Supplemental Online Content

Rugo HS, Im S-A, Cardoso F, et al; for the SOPHIA Study Group. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. Published online January 22, 2021. doi:10.1001/jamaoncol.2020.7932

eTable 1. Hardy-Weinberg Equilibrium Analysis of CD16A, CD32A, and CD32B Genotype Frequencies

eTable 2. Demographic and Baseline Disease Characteristics by CD16A-158 Genotype

eTable 3. Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

eTable 4. Summary of Adverse Events in the Safety Population (Apr 2019 Cutoff)

eFigure 1. Prespecified Exploratory Primary PFS Analysis, by CD16A Genotype (Oct 2018 Cutoff)

eFigure 2. Pre-specified Exploratory OS Analysis, per CD16A Genotype by Treatment Group (Sep 2019 Cutoff)

eFigure 3. Overall Survival (OS) per Treatment Group by CD16A Genotype (Sep 2019 Cutoff)

eFigure 4. Prespecified Exploratory PFS Subgroup Analyses (CBA) - Oct 2018 Cutoff

eFigure 5. Prespecified Exploratory OS Subgroup Analyses – Sep 2019 Cutoff

This supplemental material has been provided by the authors to give readers additional information about their work.

SUPPLEMENTARY TABLES

	Margetuximab Plus Chemotherapy (N = 258)		Trastuzumab Plus Chemotherap (N = 248)	
	Observed	Expected	Observed	Expected
CD16A-158 (rs396991)				
CD16A – FF	0.395	0.392	0.363	0.381
CD16A – FV	0.461	0.468	0.508	0.473
CD16A – VV	0.143	0.140	0.129	0.147
χ^2 (P value)	0.058 (0.810)	1.392 (0.238)	
CD32A-131 (rs1801274)				
CD32A – HH	0.302	0.288	0.238	0.242
CD32A – HR	0.469	0.497	0.508	0.500
CD32A – RR	0.229	0.215	0.254	0.258
χ^2 (P value)	0.835 (0.361)	0.067 (0.796)	
CD32B-232 (rs1050501)				
CD32B – II	0.775	0.771	0.726	0.731
CD32B – IT	0.205	0.214	0.258	0.248
CD32B – TT	0.019	0.015	0.016	0.021
χ^2 (<i>P</i> value)	0.449 (0.503)	0.393 (0.530)	

eTable 1. Hardy-Weinberg Equilibrium Analysis of CD16A, CD32A, and CD32B Genotype Frequencies

	CD16A-158FF		CD16A-158FV		CD16A-158VV	
	M + C	T + C	M + C	T + C	M + C	T + C
	(n = 102)	(n = 90)	(n = 119)	(n = 126)	(n = 37)	(n = 32)
Sites of metastases at study entry — n (%)						
Brain	11 (11)	12 (13)	17 (14)	17 (14)	8 (22)	3 (9)
Breast	14 (14)	15 (17)	20 (17)	15 (12)	10 (27)	5 (16)
Liver	38 (37)	34 (38)	35 (29)	49 (39)	16 (43)	10 (31)
Lung	54 (53)	44 (49)	57 (48)	56 (44)	11 (30)	13 (41)
Lymph node	56 (55)	51 (57)	58 (49)	69 (55)	21 (57)	16 (50)
HER2 IHC 3+ — n (%)	61 (60)	50 (56)	65 (55)	62 (49)	19 (51)	18 (56)
ER-positive, PgR-positive, or both — n (%)	64 (63)	52 (58)	70 (59)	88 (70)	23 (62)	18 (56)
ECOG performance status 1 — n (%)	45 (44)	38 (42)	54 (45)	45 (36)	14 (38)	16 (50)
>60 years of age — n (%)	33 (32)	33 (37)	32 (27)	43 (34)	16 (43)	5 (16)
>2 prior metastatic lines of anti-HER2 therapy — n (%)	31 (30)	25 (28)	34 (29)	30 (24)	13 (35)	9 (28)
Albumin, mean (SD) — g/L	41.0 (4.2)	41.1 (4.0)	40.8 (4.1)	40.9 (3.6)	40.3 (4.2)	42.1 (3.6)
Lymphocytes, mean (SD) — 10 ⁹ /L	1.4 (0.6)	1.5 (0.6)	1.5 (0.7)	1.5 (0.7)	1.5 (0.6)	1.7 (0.7)

eTable 2. Demographic and Baseline Disease Characteristics by CD16A-158 Genotype

Abbreviations: C, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; M, margetuximab; PgR, progesterone receptor.

