clinical trial updates

Margetuximab Versus Trastuzumab in Patients With Previously Treated HER2-Positive Advanced Breast Cancer (SOPHIA): Final Overall Survival Results From a Randomized Phase 3 Trial

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Final overall survival (OS) in SOPHIA (ClinicalTrials.gov identifier: NCT02492711), a study of margetuximab versus trastuzumab, both with chemotherapy, in patients with previously treated human epidermal growth factor receptor 2–positive advanced breast cancer, is reported with updated safety. Overall, 536 patients in the intention-to-treat population were randomly assigned to margetuximab (15 mg/kg intravenously once every 3 weeks; n = 266) plus chemotherapy or trastuzumab (6 mg/kg intravenously once every 3 weeks after a loading dose of 8 mg/kg; n = 270) plus chemotherapy. Primary end points were progression-free survival, previously reported, and OS. Final OS analysis was triggered by 385 prespecified events. The median OS was 21.6 months (95% CI, 18.89 to 25.07) with margetuximab versus 21.9 months (95% CI, 18.69 to 24.18) with trastuzumab (hazard ratio [HR], 0.95; 95% CI, 0.77 to 1.17; $P = .620$). Preplanned, exploratory analysis of CD16A genotyping suggested a possible improvement in OS for margetuximab in CD16A-158FF patients versus trastuzumab (median OS, 23.6 *v* 19.2 months; HR, 0.72; 95% CI, 0.52 to 1.00) and a possible improvement in OS for trastuzumab in CD16A-158VV patients versus margetuximab (median OS, 31.1 *v* 22.0 months; HR, 1.77; 95% CI, 1.01 to 3.12). Margetuximab safety was comparable with trastuzumab. Final overall OS analysis did not demonstrate margetuximab advantage over trastuzumab. Margetuximab studies in patients with human epidermal growth factor receptor 2–positive breast cancer with different CD16A allelic variants are warranted.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Margetuximab-cmkb is an Fc-engineered anti–human epidermal growth factor receptor 2 (anti-HER2) immunoglobulin G monoclonal antibody that targets the same epitope as trastuzumab, with similar antiproliferative effects.[1,2] Compared with trastuzumab, margetuximab was designed to increase binding affinity (in vitro) for activating Fcγ receptor (FcγR) CD16A (FcγRIIIa) and decrease binding affinity for inhibitory FcγR CD32B (FcγRIIb).[1-3] Margetuximab has improved binding affinity for both polymorphic allelic variants (158V or 158F) of CD16A, binds CD16A-158F with higher affinity than trastuzumab binds CD16A-158V, and enhances innate immunity, including CD16A-mediated antibody-dependent cellular cytotoxicity, more effectively than trastuzumab.[1-4]

Primary analysis of progression-free survival (PFS) by central review of the phase 3 study SOPHIA (ClinicalTrials.gov identifier: NCT02492711)[5] led to the US Food and Drug Administration approval of

TABLE 1. Demographic and Baseline Disease Characteristics in the Intention-to-Treat Population (N = 536)

Characteristic	Margetuximab Plus Chemotherapy (n = 266)	Trastuzumab Plus Chemotherapy (n = 270)
Female sex, No. (%)	266 (100)	267 (98.9)
Age, years		
Median (range)	55.0 (29-83)	56.0 (27-86)
Race, No. (%)		
Asian	20 (7.5)	14 (5.2)
Black or African American	16 (6.0)	12 (4.4)
White	205 (77.1)	222 (82.2)
Others	25 (9.4)	22 (8.1)
ECOG performance status, No. (%)		
0	149 (56.0)	161 (59.6)
1	117 (44.0)	109 (40.4)
Disease extent at screening, No. (%)		
Metastatic	260 (97.7)	264 (97.8)
Locally advanced, unresectable	6 (2.3)	6 (2.2)
No. of metastatic sites, No. (%)		
≤ 2	138 (51.9)	144 (53.3)
> 2	128 (48.1)	126 (46.7)
No. of prior lines of therapy in the metastatic setting, No. (%)		
≤ 2	175 (65.8)	180 (66.7)
> 2	91 (34.2)	90 (33.3)
Prior systemic therapy in early and metastatic settings, No. (%)		
Chemotherapy		
Taxane	252 (94.7)	249 (92.2)
Anthracycline	118 (44.4)	110 (40.7)
Platinum	34 (12.8)	40 (14.8)
Prior HER2-targeted therapy in early and metastatic settings, No. (%)		
Trastuzumab	266 (100)	270 (100)
Pertuzumab	266 (100)	269 (99.6)
Ado-trastuzumab emtansine	242 (91.0)	247 (91.5)
Lapatinib	41 (15.4)	39 (14.4)
Other HER2	6 (2.3)	6 (2.2)
Prior endocrine therapy in early and metastatic settings	126 (47.4)	133 (49.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

margetuximab with chemotherapy in patients with HER2+ metastatic breast cancer (BC) who have received ≥ 2 prior anti-HER2 regimens, at least one of which was for metastatic disease.[6] Here, we report the final overall survival (OS) analysis after 385 deaths, with updated safety information.

