Abstract #752

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

Phase 3 SOPHIA study of margetuximab + chemotherapy vs trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer after prior anti-HER2 therapies: second interim overall survival analysis

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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 include sequential chemotherapy with trastuzumab and/or lapatinib[6,7]
  - Continued anti-HER2 therapy after progression is preferred, generally in combination with chemotherapy[8-11]

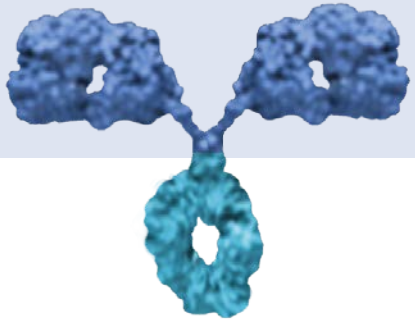
HER2=human epidermal growth factor receptor 2; MBC=metastatic breast cancer; T-DM1=ado-trastuzumab emtansine.

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 engineering Alters Fc Receptor Affinities

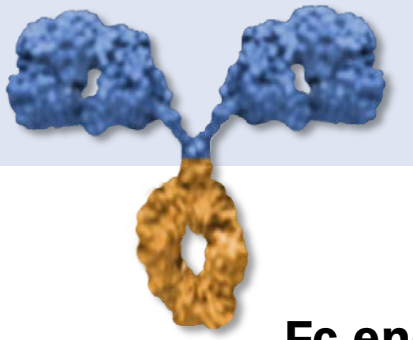
Trastuzumab

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 Fcγ RIIIA (**CD16A**)
- ⬇ Affinity for inhibitory Fcγ RIIB (**CD32B**)

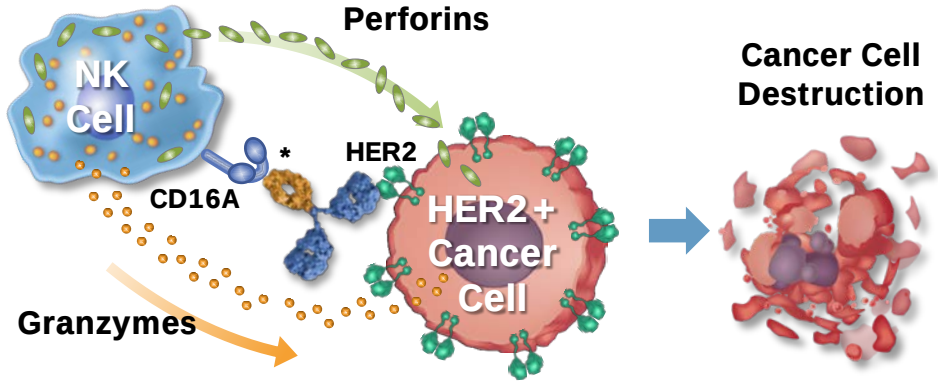
1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Margetuximab: Fc engineering Activates Immune Responses

Trastuzumab vs Margetuximab Fc Receptor Affinities[1]

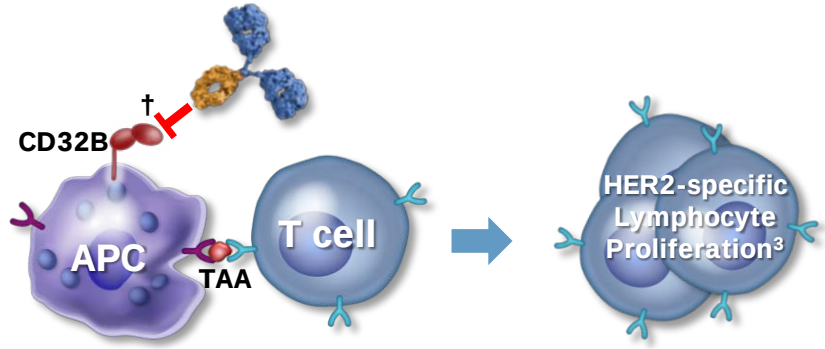
Antibody	Binding affinity (K_D, nM) (range)		
	Trastuzumab (wild type Fc)	Margetuximab (engineered Fc)	Fold difference in affinity
CD16A-158V	**356** (348-364)	**84** (84-84)	**4.2** ⬆
CD16A-158F	**595** (584-605)	**127** (121-133)	**4.7** ⬆
CD32B	**59** (58-59)	**405** (400-410)	**6.9** ⬇

Intent: Enhance Innate Immunity (ADCC)



*Increased CD16A Engagement → more potent ADCC stimulation[2]

Intent: Enhance Adaptive Immunity (HER2-specific T-cell reactivity and antibodies)