eTable 3. Objective Response Rate (ORR) and Clinical Benefit Rate (CBR)

	Central Blinded Anal the Response Evalua 2018 C	ble Population (Oct	Investigator-Assessed Response in the Response Evaluable Population (Sep 2019 Cutoff)		
Responses	Margetuximab Plus Chemotherapy (N = 262)	Trastuzumab Plus Chemotherapy (N = 262)	Margetuximab Plus Chemotherapy (N = 266)	Trastuzumab Plus Chemotherapy (N = 270)	
Best overall response (BOR) — n (%)					
Complete response (CR)	7 (2.7)	4 (1.5)	5 (1.9)	4 (1.5)	
Partial response (PR)	51 (19.5)	38 (14.5)	62 (23.3)	33 (12.2)	
Stable disease (SD)	149 (56.9)	147 (56.1)	143 (53.8)	158 (58.5)	
Progressive disease (PD)	35 (13.4)	46 (17.6)	40 (15.0)	57 (21.1)	
Not evaluable (NE)/Not Available (NA)	20 (7.6)	27 (10.3)	16 (6.0)	18 (6.7)	
Objective response rate — n (%)	58 (22.1)	42 (16.0)	67 (25.2)	37 (13.7)	
[95% CI]	[17.11–27.16]	[11.59–21.47]	[20.1–30.9]	[9.8–18.4]	
Stratified Mantel-Haenszel test P value (2-sided)	0.05	597	0.0006		
Clinical benefit rate (CR+PR+SD>6 months duration) — n (%) [95% CI]	96 (36.6) [30.81–42.48]	65 (24.8) [19.58–30.04]	128 (48.1) [42.0–54.3]	96 (35.6) [29.9–41.6]	
Stratified Mantel-Haenszel test P value (2-sided)	0.0026		0.00	025	
Median duration of complete or partial response — months (95% Cl)	6.1 (4.11–9.13)	6.0 (4.01–6.93)	6.9 (5.45–7.49)	7.0 (5.55–8.15)	
Log-rank P value (2-sided)	0.54	07ª	0.74	400 ^b	

^aUnstratified.

^bStratified.

	Margetuximab Plus Chemotherapy	Trastuzumab Plus Chemotherapy	
	(N = 264)	(N = 266)	
Any-grade AE — n (%)	260 (98.5)	261 (98.1)	
HER2-targeted treatment-related AE of any grade — n (%)	160 (60.6)	132 (49.6)	
Chemotherapy-related AEs of any grade — n (%)	238 (90.2)	239 (89.8)	
Any-grade infusion-related AEs — n (%)	35 (13.3)	9 (3.4)	
Grade ≥3 infusion-related AEs — n (%)	4 (1.5)	0	
Any-grade LVEF dysfunction — n (%)	7 (2.7)	7 (2.6)	
Grade ≥3 LVEF dysfunction — n (%)	3 (1.1)	1 (0.4)	
Grade ≥3 AE — n (%)	142 (53.8)	140 (52.6)	
HER2-targeted treatment-related Grade ≥3 AE — n (%)	34 (12.9)	22 (8.3)	
Chemotherapy-related Grade ≥3 AE — n (%)	110 (41.7)	108 (40.6)	
Any SAE — n (%)	43 (16.3)	49 (18.4)	
HER2-targeted treatment-related SAE — n (%)	5 (1.9)	4 (1.5)	
Chemotherapy-related SAE — n (%)	14 (5.3)	24 (9.0)	
AE leading to treatment discontinuation from combined antibody plus chemotherapy — n (%)	8 (3.0)	7 (2.6)	
Discontinuation due to IRRs — n (%)	2 (0.8)	0	
LVEF dysfunction leading to dose delay or discontinuation — n (%)	4 (1.5)	6 (2.3)	
AE resulting in deaths — n (%)	3 (1.1) ^a	2 (0.8) ^b	
HER2-targeted treatment-related AE resulting in deaths — n (%)	0	0	

eTable 4. Summary of Adverse Events in the Safety Population (Apr 2019 Cutoff)

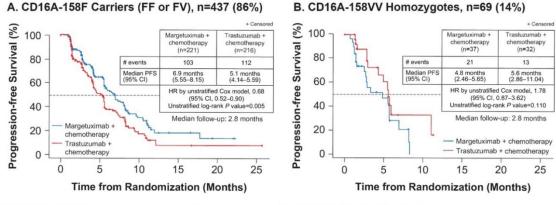
^aTwo patients had pneumonia, one had pneumonia aspiration. ^bOne patient had pneumonia, the other had acute kidney injury.