PATIENTS AND METHODS

Study Design and Participants

Study design, eligibility criteria, treatment plan, and statistical analyses are detailed in a prior publication[5] and are summarized in Appendix Figure A1 (online only). Sequential primary end points were PFS by central review followed by OS. These two end points were tested in a hierarchical manner, with PFS being tested first with full allocation of two-sided $\alpha = .05$. OS was tested at two-sided $\alpha = .05$ only when a statistically significant difference in PFS was obtained (ie, PFS test $P < .05$). Final analysis of PFS took place when 257 PFS events had occurred in the randomly assigned population. Final OS analysis was triggered when 385 events had occurred. Investigator-assessed PFS was a secondary end point. Additional planned end points included investigator-assessed objective response rate, safety, and exploratory evaluation of FcγR allelic variation on efficacy. Trial conduct was in accordance with Good Clinical Practice and Principles in the Declaration of Helsinki. An independent ethics committee approved the Protocol (online only) at each participating site. All patients provided written informed consent.

RESULTS AND DISCUSSION

Study Population

Baseline characteristics, previously published,[5] show that all patients had received prior trastuzumab, all but one had received prior pertuzumab, and 489 (91.2%) had received prior ado-trastuzumab emtansine (Table 1).[5] Patient disposition is summarized in Appendix Figure A2 (online only). At the data cutoff date for this analysis (June 14, 2021), 8 (3.0%) of 266 patients in the margetuximab group and 5 (1.9%) of 270 patients in the trastuzumab group remained on study, including three patients remaining exclusively on margetuximab and one patient remaining exclusively on trastuzumab. Patients received a median of seven cycles of margetuximab plus chemotherapy versus six cycles of trastuzumab plus chemotherapy, with a median treatment duration of 20.7 months (0.7-61.4) for the margetuximab group and 19.4 months (0.1-64.5) for the trastuzumab group.

Efficacy

At data cutoff, with a median follow-up of 20.2 months among all intention-to-treat (ITT) patients (0.1-64.5), 385 deaths had occurred (194 [73%] in the margetuximab group and 191 [71%] in the trastuzumab group). The median OS in the ITT population was not statistically different between the two treatment groups: 21.6 months with margetuximab