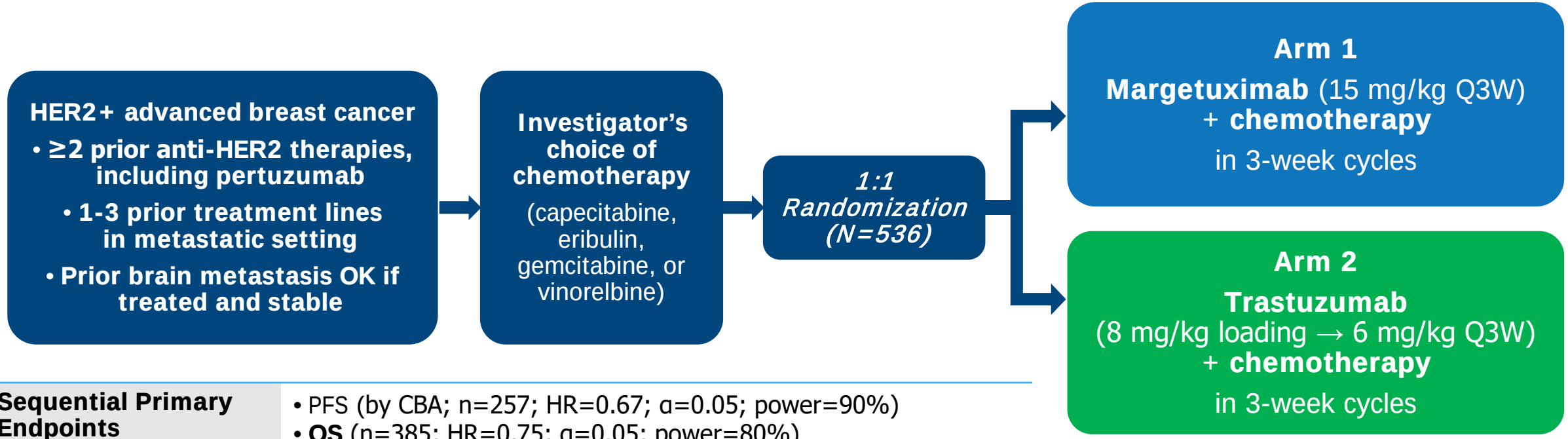


†Reduced CD32B binding → increased immune activation[4]

ADCC=antibody-dependent cellular cytotoxicity; APC=antigen-presenting cell; CD=cluster of differentiation; NK=natural killer; TAA=tumor-associated antigen.

1. MacroGenics; internal data. 2. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 3. Nordstrom JL, et al. *J Clin Oncol.* 2019;37(suppl 15):Abstr. 1030. 4. Clynes RA, et al. *Nat Med.* 2000;6:443-446.

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 (ORR) by CBA
Tertiary/Exploratory Endpoints	• **ORR** (Investigator assessed) • **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)

CBA=central blinded analysis; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; Q3W=every 3 weeks.

1. Rugo HS, et al. *J Clin Oncol*. 2016;34(suppl 15):TPS630. 2. Clinicaltrials.gov. NCT02492711. https://clinicaltrials.gov/ct2/show/NCT02492711. Accessed September 30, 2019.

ITT Population (n=536): Baseline Characteristics

Treatment arms balanced overall

		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%)

ECOG=Eastern Cooperative Oncology Group; hormone receptor positive=ER (estrogen receptor)+ and/or PgR (progesterone receptor)+; hormone receptor negative=ER- and PgR-; PS=performance status.

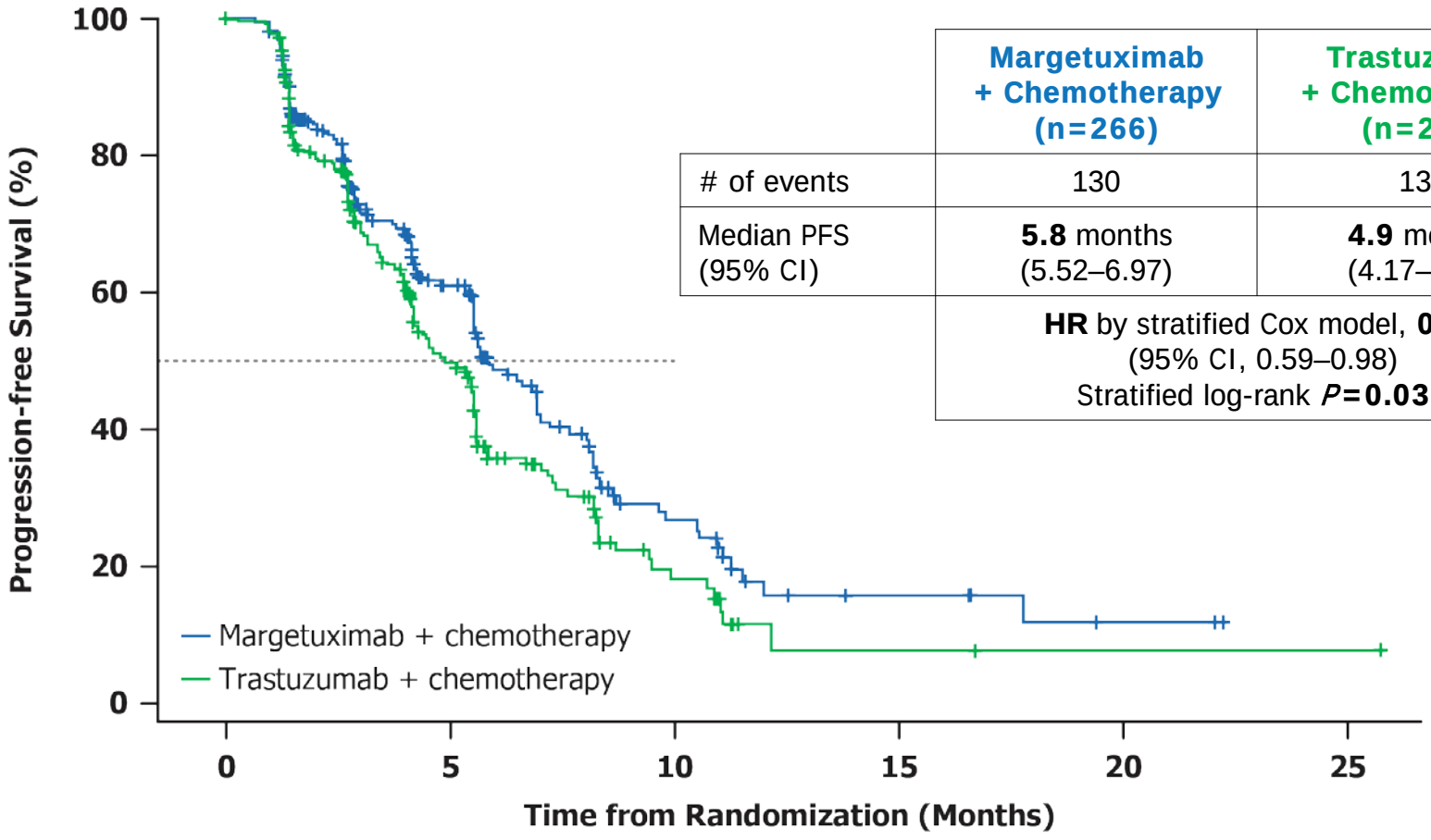
ITT Population (n=536): Prior Cancer Therapy