Abbreviations: AE, adverse event; LVEF, left ventricular ejection fraction; SAE, serious adverse event.

SUPPLEMENTARY FIGURES

eFigure 1. Prespecified Exploratory Primary PFS Analysis, by CD16A Genotype (Oct 2018 Cutoff)^a

Kaplan-Meier estimates of PFS by CBA in CD16A-158F carriers (FF or FV; Panel A), CD16A-158VV homozygotes (Panel B), CD16A-158FF homozygotes (Panel C), and CD16A-158FV heterozygotes (Panel D).



 Margetuximab
 221
 157
 84
 42
 21
 8
 6
 4
 2
 0

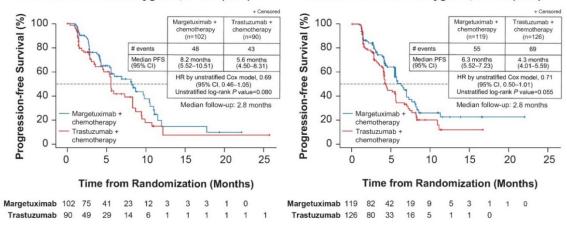
 Trastuzumab
 216
 129
 62
 30
 11
 2
 2
 1
 1
 1

 Margetuximab
 37
 16
 10
 3
 0

 Trastuzumab
 32
 18
 10
 2
 2
 0

C. CD16A-158FF Homozygotes, n=192 (38%)

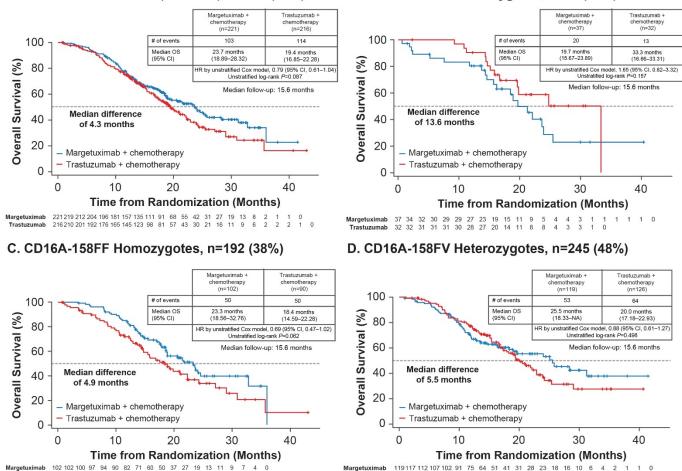
D. CD16A-158FV Heterozygotes, n=245 (48%)



^a506 of 536 ITT patients genotyped (94%). Treatment by CD16A genotype (F carrier vs VV) interaction P = .012. Abbreviation: Tx, treatment.

eFigure 2. Pre-specified Exploratory OS Analysis, per CD16A Genotype by Treatment Group (Sep 2019 Cutoff)^a

Kaplan-Meier estimates of OS by treatment group in CD16A-158F Carriers (FF or FV; Panel A), CD16A-158VV Homozygotes (Panel B), CD16A-158FF Homozygotes (Panel C), and CD16A-158FV Heterozygotes (Panel D).



B. CD16A-158VV Homozygotes, n=69 (14%)

Trastuzumab 12612512011610599 89 77 63 50 36 25 17

^a506 of 536 ITT patients genotyped (94%). Treatment by CD16A genotype (F carrier vs VV) interaction P = .071. Abbreviations: ITT, intent-to-treat; NA, not available (because cannot be calculated).

66 56 46 35 31 21 18 13 10

Trastuzumab 90 85 81 76 71

A. CD16A-158F Carriers (FF or FV), n=437 (86%)

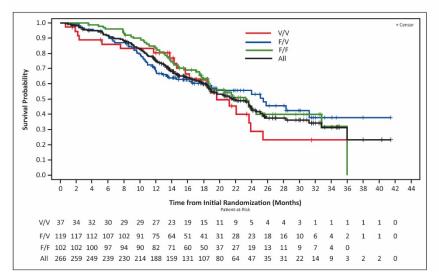
eFigure 3. Overall Survival (OS) per Treatment Group by CD16A Genotype (Sep 2019 Cutoff)

Kaplan-Meier estimates of OS in margetuximab-treated patients (Panel A) and in trastuzumab-treated patients (Panel B), by CD16A-158 genotype.

