

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

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

SUPPLEMENTARY TABLES

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

	Margetuximab Plus Chemotherapy (N = 258)		Trastuzumab Plus Chemotherapy (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 (P value)	0.449 (0.503)		0.393 (0.530)	

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

	CD16A-158FF		CD16A-158FV		CD16A-158VV	
	M + C (n = 102)	T + C (n = 90)	M + C (n = 119)	T + C (n = 126)	M + C (n = 37)	T + C (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)

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)

Responses	Central Blinded Analysis of Response in the Response Evaluable Population (Oct 2018 Cutoff)		Investigator-Assessed Response in the Response Evaluable Population (Sep 2019 Cutoff)	
	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 (%) [95% CI]	58 (22.1) [17.11–27.16]	42 (16.0) [11.59–21.47]	67 (25.2) [20.1–30.9]	37 (13.7) [9.8–18.4]
Stratified Mantel-Haenszel test P value (2-sided)	0.0597		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		0.0025	
Median duration of complete or partial response — months (95% CI)	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)	0.5407 ^a		0.7400 ^b	

^aUnstratified.

^bStratified.

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

	Margetuximab Plus Chemotherapy (N = 264)	Trastuzumab Plus Chemotherapy (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

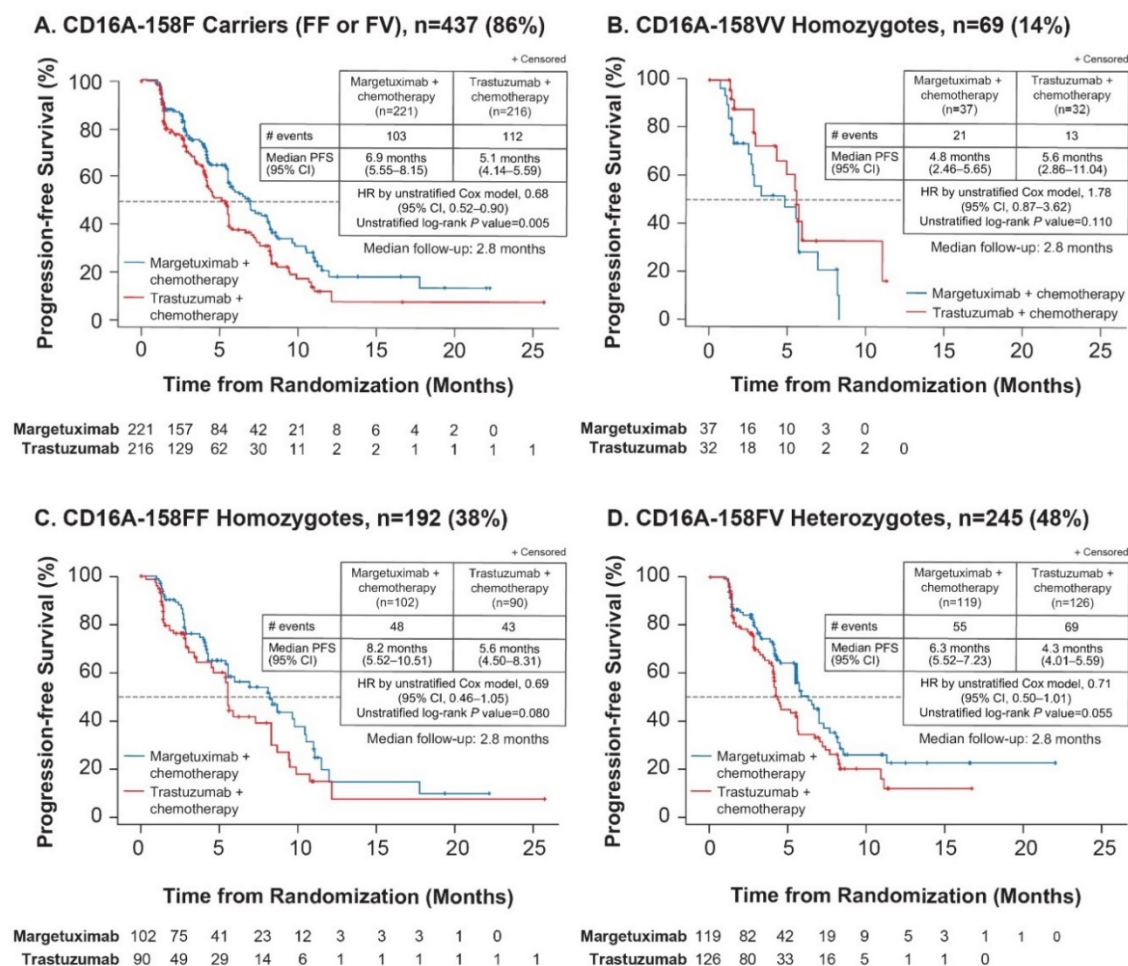
^aTwo patients had pneumonia, one had pneumonia aspiration. ^bOne patient had pneumonia, the other had acute kidney injury.