Treatment arms overall balanced

	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%)

Primary PFS by Central Blinded Analysis, Oct-2018 Cutoff

24% Risk Reduction of Disease Progression[a]

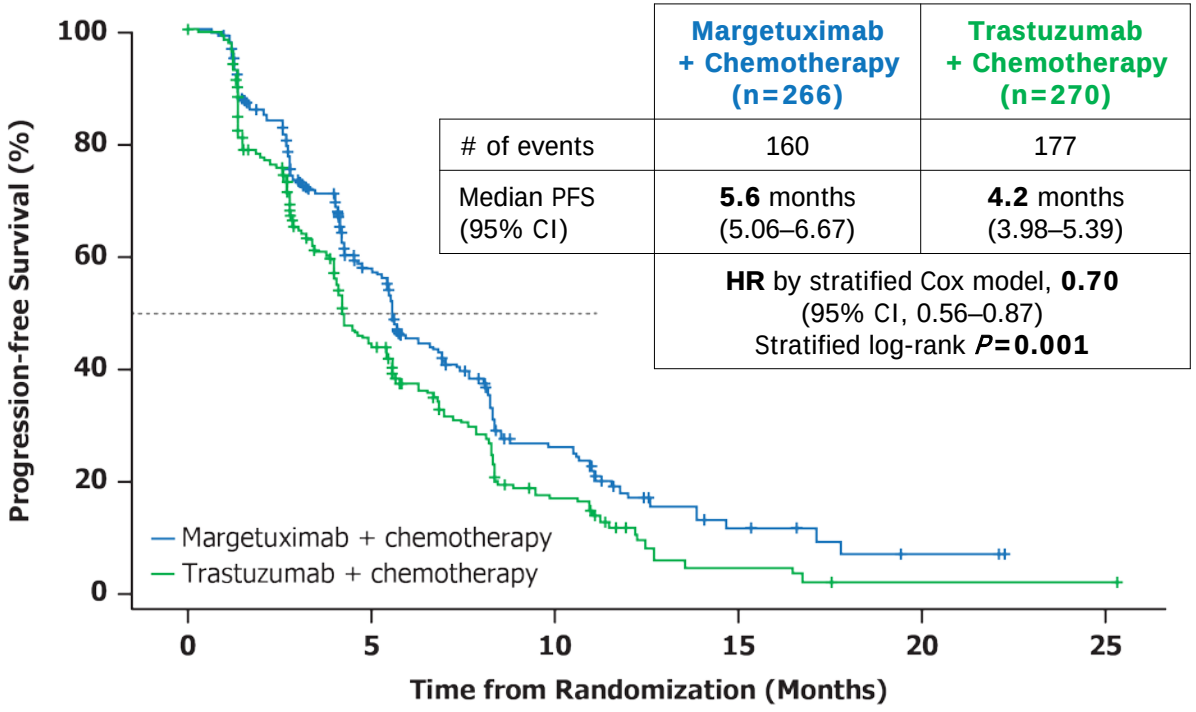


	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	130	135
Median PFS (95% CI)	**5.8** months (5.52–6.97)	**4.9** months (4.17–5.59)
HR by stratified Cox model, **0.76** (95% CI, 0.59–0.98) Stratified log-rank ***P*=0.033**		

ITT population: N=536. [a]PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred. CI=confidence interval.

Investigator-Assessed PFS

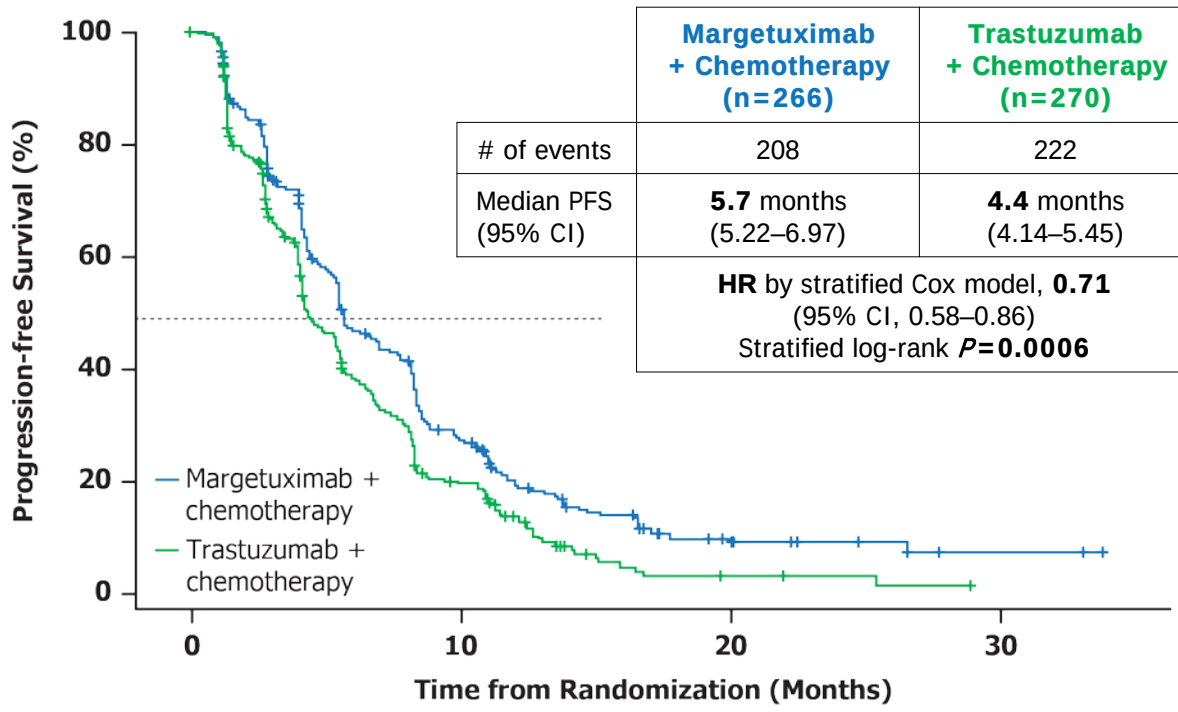
Investigator-Assessed PFS (Oct-2018 Cutoff)[a]
30% Risk Reduction of Disease Progression



