Partial Response	51 (19.5%)	38 (14.5%)	
Stable Disease	149 (56.9%)	147 (56.1%)	
Progressive Disease	35 (13.4%)	46 (17.6%)	
Not Evaluable/Not Available	20 (7.6%)	27 (10.3%)	
Duration of Response (CR, PR), median months (95% CI)	6.1 (4.11–9.13)	6.0 (4.01–6.93)	0.541†

Response evaluable population (randomized patients with baseline measurable disease): N=524.
*Stratified Mantel-Haenszel test *P* value (2-sided). †Unstratified log-rank *P* value (2-sided).

Summary of Adverse Events (AEs)

Similar overall safety profiles

	Margetuximab + Chemotherapy (n=264)	Trastuzumab + Chemotherapy (n=265)
Any grade AE, n (%)	258 (97.7)	255 (96.2)
Grade ≥3 AE, n (%)	138 (52.3)	128 (48.3)
SAE, n (%)	39 (14.8)	46 (17.4)
AE leading to treatment discontinuation, n (%)	8 (3.0)	7 (2.6)
AEs resulting in death,* n (%)	2 (0.8)†	2 (0.8)‡

Safety Population (randomized patients who received any study treatment): N=529.
*No AEs resulting in death were considered related to anti-HER2 study therapy.
†Pneumonia (n=1), pneumonia aspiration (n=1).
‡Pneumonia (n=1), acute kidney injury (n=1).
SAE=serious AE.

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)
Anemia	48 (18.2)	12 (4.5)	55 (20.8)	17 (6.4)
Neutrophil count decreased	32 (12.1)	22 (8.3)	35 (13.2)	25 (9.4)
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

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).

Conclusions

- Margetuximab is a novel Fc-engineered HER2 targeted antibody that stimulates mechanisms of both innate and adaptive immunity
- In patients with HER2+ MBC progressing after trastuzumab, pertuzumab, chemotherapy, and T-DM1:
  - Margetuximab plus chemotherapy improved PFS (CBA: HR=0.76, *P*=0.033; Inv: HR=0.70, *P*=0.001), ORR, and CBR, compared with trastuzumab plus chemotherapy
- This is the first prospective analysis of CD16A genotype as predictor of efficacy from anti-HER2 therapy
  - Enhanced PFS benefit with margetuximab in exploratory subpopulation of low-affinity CD16A-158F carriers (HR=0.68, *P*=0.005)
- Acceptable safety, similar to trastuzumab[1]
  - Increased IRRs (primarily low grade) on margetuximab (13% vs 4%), managed with premedications
- Next milestone: second interim OS analysis, expected late 2019

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IRR=infusion-related reaction. 1. Thompson LM, et al. *Oncologist.* 2014;19(3):228-234.

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