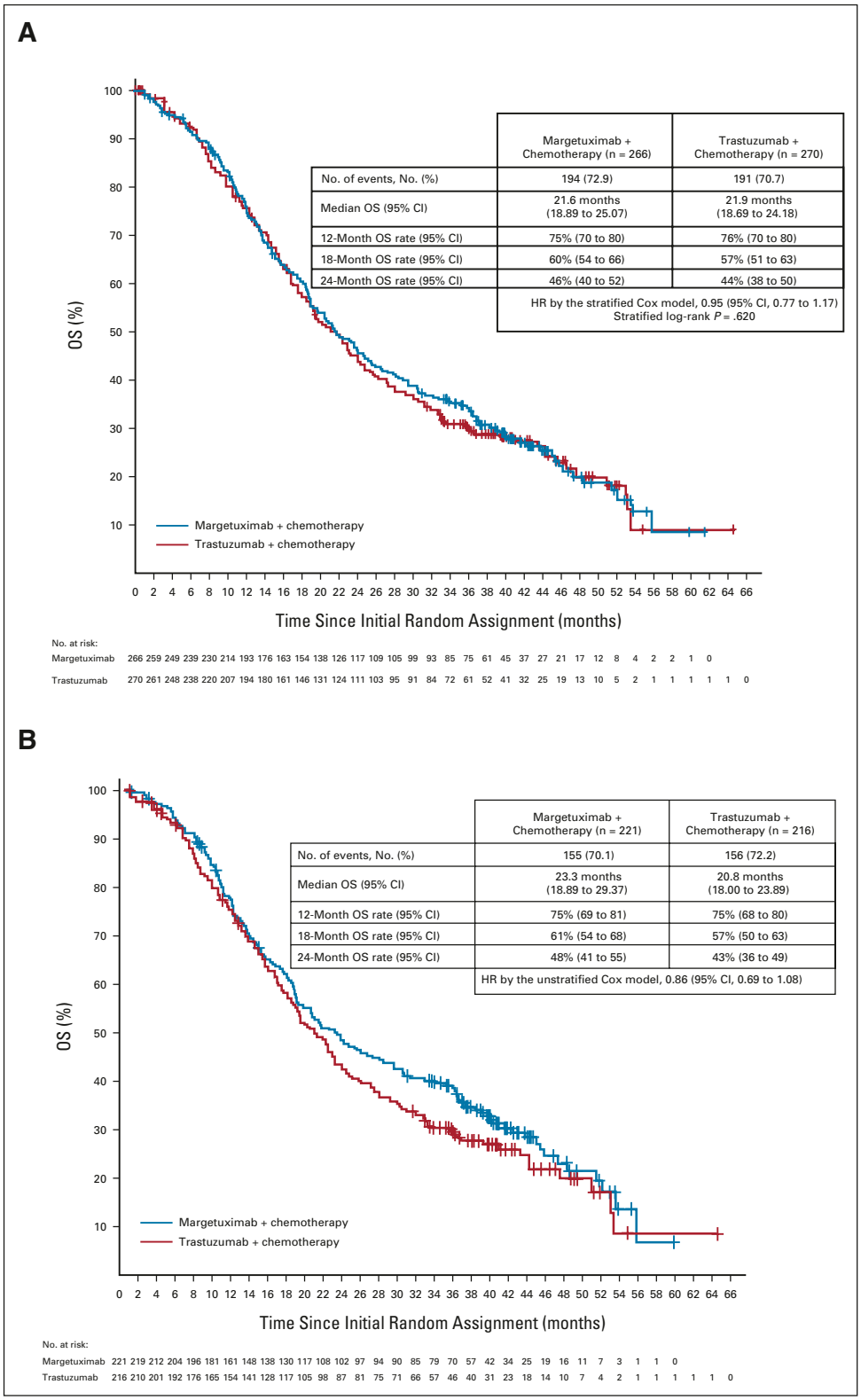
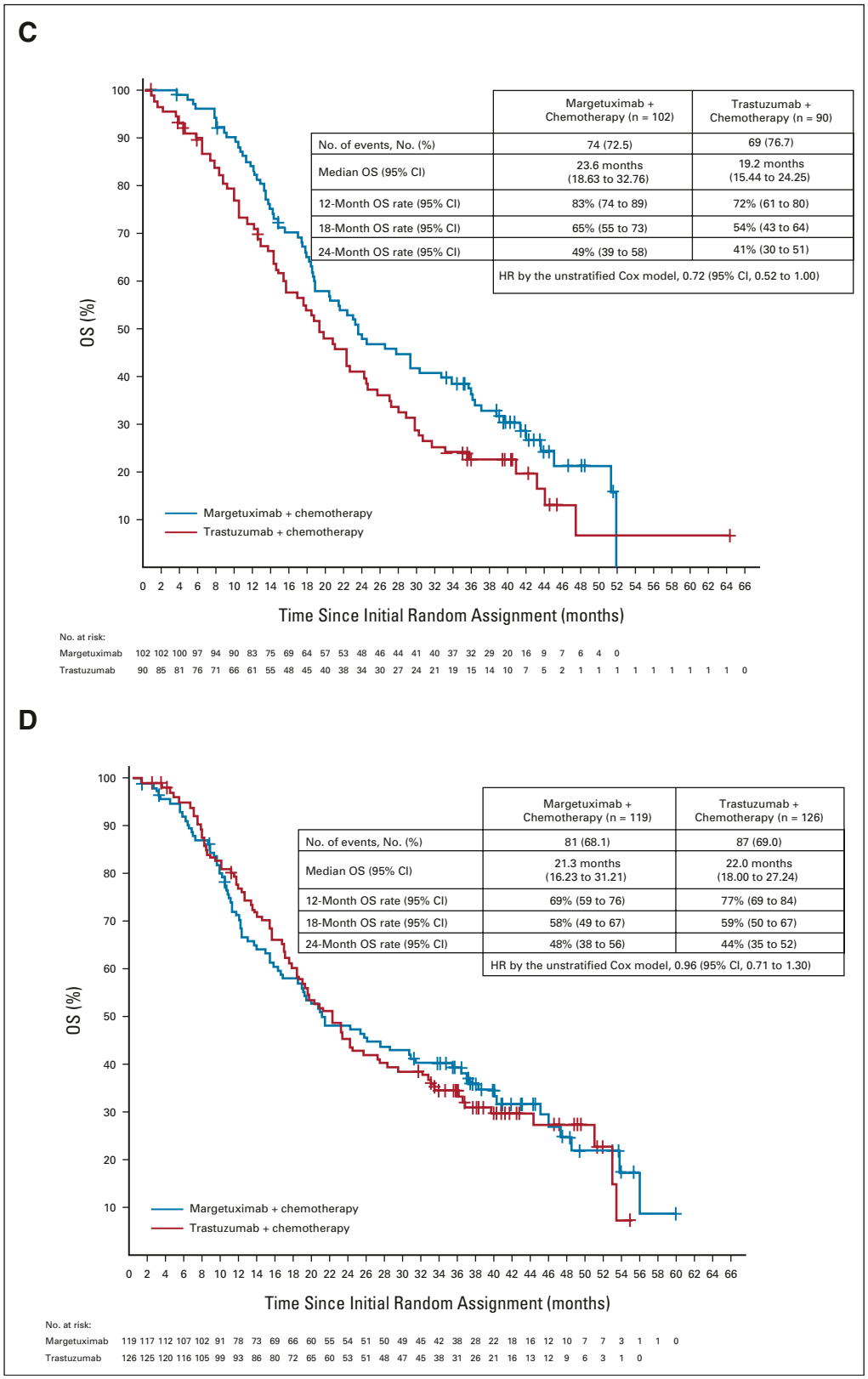