	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

Investigator-Assessed PFS (Sep-2019 Cutoff)[b]
29% Risk Reduction of Disease Progression



	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)
# of events	208	222
Median PFS (95% CI)	**5.7** months (5.22–6.97)	**4.4** months (4.14–5.45)
HR by stratified Cox model, **0.71** (95% CI, 0.58–0.86) Stratified log-rank ***P*=0.0006**		

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					

ITT population: N=536. [a]PFS analysis triggered by last randomization on October 10, 2018, after 265 PFS events. [b]PFS analysis performed as of September 10, 2019, after 430 PFS events occurred.

Investigator-Assessed Response, Clinical Benefit Rates, Sep-2019 Cutoff

	ITT Population (N=536)		
	Margetuximab + Chemotherapy (n=266)	Trastuzumab + Chemotherapy (n=270)	Nominal *P* Value
Objective Response Rate (CR+PR), n (%) [95% CI]	67 (**25.2%**) [20.1–30.9]	37 (**13.7%**) [9.8–18.4]	0.0006[a]
Clinical Benefit Rate (CR+PR+SD>6 months), n (%) [95% CI]	128 (**48.1%**) [42.0–54.3]	96 (**35.6%**) [29.9–41.6]	0.0025[a]
Best Overall Response, n (%)			
Complete Response	5 (1.9%)	4 (1.5%)	
Partial Response	62 (23.3%)	33 (12.2%)	
Stable Disease	143 (53.8%)	158 (58.5%)	
Progressive Disease	40 (15.0%)	57 (21.1%)	
Not Evaluable/Not Available	16 (6.0%)	18 (6.7%)	
Duration of Response (CR, PR), median months (95% CI)	**6.9** (5.45–7.49)	**7.0** (5.55–8.15)	0.7400[b]

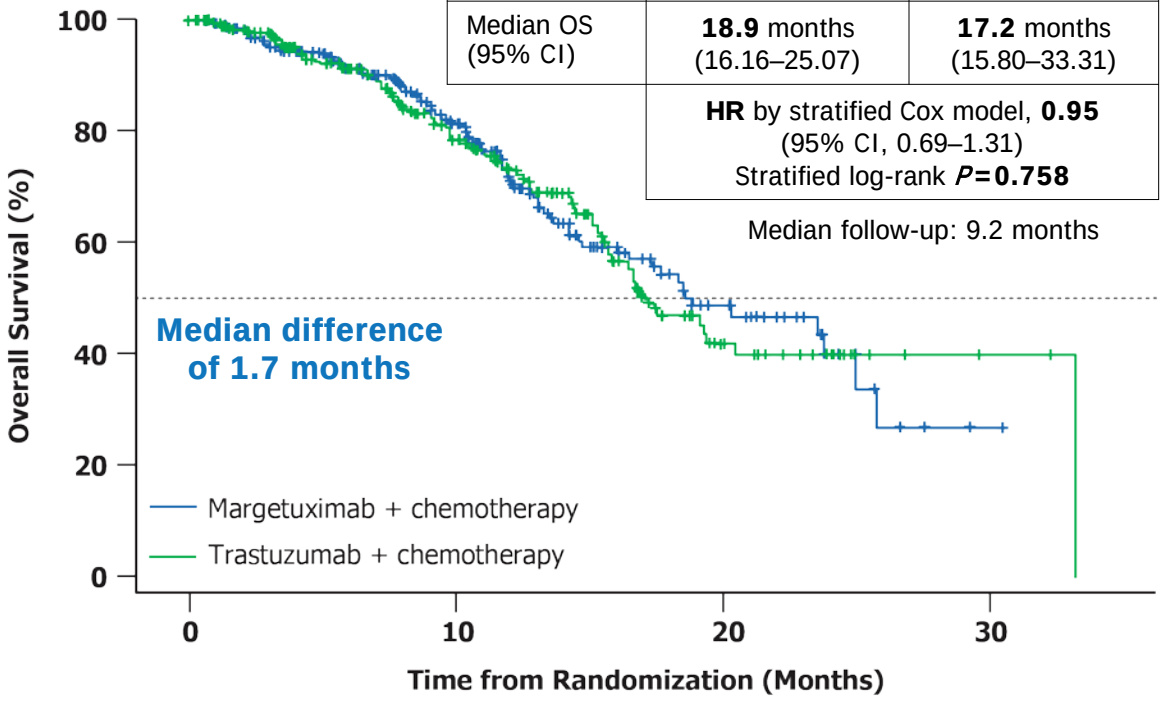
[a] Stratified Mantel-Haenszel test *P* value (2-sided). [b] Stratified log-rank *P* value (2-sided).