A. Margetuximab

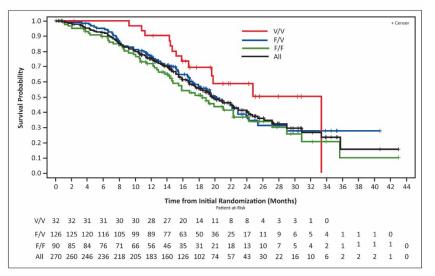
B. Trastuzumab

	All (N=266)	V/V (n=37)	F/V (n=119)	F/F (n=102)
# of events	131	20	53	50
Median OS (95% CI)	21.6 months (18.9 –24.1)	19.7 months (15.7 –23.9)	25.5 months (18.3 –NA)	23.3 months (18.6 –32.8)



Abbreviations: NA, not available (because cannot be calculated).

	All (N=270)	V/V (n=32)	F/V (n=126)	F/F (n=90)
# of events	139	13	64	50
Median OS (95% CI)	19.8 months (17.5 –22.3)	33.3 months (16.7 –33.3)	20.0 months (17.2 –22.9)	18.4 months (14.6 -22.3)



eFigure 4. Prespecified^a **Exploratory PFS Subgroup Analyses (CBA) – Oct 2018 Cutoff.** Median PFS, hazard ratios, and 95% confidence intervals, are shown in this figure.