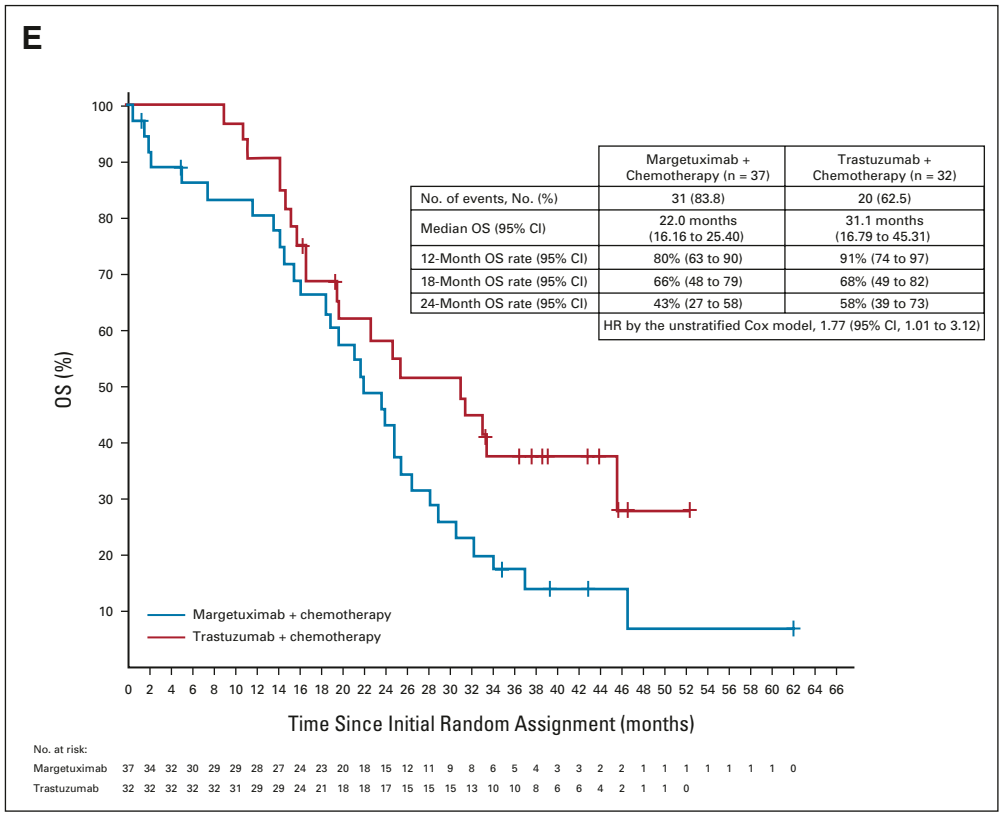
FIG 1. (A) Final OS in the ITT population and (B-E) planned prespecified[a] exploratory OS analysis, per CD16A genotype[b] by treatment group, June 14, 2021, cutoff. (A) Kaplan-Meier estimates of OS in the ITT population (n = 536). Kaplan-Meier estimates of OS by treatment group in (B) CD16A-158F carriers (FF or FV; n = 437; 86%), (C) CD16A-158FF homozygotes (n = 192; 38%), (D) CD16A-158FV heterozygotes (n = 245; 48%), and (E) CD16A-158VV homozygotes (n = 69; 14%). [a]Non–α-allocated analysis. [b]A total of 506 of 536 ITT patients genotyped (94%). HR, hazard ratio; ITT, intention-to-treat; NA, not available (because cannot be calculated); OS, overall survival. (continued on following page)