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

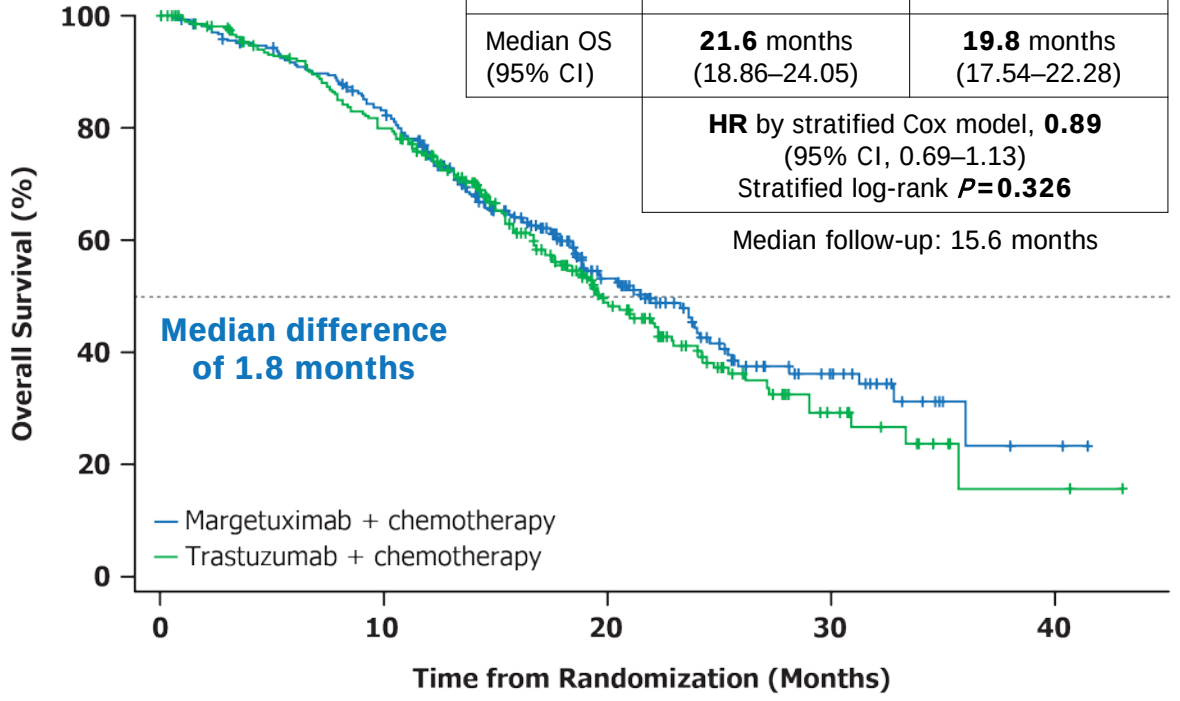


Margetuximab	266	241	209	174	125	85	57	42	29	17	8	3	1	0
Trastuzumab	270	237	194	163	122	92	63	37	24	14	6	3	2	1	0

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

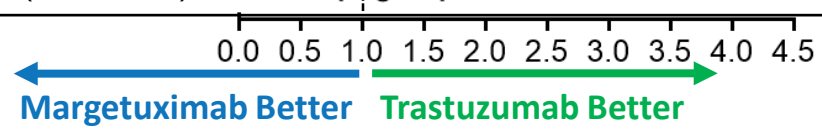


Margetuximab	266	259	249	239	230	214	188	159	131	107	80	64	47	35	31	22	14	9	3	2	2	0
Trastuzumab	270	260	246	236	218	205	183	160	126	102	74	57	43	30	22	16	10	6	2	2	2	1	0

[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.

OS Subgroup Analyses

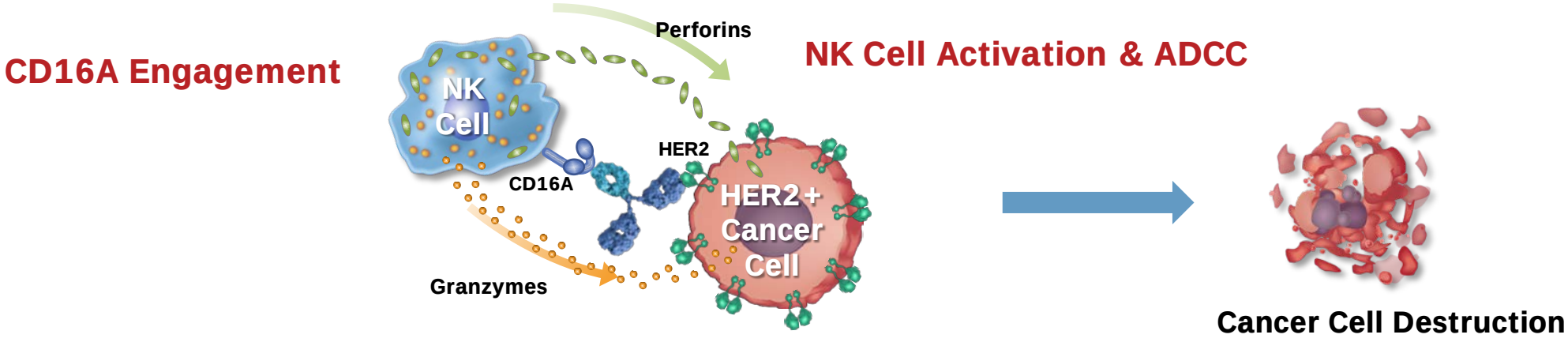
Subgroup type, n (events/total per arm)	Median OS (95% CI), Months		HR by Unstratified Cox Model	95% CI
	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy		
All patients, n=536 (131/266; 139/270)	**21.6** (18.86–24.05)	**19.8** (17.54–22.28)	0.90	(0.71–1.14)
Capecitabine, n=143 (35/71; 37/72)	**23.6** (14.85–NA)	**22.1** (17.91–29.01)	1.00	(0.63–1.59)
Eribulin, n=136 (34/66; 39/70)	**23.7** (18.56–28.32)	**16.7** (14.39–24.74)	0.73	(0.46–1.17)
Gemcitabine, n=66 (16/33; 14/33)	**21.6** (12.02–NA)	**22.3** (18.40–35.65)	1.24	(0.59–2.58)
Vinorelbine, n=191 (46/96; 49/95)	**20.4** (17.41–25.82)	**18.3** (15.84–24.25)	0.86	(0.57–1.28)
>2 metastatic sites, n=254 (74/128; 77/126)	**18.6** (14.29–23.26)	**16.8** (14.29–19.45)	0.84	(0.61–1.16)
≤2 metastatic sites, n=282 (57/138; 62/144)	**25.4** (20.40–NA)	**25.4** (19.75–29.04)	0.93	(0.65–1.33)
≤2 prior lines of Tx[a], n=355 (88/175; 84/180)	**21.6** (18.86–23.98)	**21.9** (18.83–27.14)	1.02	(0.76–1.38)
>2 prior lines of Tx[a], n=181 (43/91; 55/90)	**24.1** (16.16–NA)	**17.5** (15.61–21.03)	0.70	(0.47–1.05)
Prior T-DM1 use: yes, n=489 (121/242; 132/247)	**22.0** (18.63–24.57)	**19.5** (17.45–22.28)	0.86	(0.67–1.10)
Prior T-DM1 use: no, n=47 (10/24; 7/23)	**18.9** (12.42–NA)	**NR** (13.67–NA)	1.60	(0.60–4.28)
Hormone receptor–, n=200 (50/102; 56/98)	**20.6** (16.99–25.40)	**17.9** (15.38–22.90)	0.88	(0.60–1.30)
Hormone receptor+, n=334 (81/164; 82/170)	**22.0** (18.86–28.32)	**21.0** (18.40–24.18)	0.91	(0.67–1.24)
HER2 IHC 3+, n=291 (64/149; 75/142)	**23.6** (20.40–NA)	**19.6** (17.51–24.25)	0.71	(0.51–1.00)
HER2 ISH amplified, n=245 (67/117; 64/128)	**18.6** (13.83–24.05)	**20.5** (16.79–24.18)	1.17	(0.83–1.65)