	Median PFS (9	5% CI), Months		HR by Unstratified
Subgroup type, n (events/total per arm)	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy		Cox Model (95% CI)
All patients, n = 536 (130/266; 135/270)	5.8 (5.52–6.97)	4.9 (4.17–5.59)	H H	0.78 (0.61-0.99)
Investigator-selected chemotherapy				
Capecitabine, n = 143 (29/71; 37/72)	8.3 (5.55–11.50)	5.5 (4.17-8.28)	⊢ ∎; -1	0.77 (0.47-1.29)
Eribulin, n = 136 (35/66; 39/70)	6.0 (3.81-8.05)	4.2 (3.38–5.55)	⊢ ● H	0.66 (0.42-1.05)
Gemcitabine, n = 66 (15/33; 17/33)	5.4 (4.07–11.01)	3.5 (1.45–7.16)		0.58 (0.29-1.18)
Vinorelbine, n = 191 (51/96; 42/95)	5.6 (4.24–6.97)	5.1 (3.42–6.67)	⊢ •; <u>−</u> 1	0.90 (0.60-1.35)
Baseline characteristics				
≤2 metastatic sites, n = 282 (69/138; 67/144)	5.7 (4.47–6.97)	5.5 (4.24–5.85)	⊢•́−-i	0.94 (0.67-1.31
>2 metastatic sites, n = 254 (61/128; 68/126)	6.3 (5.42-8.08)	4.2 (3.38–5.55)	He-I	0.63 (0.44–0.89
≤2 prior lines of Tx, ^b n = 355 (82/175; 85/180)	6.5 (4.80-8.28)	4.9 (4.14–5.59)	⊢∎ ¦	0.81 (0.60-1.10
>2 prior lines of Tx, ^b n = 181 (48/91; 50/90)	5.7 (5.42-6.93)	4.8 (3.06-5.59)	⊢ e _t	0.72 (0.48-1.08
Prior T-DM1 use: yes, n = 489 (121/242; 128/247)	5.7 (5.52–6.97)	4.9 (4.14–5.59)	⊢ •-∔	0.78 (0.61-1.01
Prior T-DM1 use: no, n = 47 (9/24; 7/23)	6.9 (4.14–NA)	4.2 (3.98–10.87)	⊢ • <mark> </mark> − − − 1	0.84 (0.29-2.37
Stage IV at Dx: yes, c n = 228 (58/106; 57/122)	5.6 (3.71-6.97)	4.9 (4.07–7.16)	⊢∳ −−1	1.02 (0.71-1.47
Stage IV at Dx: no, ^c n = 308 (72/160; 78/148)	6.5 (5.55-8.21)	5.4 (4.01-5.59)	He I	0.66 (0.47-0.90
Prior (neo)adjuvant Tx: yes, c n = 303 (72/158; 77/145)	6.3 (5.55-8.05)	5.4 (4.01-5.59)	Here'	0.67 (0.48-0.93
Prior (neo)adjuvant Tx: no,° n = 233 (58/108; 58/125)	5.6 (3.71-6.97)	4.9 (4.07–7.16)	F	0.99 (0.68-1.42
Hormone Receptor+, ^d n= 334 (80/164; 85/170)	5.7 (5.52-8.18)	5.5 (4.24–7.03)		0.87 (0.64–1.19
Hormone Receptor-, e n= 200 (50/102; 50/98)	5.8 (4.80-7.23)	4.2 (2.83–5.55)	H e -1	0.58 (0.39–0.86
HER2 IHC 3+, n=291 (68/149; 65/142)	6.9 (5.55-8.31)	5.6 (3.98-5.85)	He-1	0.64 (0.46-0.90
HER2 ISH amplified, n = 245 (62/117; 70/128)	5.5 (4.01-6.60)	4.6 (4.07-5.55)	F.	1.01 (0.71-1.42
ECOG 0, n = 310 (70/149; 79/161)	6.5 (5.55-8.18)	5.4 (4.17–5.59)	⊢ ● <mark>, 1</mark>	0.80 (0.58-1.11
ECOG 1, n = 226 (60/117; 56/109)	5.7 (4.17-7.66)	4.5 (3.42–5.85)	⊢ e ⊣i	0.75 (0.52-1.09
Region: Europe, n = 290 (78/152; 66/138)	6.3 (5.52-8.15)	5.5 (4.17–6.67)	⊢e¦-1	0.88 (0.63-1.22
Region North America, n = 187 (39/85; 58/102)	5.6 (4.04-6.90)	4.1 (3.38-5.49)	⊢ e -¦i	0.67 (0.45-1.01
Region: other, n = 59 (13/29; 11/30)	7.0 (4.11-NA)	7.3 (4.11–12.16)	⊢ ● <mark> </mark> I	0.90 (0.40-2.02
Age ≤60 years, n = 366 (97/184; 94/182)	5.6 (4.24-6.97)	4.6 (4.01-5.59)	Here's	0.87 (0.66-1.16
Age >60 years, n = 170 (33/82; 41/88)	6.9 (5.52-10.51)	5.6 (4.14–5.85)	Fe-1	0.58 (0.36-0.92
Race: Asian, n = 34 (10/20; 8/14)	6.9 (2.26-NA)	2.8 (1.22-10.87)	⊢ ●H	0.40 (0.15-1.05
Race: Black, n = 28 (3/16; 6/12)	NR (7.66-NA)	2.8 (1.25-NA)	H•	0.18 (0.04-0.91
Race: White, n = 427 (104/205; 109/222)	5.6 (4.27-6.51)	5.4 (4.27–5.59)	Fe-1	0.93 (0.71-1.21
Race: other, n = 47 (13/25; 12/22)	8.2 (5.42-11.01)	4.1 (2.37–5.62)	F	0.62 (0.28-1.36
FcyR genotype				
CD16A-158F allele carrier, n = 437 (103/221; 112/216)	6.9 (5.55–8.15)	5.1 (4.14–5.59)	L +●-1	0.68 (0.52-0.90
CD16A-158FF, n = 192 (48/102; 43/90)	8.2 (5.52-10.51)	5.6 (4.50-8.31)		0.69 (0.46-1.05
CD16A-158FV, n = 245 (55/119; 69/126)	6.3 (5.52-7.23)	4.3 (4.01-5.59)		0.71 (0.50-1.01
CD16A-158VV, n = 69 (21/37; 13/32)	4.8 (2.46-5.65)	5.6 (2.86-11.04)	k <u>1</u> ●1	1.78 (0.87-3.62
CD32A-131RR, n = 122 (26/59; 33/63)	5.7 (4.80-10.55)	5.5 (2.76-8.21)		0.69 (0.41-1.17
CD32A-131RH, n = 247 (60/121; 62/126)	6.9 (5.55-8.15)	5.6 (4.17-6.67)	F===_1	0.74 (0.52-1.06
CD32A-131HH, n = 137 (38/78; 30/59)	5.6 (3.29-8.28)	4.1 (2.79-5.59)		0.80 (0.49-1.30
CD32B-232ll, ^f n = 380 (101/200; 91/180)	5.8 (5.55-7.66)	5.5 (4.17-5.65)		0.85 (0.64-1.13
CD32B-232IT, ^r n = 117 (21/53; 31/64)	6.0 (4.14-NA)	5.5 (2.79-7.16)		0.63 (0.36-1.10