	Margetuximab + Chemotherapy (n = 102)	Trastuzumab + Chemotherapy (n = 90)
No. of events, No. (%)	74 (72.5)	69 (76.7)
Median OS (95% CI)	23.6 months (18.63 to 32.76)	19.2 months (15.44 to 24.25)
12-Month OS rate (95% CI)	83% (74 to 89)	72% (61 to 80)
18-Month OS rate (95% CI)	65% (55 to 73)	54% (43 to 64)
24-Month OS rate (95% CI)	49% (39 to 58)	41% (30 to 51)
HR by the unstratified Cox model, 0.72 (95% CI, 0.52 to 1.00)		

	Margetuximab + Chemotherapy (n = 119)	Trastuzumab + Chemotherapy (n = 126)
No. of events, No. (%)	81 (68.1)	87 (69.0)
Median OS (95% CI)	21.3 months (16.23 to 31.21)	22.0 months (18.00 to 27.24)
12-Month OS rate (95% CI)	69% (59 to 76)	77% (69 to 84)
18-Month OS rate (95% CI)	58% (49 to 67)	59% (50 to 67)
24-Month OS rate (95% CI)	48% (38 to 56)	44% (35 to 52)
HR by the unstratified Cox model, 0.96 (95% CI, 0.71 to 1.30)		

FIG 1. (continued on following page)



	Margetuximab + Chemotherapy (n = 37)	Trastuzumab + Chemotherapy (n = 32)
No. of events, No. (%)	31 (83.8)	20 (62.5)
Median OS (95% CI)	22.0 months (16.16 to 25.40)	31.1 months (16.79 to 45.31)
12-Month OS rate (95% CI)	80% (63 to 90)	91% (74 to 97)
18-Month OS rate (95% CI)	66% (48 to 79)	68% (49 to 82)
24-Month OS rate (95% CI)	43% (27 to 58)	58% (39 to 73)
HR by the unstratified Cox model, 1.77 (95% CI, 1.01 to 3.12)		

FIG 1. (Continued).

versus 21.9 months with trastuzumab (hazard ratio [HR], 0.95; 95% CI, 0.77 to 1.17; $P = .620$; Fig 1A).

A planned, prespecified non–α-allocated subgroup analyses of OS by chemotherapy backbone, HER2 status, showed no difference in survival between margetuximab and trastuzumab (Fig 2). Prespecified non–α-allocated subgroup analyses of OS by FcγR genotype were also conducted: genotyping was available for 506 patients (94%). Although no association was observed between CD32A or CD32B genotypes and survival benefit, OS subgroup analysis by CD16A genotype suggested a possible improvement in OS in favor of margetuximab in the CD16A-158FF patients, along with a possible improvement in OS in favor of trastuzumab in the CD16A-158VV patients. In 437 patients (86%) who carried the CD16A-158F low-affinity allele (F carriers), margetuximab prolonged the OS by 2.5 months compared with trastuzumab (Fig 1B). Median OS was 23.3 months with margetuximab versus 20.8 months with trastuzumab (HR, 0.86; 95% CI, 0.69 to 1.08; Fig 1B). Among 192 CD16A-158FF patients (38%), margetuximab prolonged the OS by 4.4 months compared with trastuzumab. Median OS was 23.6 months with margetuximab versus 19.2 months with trastuzumab (HR, 0.72; 95% CI, 0.52 to 1.00; Fig 1C). In 245 CD16A-158FV patients (48%), the median OS was 21.3 months with margetuximab versus 22.0 months with trastuzumab (HR, 0.96; 95% CI, 0.71 to 1.30; Fig 1D). By contrast, in the 69 CD16A-158VV patients (14%), the median OS was 22.0 months with margetuximab versus 31.1 months with trastuzumab (HR, 1.77; 95% CI, 1.01 to 3.12; Fig 1E). Additional efficacy results are shown in Appendix Figure A3 (online only), Appendix Table A1 (online only), and are presented in Appendix 2 (online only), Supplemental Efficacy Results.