[a]In the metastatic setting. IHC=immunohistochemistry; ISH=in situ hybridization; NA=not available (because cannot be calculated); NR=not reached; Tx=treatment.

CD16A Biology Impacts Trastuzumab Outcome in NSABP-B31

CD16A-158 Genotype	Population Prevalence[1,2]	IgG1 binding affinity (K_D), nM (range)[3]	IgG1 NK cell binding, MFI ± SD[4]	*Ex vivo* ADCC[5-8]	NSABP-B31 Disease-Free Survival, HR[9]
V/V	9–11%	411 (403–419)	1,814 ± 507	Greater	0.118
V/F	35–44%	—	1,257 ± 608	Intermediate	0.336
F/F	47–54%	1,066 (981–1,150)	913 ± 317	Lesser	0.713
Implication	Distribution globally similar	V allotype has higher affinity for IgG1 Fc	V/V NK cells bind more IgG1 than F/F NK cells	V/V effectors generally activate ADCC best	V alleles associate with benefit[5,9,10]

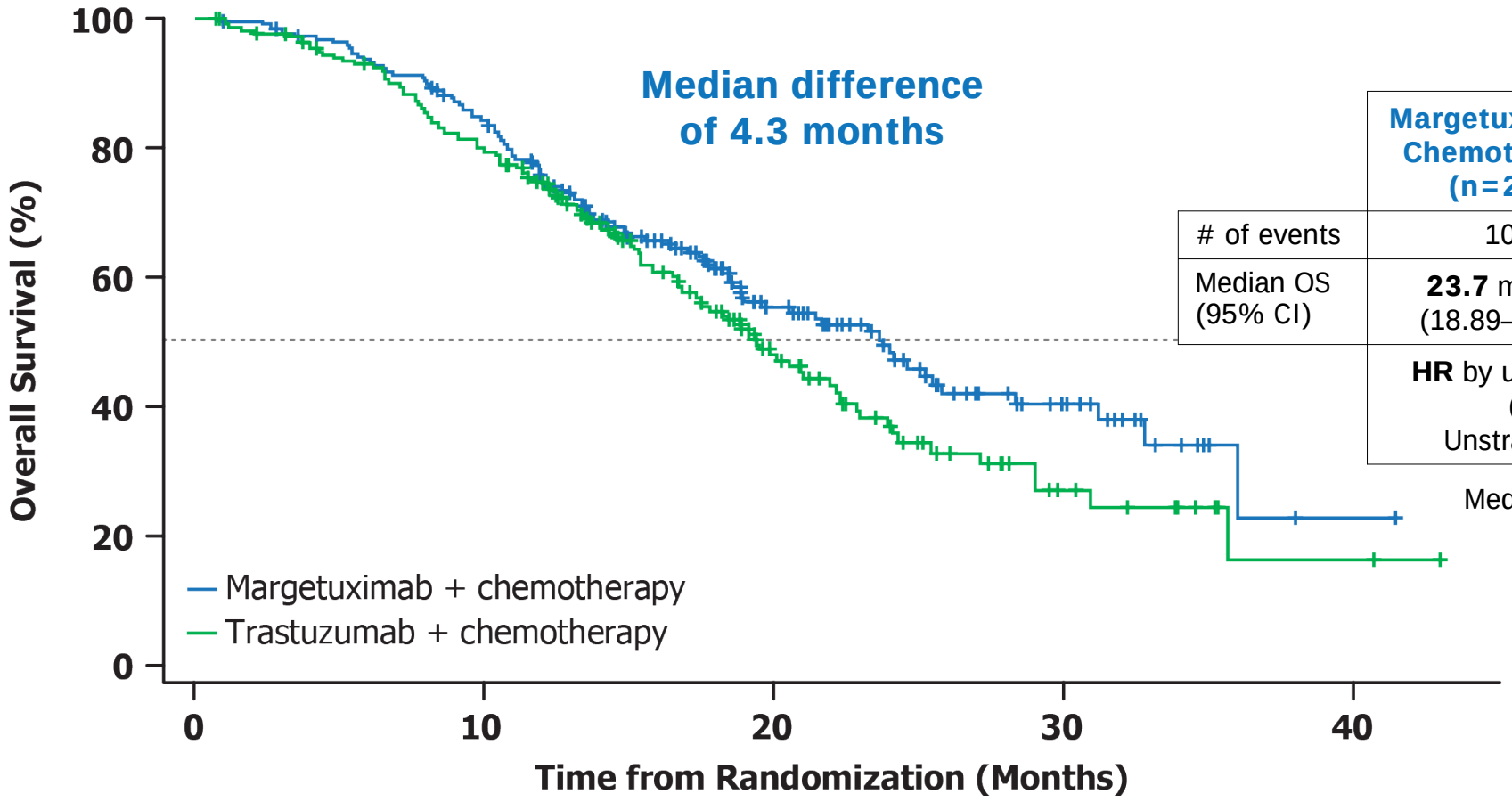