-0.5 0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

^aNon-alpha allocating analysis; median follow-up: 2.8 months. ^bIn the metastatic setting. ^cAd hoc analyses (nonprespecified). ^dHormone receptor positive=ER+ and/or PgR+. ^eHormone receptor negative=ER- and PgR-. ^fCD32B-232TT not included in the forest plot because n = 9 is too small (5 on margetuximab, 4 on trastuzumab) to make the analysis meaningful. Abbreviations: Dx, diagnosis (initial presentation); ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IHC, immunohistochemistry; ISH, in situ hybridization; NA, not available (because cannot be calculated); NR, not reached; PgR, progesterone receptor. T-DM1, ado-trastuzumab emtansine; Tx, treatment.

eFigure 5. Prespecified ^a Exploratory OS Subgroup Analyses – Sep 2019 Cutoff. Median PFS, hazard
ratios, and 95% confidence intervals are shown in this figure.

	Median OS (9	5% CI), Months		HR by Unstratifie
Subgroup type, n (events/total per arm)	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy		Cox Model (95% CI)
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
Investigator-selected chemotherapy			1	
Capecitabine, n = 143 (35/71; 37/72)	23.6 (14.85-NA)	22.1 (17.91-29.01)	⊢♦ −−1	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)	He I	0.73 (0.46-1.17
Gemcitabine, n = 66 (16/33; 14/33)	21.6 (12.02-NA)	22.3 (18.40-35.65)	⊢ ,•i	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)	⊢ ●, -1	0.86 (0.57-1.28
Baseline characteristics				
≤2 metastatic sites, n = 282 (57/138; 62/144)	25.4 (20.40-NA)	25.4 (19.75-29.04)	H H	0.93 (0.65-1.33
>2 metastatic sites, n = 254 (74/128; 77/126)	18.6 (14.29-23.26)	16.8 (14.29–19.45)	Her.	0.84 (0.61-1.16
≤2 prior lines of Tx, ^ь n = 355 (88/175; 84/180)	21.6 (18.86-23.98)	21.9 (18.83-27.14)	Hard I have a second se	1.02 (0.76-1.38
>2 prior lines of Tx, ^b n = 181 (43/91; 55/90)	24.1 (16.16-NA)	17.5 (15.61-21.03)	⊢ e −µ	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)	Heri	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)	⊢ I ● II	1.60 (0.60-4.28
Stage IV at Dx: yes, ^c n = 228 (47/106; 58/122)	22.0 (17.48-NA)	21.0 (17.91-30.88)	⊢∎ <mark>,</mark> · · · ·	0.92 (0.62-1.3
Stage IV at Dx: no, ^c n = 308 (84/160; 81/148)	21.6 (18.53-24.57)	19.6 (15.84-22.28)		0.88 (0.65-1.1
Prior (neo)adjuvant Tx: yes, c n = 303 (83/158; 79/145)	21.5 (18.43-24.57)	19.8 (15.84-22.28)	⊢ ● □	0.90 (0.66-1.2
Prior (neo)adjuvant Tx: no, ^c n = 233 (48/108; 60/125)	22.0 (17.71-NA)	19.5 (17.18-30.88)	⊢ e ri	0.89 (0.61-1.3
Hormone Receptor+, ^d n= 334 (81/164; 82/170)	22.0 (18.86-28.32)	21.0 (18.40-24.18)	⊢∎ <mark>,</mark> I	0.91 (0.67-1.2
Hormone Receptor-, e n= 200 (50/102; 56/98)	20.6 (16.99-25.40)	17.9 (15.38-22.90)	F ● T → T	0.88 (0.60-1.3