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).



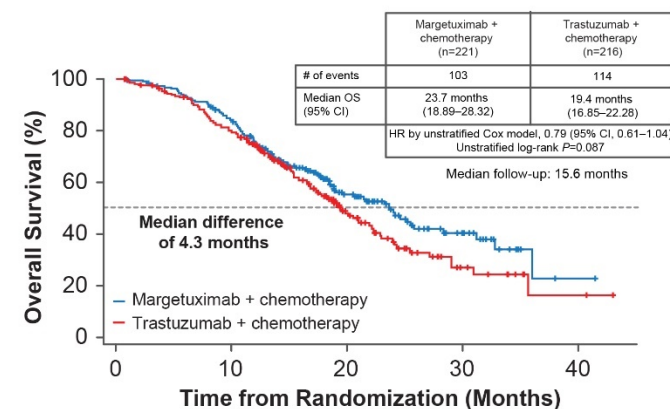
^a506 of 536 ITT patients genotyped (94%). Treatment by CD16A genotype (F carrier vs VV) interaction $P = .012$.

Abbreviation: Tx, treatment.

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

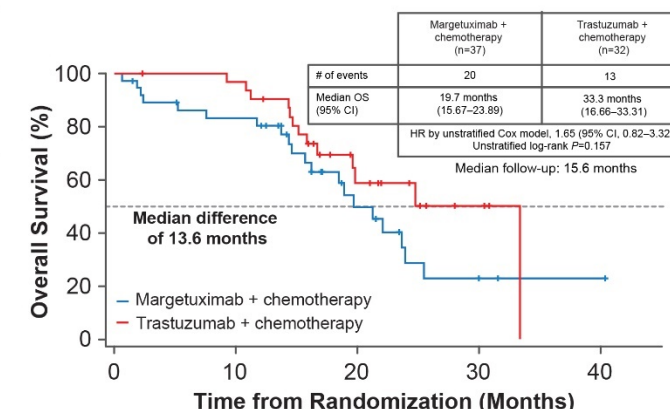
Kaplan-Meier estimates of OS by treatment group in CD16A-158F Carriers (FF or FV; Panel A), CD16A-158VV Homozygotes (Panel B), CD16A-158FF Homozygotes (Panel C), and CD16A-158FV Heterozygotes (Panel D).

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



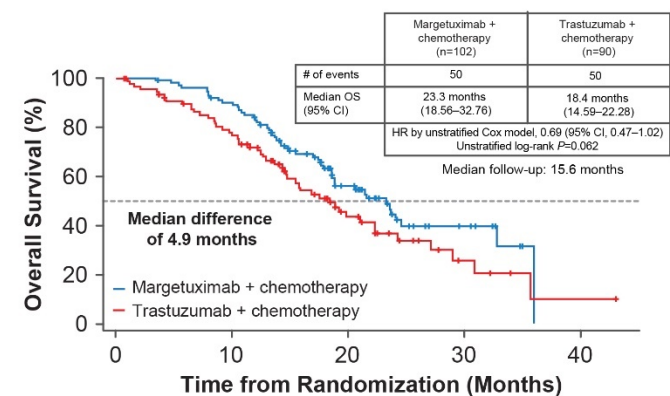
Margetuximab 221 219 212 204 196 181 157 135 111 91 68 55 42 31 27 19 13 8 2 1 1 0
Trastuzumab 216 210 201 192 176 165 145 123 98 81 57 43 30 21 16 11 9 6 2 2 1 0