Safety

As of June 14, 2021, the safety population included 264 patients in the margetuximab group and 266 patients in the trastuzumab group (Appendix Table A2, online only). Common adverse events (AEs) occurring in ≥ 20% of patients, regardless of causality, were fatigue, nausea, diarrhea, and neutropenia in both groups, as well as vomiting and pyrexia (margetuximab group) and anemia (trastuzumab group; Appendix Table A3, online only). Grade 3 or greater AEs in at least 5% of patients were neutrophil count decreased and anemia in both groups, as well as fatigue (margetuximab group) and febrile neutropenia (trastuzumab group; Appendix Table A3). Discontinuations from study treatment because of AEs were 4% (10 patients) in each treatment group (Appendix Table A2). There were six deaths because of AEs, none of which were considered treatment-related: four patients (2%) in the margetuximab group and two patients (1%) in the trastuzumab group (Appendix Table A2). Additional safety results are presented in Appendix 2, Supplemental Safety Results.

Subgroup	No. of Events/Total		Median OS, Months (95% CI)		HR by the Unstratified Cox Model (95% CI)
	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy	Margetuximab + Chemotherapy	Trastuzumab + Chemotherapy	
All patients	194/266	191/270	21.6 (18.89 to 25.07)	21.9 (18.69 to 24.18)	0.96 (0.79 to 1.18)
Investigator-selected chemotherapy					
Capecitabine	52/71	51/72	23.6 (15.05 to 32.76	23.5 (19.19 to 31.24)	1.05 (0.72 to 1.55)
Eribulin	51/66	49/70	20.7 (18.37 to 25.49)	16.7 (14.39 to 27.24)	1.01 (0.68 to 1.49)
Gemcitabine	23/33	22/33	21.3 (12.02 to 29.44)	22.6 (18.00 to 31.90)	0.98 (0.54 to 1.75)
Vinorelbine	68/96	69/95	21.5 (17.48 to 30.62)	21.0 (16.66 to 24.67)	0.88 (0.63 to 1.23)
HER2 status					
HER2 IHC 3+	101/149	101/142	25.5 (20.83 to 35.12)	20.8 (18.00 to 25.40)	0.81 (0.62 to 1.07)
HER2 ISH–amplified	93/117	90/128	18.6 (14.19 to 23.06)	22.3 (16.85 to 26.15)	1.21 (0.91 to 1.62)
FcγR genotype					
CD16A-158F allele carrier (FV or FF)	155/221	156/216	23.3 (18.89 to 29.37)	20.8 (18.00 to 23.89)	0.86 (0.69 to 1.08)
CD16A-158FF	74/102	69/90	23.6 (18.63 to 32.76)	19.2 (15.44 to 24.25)	0.72 (0.52 to 1.00)
CD16A-158FV	81/119	87/126	21.3 (16.23 to 31.21)	22.0 (18.00 to 27.24)	0.96 (0.71 to 1.30)
CD16A-158VV	31/37	20/32	22.0 (16.16 to 25.40)	31.1 (16.79 to 45.31)	1.77 (1.01 to 3.12)
CD32A-131RR	39/59	47/63	30.5 (17.77 to 38.24)	22.8 (18.89 to 27.86)	0.83 (0.54 to 1.27)
CD32A-131HR	88/121	90/126	23.7 (18.89 to 28.32)	22.0 (16.79 to 27.07)	0.92 (0.68 to 1.23)
CD32A-131HH	59/78	39/59	19.6 (16.07 to 23.89)	19.5 (16.66 to 30.36)	1.11 (0.74 to 1.67)
CD32B-232II[c]	146/200	125/180	23.1 (18.89 to 25.82)	22.9 (19.19 to 27.24)	1.06 (0.84 to 1.35)
CD32B-232IT[c]	36/53	47/64	21.5 (17.48 to 37.16)	18.8 (15.05 to 24.25)	0.71 (0.46 to 1.11)

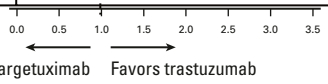


FIG 2. Planned prespecified[a] exploratory OS subgroup analyses (cutoff, June 14, 2021)[b]. Median OS, HRs, and 95% CIs are shown by subgroup. [a]Non-α-allocated analysis. [b]A total of 506 of 536 ITT patients genotyped (94%). [c]CD32B-232TT not included in the forest plot because n = 9 is too small (five on margetuximab and four on trastuzumab) to make the analysis meaningful. HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival.