HER2 IHC 3+, n=291 (64/149; 75/142)	23.6 (20.40-NA)	19.6 (17.51-24.25)	⊢ e ⊸i	0.71 (0.51-1.0
HER2 ISH amplified, n = 245 (67/117; 64/128)	18.6 (13.83-24.05)	20.5 (16.79-24.18)	⊢ ⊢	1.17 (0.83-1.6
ECOG 0, n = 310 (66/149; 78/161)	23.9 (18.89–32.76)	21.9 (18.89-25.40)		0.93 (0.67–1.2
ECOG 1, n = 226 (65/117; 61/109)	19.6 (17.48-23.66)	16.8 (14.29-21.03)	⊢●┬┥	0.83 (0.58-1.1
Region: Europe, n = 290 (75/152; 83/138)	21.5 (17.77-25.07)	17.5 (15.41–19.75)	⊢ e −i	0.73 (0.54-1.0
Region North America, n = 187 (46/85; 42/102)	18.9 (15.67-25.82)	24.2 (20.53-NA)	⊢ ⊢	1.34 (0.88-2.0
Region: other, n = 59 (10/29; 14/30)	23.6 (21.19-NA)	19.6 (14.32-35.65)		0.61 (0.27-1.4
Age ≤60 years, n = 366 (85/184; 98/182)	23.7 (18.89-32.76)	19.5 (16.66-22.93)	⊢ e ¦i	0.80 (0.60-1.0
Age >60 years, n = 170 (46/82; 41/88)	18.9 (17.77–23.98)	22.1 (16.79-27.14)	⊢¦∙—-i	1.17 (0.77-1.7
Race: Asian, n = 34 (6/20; 4/14)	NR (14.19-NA)	NR (15.11-NA)	⊢	1.15 (0.32-4.0
Race: Black, n = 28 (5/16; 6/12)	NR (18.63-NA)	17.9 (12.48-NA)	F	0.54 (0.16-1.8
Race: White, n = 427 (115/205; 121/222)	19.6 (16.99-23.26)	18.9 (16.66-22.28)	⊨ ∔ ⊣	0.99 (0.77-1.2
Race: other, n = 47 (5/25; 8/22)	NA (NA-NA)	24.3 (15.11-NA)	⊢ ● ¹ / ₁	0.42 (0.14-1.2
FcyR genotype				
CD16A-158F allele carrier, n = 437 (103/221; 114/216)	23.7 (18.89-28.32)	19.4 (16.85-22.28)	r•+	0.79 (0.61-1.0
CD16A-158FF, n = 192 (50/102; 50/90)	23.3 (18.56-32.76)	18.4 (14.59-22.28)	⊢ •-}	0.69 (0.47-1.02
CD16A-158FV, n = 245 (53/119; 64/126)	25.5 (18.33-NA)	20.0 (17.18-22.93)		0.88 (0.61-1.2
CD16A-158VV, n = 69 (20/37; 13/32)	19.7 (15.67–23.89)	33.3 (16.66-33.31)	i ⊨ <u>i</u> ●i	1.65 (0.82-3.32
CD32A-131RR, n = 122 (25/59; 33/63)	32.8 (15.67-35.98)	20.0 (18.27-25.40)		0.79 (0.47-1.34
CD32A-131RH, n = 247 (57/121; 63/126)	23.7 (18.89–28.32)	21.0 (15.44-29.01)		0.83 (0.58-1.1
CD32A-131HH, n = 137 (41/78; 31/59)	19.6 (16.16-24.05)	18.8 (15.84–23.89)		1.01 (0.64-1.62
CD32B-232II, ^f n = 380 (98/200; 89/180)	23.3 (18.53-24.57)	20.5 (18.27-24.74)	F#-1	1.00 (0.75-1.33
CD32B-232IT, ^f n = 117 (23/53; 35/64)	25.1 (17.48-NA)	17.9 (14.16-22.28)		0.65 (0.38-1.11

0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5

^aNon-alpha allocating analysis; median follow-up: 15.6 months. ^bIn the metastatic setting. ^cAd hoc analyses (nonprespecified). ^dHormone receptor positive=ER+ and/or PgR+. ^eHormone receptor negative=ER- and PgR-. ^fCD32B-232TT not included in the forest plot because n = 9 is too small (5 on margetuximab, 4 on trastuzumab) to make the analysis meaningful. Abbreviations: Dx, diagnosis (initial presentation); ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IHC, immunohistochemistry; ISH, in situ hybridization; NA, not available (because cannot be calculated); NR, not reached; PgR, progesterone receptor; T-DM1, ado-trastuzumab emtansine; Tx=treatment.