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



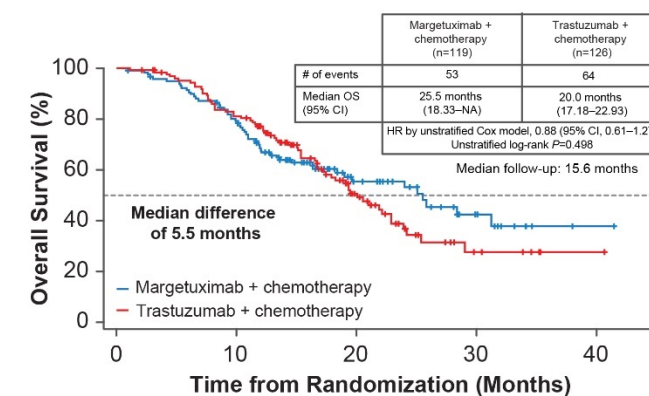
Margetuximab 37 34 32 30 29 27 23 19 15 11 9 5 4 4 3 1 1 1 1 1 0
Trastuzumab 32 32 31 31 31 30 28 27 20 14 11 8 4 3 3 1 0

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



Margetuximab 102 102 100 97 94 90 82 71 60 50 37 27 19 13 11 9 7 4 0
Trastuzumab 90 85 81 76 71 66 56 46 35 31 21 18 13 10 7 5 4 2 1 1 1 0

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



Margetuximab 119 117 112 107 102 91 75 64 51 41 31 28 23 18 16 10 6 4 2 1 1 0
Trastuzumab 126 125 120 116 105 99 89 77 63 50 36 25 17 11 9 6 5 4 1 1 1 0

^a506 of 536 ITT patients genotyped (94%). Treatment by CD16A genotype (F carrier vs VV) interaction P = .071.

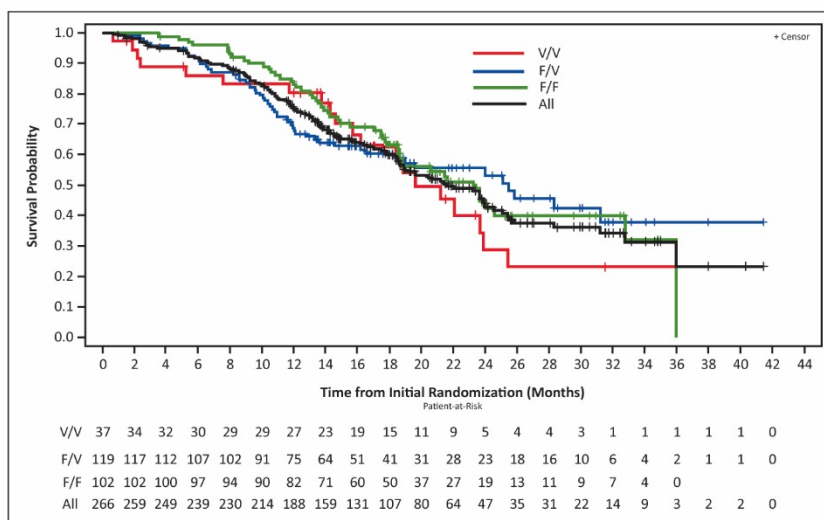
Abbreviations: ITT, intent-to-treat; NA, not available (because cannot be calculated).

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.

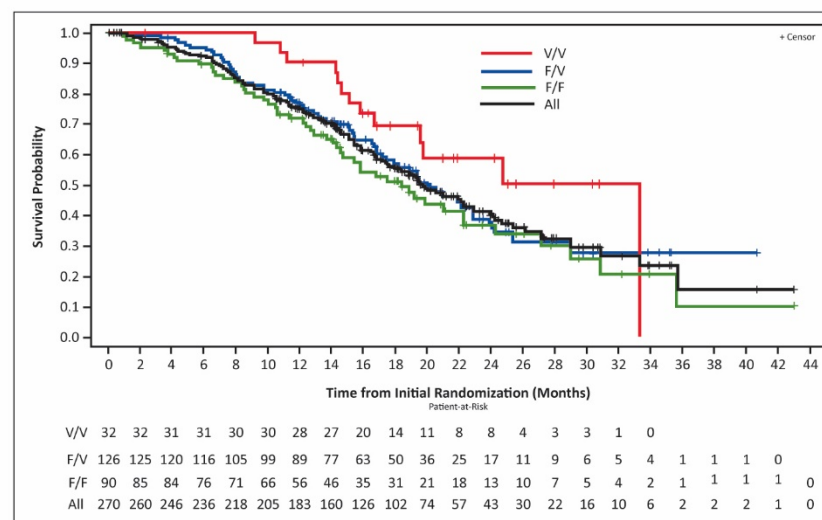
A. Margetuximab

	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)