In SOPHIA, the final OS analysis after 385 deaths in the ITT population did not demonstrate a survival advantage for margetuximab plus chemotherapy compared with trastuzumab plus chemotherapy in patients with pretreated HER2+ advanced BC.

The prespecified non–α-allocated evaluation of FcγR allelic variation on efficacy including an analysis of CD16A genotypes (FF, FV, and VV) suggested a possible improvement in OS in favor of margetuximab in the CD16A-158FF patients, along with a possible improvement in OS in favor of trastuzumab in the CD16A-158VV patients. Of note, there was an imbalance in poor prognostic characteristics between the two treatment groups in the CD16A-158VV patients[5] although there is no other clear explanation for why margetuximab did not provide a greater clinical benefit in these patients. In this study, the proportion of CD16A-158FF patients versus CD16A-158VV patients was 38% versus 14%, similar to other studies of HER2 agents in HER2+ BC.[7-13] Margetuximab improved median PFS (27% relative risk reduction) and objective response rate assessed by the investigator over trastuzumab, at the time of this final OS analysis.

The safety profile of margetuximab plus chemotherapy assessed at the time of this final OS analysis of SOPHIA confirmed an acceptable profile comparable with trastuzumab plus chemotherapy, similar to previous reports[5] and consistent with the US Food and Drug Administration–approved label for margetuximab.[6] Infusion-related reactions occurred at a higher frequency in the margetuximab plus chemotherapy arm but were manageable with premedications. Left ventricular dysfunctions occurred at a similar frequency in both arms. Left ventricular dysfunction requiring delay or cessation of margetuximab/trastuzumab administration occurred in fewer patients receiving margetuximab than in patients receiving trastuzumab.

In conclusion, PFS advantage with margetuximab plus chemotherapy observed in the previous analysis[5] and confirmed in this analysis did not translate into a significant difference in OS in the ITT population of SOPHIA. However, margetuximab plus chemotherapy is an available treatment option for patients with pretreated HER2+ advanced BC. Studies of margetuximab in patients with HER2+ BC with different CD16A allelic variants are warranted, including MARGOT (ClinicalTrials.gov identifier: NCT04425018), a randomized phase 2, neoadjuvant investigator-initiated study on the efficacy of margetuximab versus trastuzumab (both plus pertuzumab and paclitaxel) in patients with stage II–III HER2+ BC carrying the CD16A-158F low-affinity allele.

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DISCLAIMER

This study was designed by academic investigators and sponsor representatives. The sponsor participated in regulatory/ethics approval, safety monitoring, data cleaning/collection, and statistical analysis. The sponsor and coauthors analyzed data.

PRIOR PRESENTATION

Presented at the ASCO Annual Meeting, Chicago, IL, May 31-June 4, 2019; the San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2019; and the San Antonio Breast Cancer Symposium, San Antonio, TX, December 7-10, 2021.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02937.

DATA SHARING STATEMENT

Overall data will be available but not individual patient data.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Margetuximab Versus Trastuzumab in Patients With Previously Treated HER2-Positive Advanced Breast Cancer (SOPHIA): Final Overall Survival Results From a Randomized Phase 3 Trial

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APPENDIX 2. SUPPLEMENTAL MATERIAL