MFI=mean fluorescence intensity; NK=natural killer; SD=standard deviation. 1. Lehrnbecher T, et al. *Blood.* 1999;94:4220-4232. 2. Tanaka Y, et al. *Nephrol Dial Transplant.* 2005;20:2439-2445. 3. Stavenhagen JB et al. *Cancer Res.* 2007;67:8882-8890. 4. Koene HR, et al. *Blood.* 1997;90:1109-1114. 5. Musolino A, et al. *J Clin Oncol.* 2008;26:1789-1796. 6. Nordstrom JL, et al. *Breast Cancer Res.* 2011;13:R123. 7. Shields JM, et al. *J Biol Chem.* 2002;277:9790-9799. 8. Varchetta S, et al. *Cancer Res.* 2007;67:11991-11999. 9. Gavin PG, et al. *JAMA Oncol.* 2017;3:335-341. 10. Musolino A, et al. *Pharmacogenomics J.* 2016;16:472-477.

Pre-specified Exploratory OS in CD16A-185 F Carriers[1]

[1]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**		

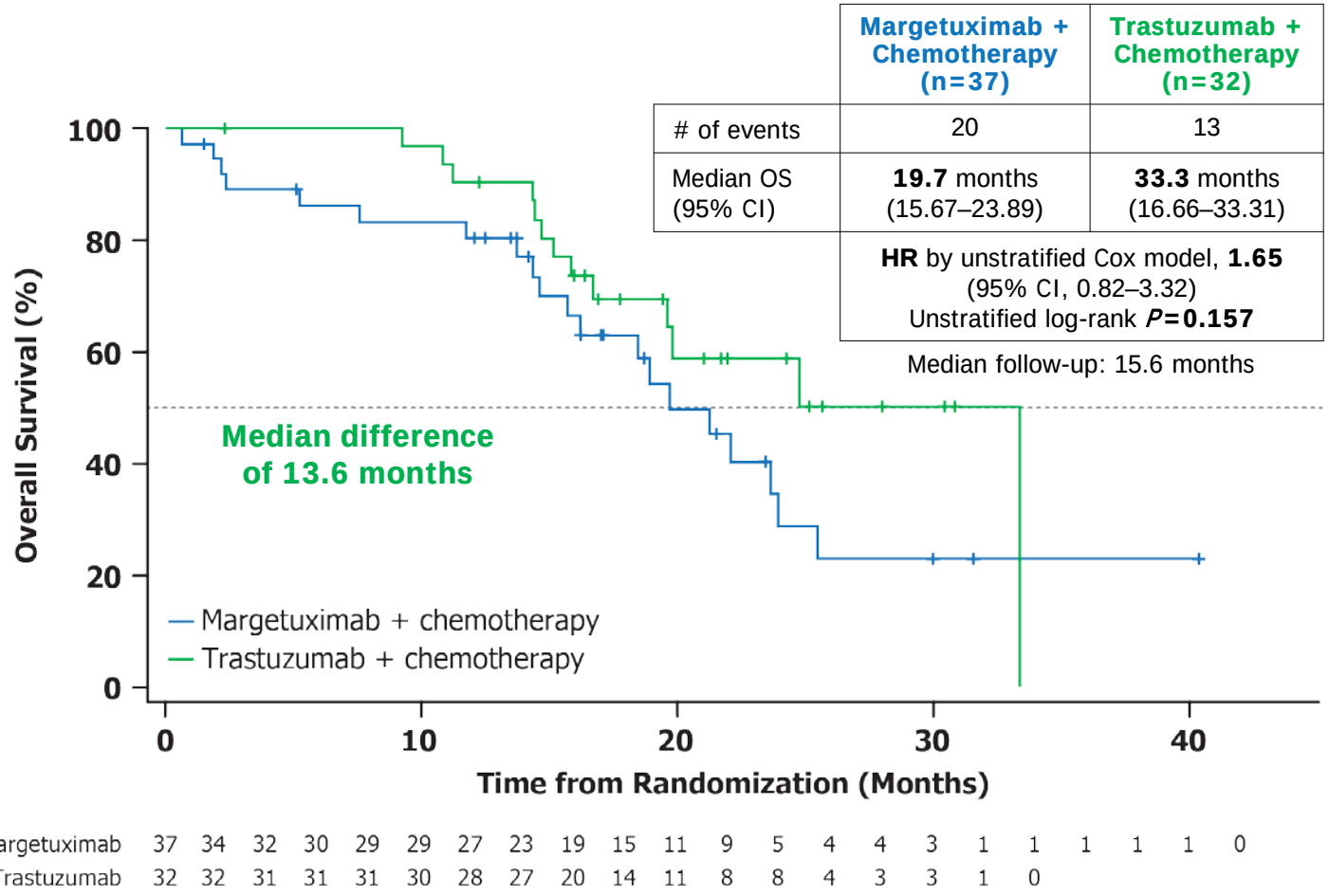
Median follow-up: 15.6 months

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

Pre-specified Exploratory OS in CD16A-158 VV Homozygotes[1]