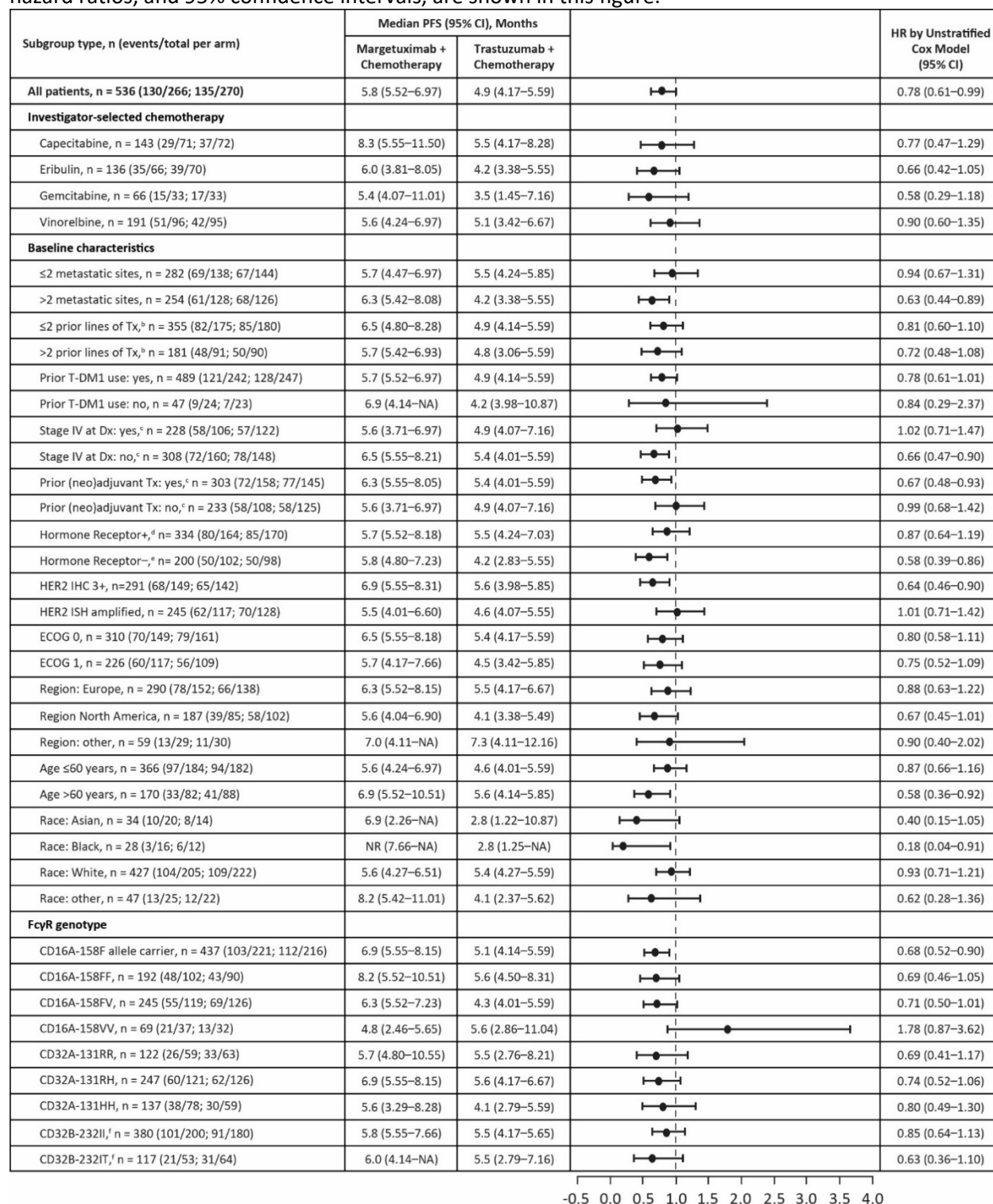
B. Trastuzumab

	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)



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

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.

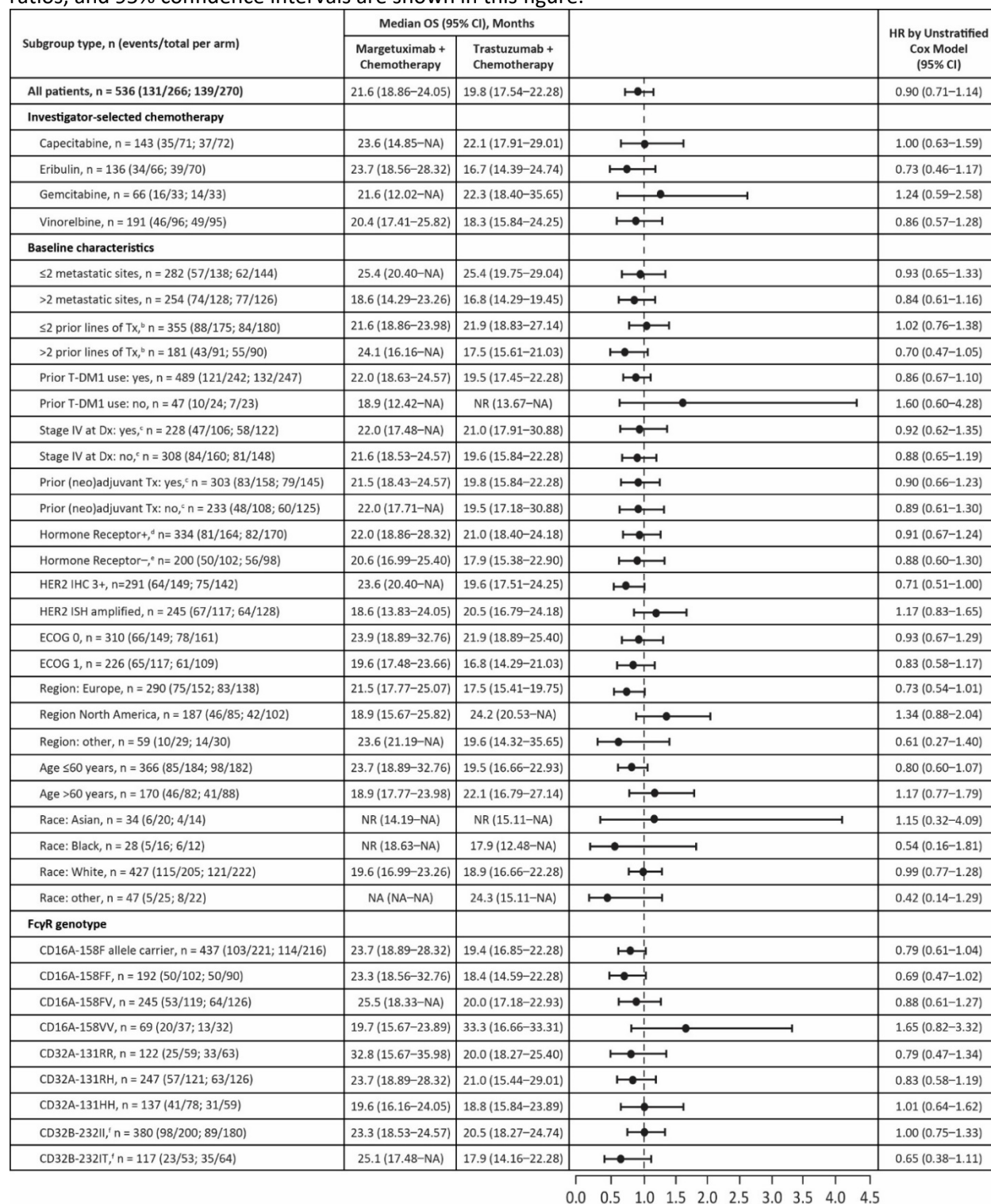


^aNon-alpha allocating analysis; median follow-up: 2.8 months. ^bIn the metastatic setting. ^cAd hoc analyses (nonprespecified).

^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.



^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.