[1]Sep-2019 Cutoff

CD16A-158VV Homozygotes, n=69 of 506 (14%) genotyped



	Margetuximab + Chemotherapy (n=37)	Trastuzumab + Chemotherapy (n=32)
# of events	20	13
Median OS (95% CI)	**19.7** months (15.67–23.89)	**33.3** months (16.66–33.31)

HR by unstratified Cox model, **1.65** (95% CI, 0.82–3.32)
Unstratified log-rank ***P*=0.157**

Median follow-up: 15.6 months

Unbalanced patient characteristics

Baseline Characteristic	Margetuximab + Chemotherapy (n=37)	Trastuzumab + Chemotherapy (n=32)
Cancer disease history		
Brain, n (%)	8 (**22%**)	3 (**9%**)
Breast, n (%)	10 (**27%**)	5 (**16%**)
Liver, n (%)	16 (**43%**)	10 (**31%**)
Lung, n (%)	11 (**30%**)	13 (**41%**)
Lymph node, n (%)	21 (**57%**)	16 (**50%**)
HER2 IHC 3+, n (%)	19 (**51%**)	18 (**56%**)
Hormone receptor +, n (%)	23 (**62%**)	18 (**56%**)
ECOG PS 1, n (%)	14 (**38%**)	16 (**50%**)
>60 years of age, n (%)	16 (**43%**)	5 (**16%**)
>2 prior metastatic lines of therapy, n (%)	15 (**41%**)	9 (**28%**)

Less favorable

Adverse Events (AEs), Apr-2019 Cutoff

Similar overall safety profiles

	Margetuximab + Chemotherapy (n=264)		Trastuzumab + Chemotherapy (n=266)	
Any grade AE, n (%)	260 (98.5)		261 (98.1)	
Any margetuximab or trastuzumab-related AE, n (%)	160 (60.6)		132 (49.6)	
Grade ≥3 AE, n (%)	142 (53.8)		140 (52.6)	
Grade ≥3 margetuximab or trastuzumab-related AE, n (%)	34 (12.9)		22 (8.3)	
Any SAE, n (%)	43 (16.3)		49 (18.4)	
Any margetuximab or trastuzumab-related SAE, n (%)	5 (1.9)		4 (1.5)	
AE leading to treatment[a] discontinuation, n (%)	8 (3.0)		7 (2.6)	
AEs resulting in death,[b] n (%)	3 (1.1)[c]		2 (0.8)[d]	
AEs of special interest, n (%)	**All Grade**	**Grade ≥3**	**All Grade**	**Grade ≥3**
Infusion-related reaction (IRR)[e]	35 (13.3)	4 (1.5)	9 (3.4)	0
Discontinuation due to IRRs, n (%)	2 (0.6)	0	0	0
LV dysfunction leading to dose delay or discontinuation, n (%)	4 (1.5)	0	6 (2.3)	0

Safety Population (randomized patients who received any study treatment): N=530.

[a]Including both anti-HER2 study therapy and chemotherapy. [b]No AEs resulting in death were considered related to anti-HER2 study therapy. [c]Pneumonia (n=2), pneumonia aspiration (n=1). [d]Pneumonia (n=1), acute kidney injury (n=1). [e]In pivotal trials of trastuzumab, IRRs occurred in 21% to 40% of patients (US package insert). LV=left ventricular; SAE=serious AE.

Conclusions from SOPHIA Trial

- **Margetuximab – increased affinity for activating and decreased affinity for inhibitory Fcγ receptors**
  - Fc engineering intent: coordinate engagement of innate and adaptive immunity
- **First Phase 3 head to head comparison to show PFS superiority versus active control trastuzumab**
  - Primary analysis (Oct-2018 cutoff): 24% risk reduction in centrally blinded PFS (HR 0.76, *P*=0.033)
  - Investigator PFS (Sep-2019 cutoff): also favors margetuximab with 29% risk reduction (HR 0.71, nominal *P*=0.0006)
- **2nd interim OS (Sep-2019 cutoff): favors margetuximab** (mOS 21.6 vs 19.8 mos; HR=0.89, *P*=0.326)
- **First prospective analysis of CD16A genotype as a predictor of anti-HER2 antibody efficacy (exploratory)**
  - Primary PFS analysis (Oct-2018 cutoff), CD16A-F carrier: mPFS difference 1.8 mos (HR 0.68, nominal *P*=0.005)
  - 2nd interim OS (Sep-2019 cutoff), CD16A-F carriers: mOS difference 4.3 mos (HR=0.79, nominal *P*=0.087)
- **Acceptable safety, similar to trastuzumab[1]**
  - ≥ Grade 3 adverse events, SAEs, discontinuations, fatal AEs, left ventricular dysfunction all balanced
  - Higher IRRs on margetuximab (13% vs 3%), most on first infusion only, Grade 1-2
  - Infusion substudy: 30-minute infusions without effect on safety, IRR risk, or severity[2]
- **Next milestone: final OS analysis (after 385 events), expected late 2020**

1. Thompson LM, et al. *Oncologist.* 2014;19(3):228-234. 2. Gradishar WJ, et al., SABCS 2019, #P1-18-04, 11-Dec-2019 from 5PM to 7PM, Hall 1.

Acknowledgments

- We gratefully acknowledge participating patients and their families
- We also thank SOPHIA investigators and the clinical study teams
- The SOPHIA trial is sponsored by MacroGenics, Inc.

Professional medical writing support was provided by Francesca Balordi, PhD, and Emily Cullinan, PhD, of The Lockwood Group (Stamford, CT, USA), in accordance with Good Publication Practice (GPP3) guidelines, funded by MacroGenics, Inc.

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