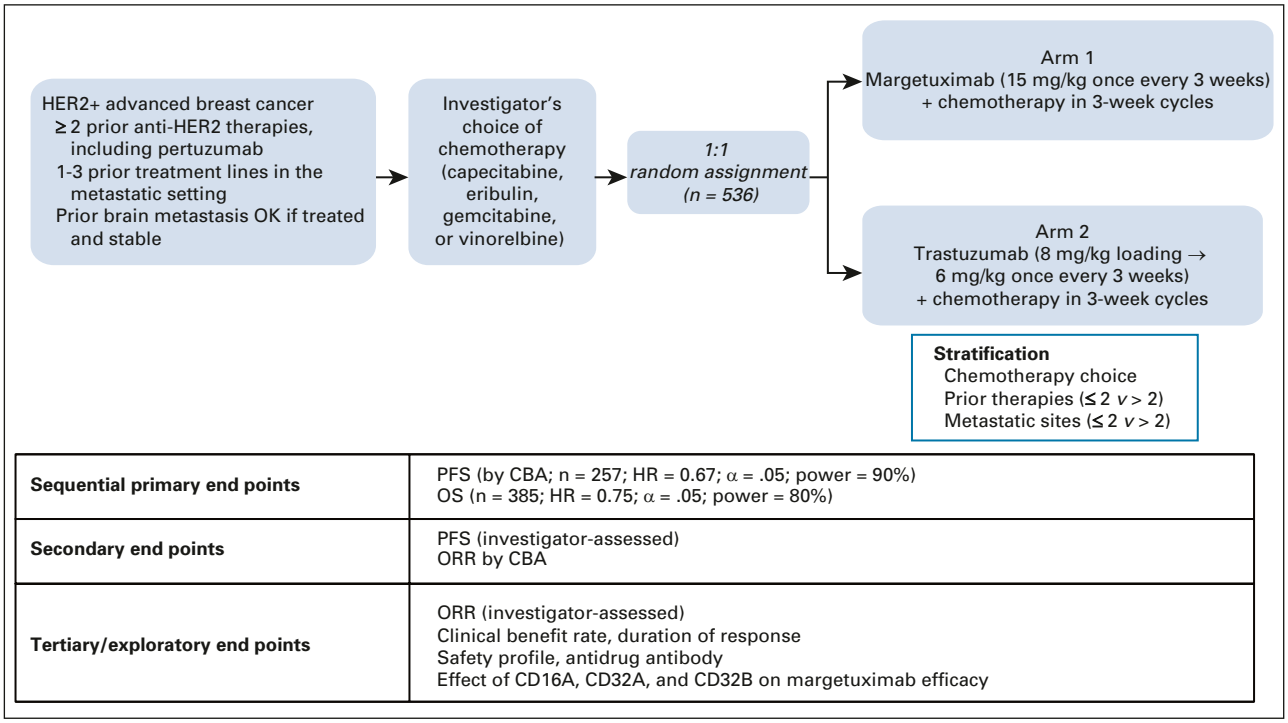
Supplemental Efficacy Results

The median progression-free survival assessed by the investigator in the intention-to-treat population was nominally statistically different between the two treatment groups: 5.7 months with margetuximab versus 4.4 months with trastuzumab (hazard ratio, 0.73; 95% CI, 0.60 to 0.88; $P = .001$; Appendix Fig A3). These findings were similar at the cutoff of September 2019 when the median progression-free survival assessed by the investigator was 5.7 months with margetuximab versus 4.4 months with trastuzumab (hazard ratio, 0.71; 95% CI, 0.58 to 0.86; $P < .001$).[5]

All 536 patients were evaluable for response. Margetuximab recipients had higher investigator-assessed objective response rate (ORR) than trastuzumab recipients (26% *v* 14%; Appendix Table A1). These rates were similar at the cutoff of September 2019 when the investigator-assessed ORR was 25% versus 14%.[5] Subgroup analysis of ORR by CD16A genotype showed that margetuximab improved ORR over trastuzumab across all CD16A-158 genotypes, except in the CD16A-158V homozygous patients, who experienced improved ORR from trastuzumab treatment instead (Appendix Table A1).

Supplemental Safety Results

Adverse events (AEs) of special interest included infusion-related reactions (IRRs) and left ventricular (LV) dysfunction. All-grade IRRs were more common with margetuximab than with trastuzumab (36 [14%] *v* 9 [3%], respectively; Appendix Tables A2 and A3). Among margetuximab recipients, grade ≥ 3 IRRs were reported in five (2%) patients and IRRs leading to discontinuation in three (1.1%) patients. No trastuzumab recipients had grade ≥ 3 IRRs or IRRs leading to discontinuation. AEs of LV dysfunction occurred in eight patients (3%) in both treatment groups (Appendix Table A2). Grade ≥ 3 LV dysfunction AEs were observed in three margetuximab recipients (1%) and one trastuzumab recipient (0.4%). AEs of LV dysfunction requiring dose delay or discontinuation were experienced in four margetuximab-treated (2%) versus seven trastuzumab-treated patients (3%).



Sequential primary end points	PFS (by CBA; n = 257; HR = 0.67; α = .05; power = 90%) OS (n = 385; HR = 0.75; α = .05; power = 80%)
Secondary end points	PFS (investigator-assessed) ORR by CBA
Tertiary/exploratory end points	ORR (investigator-assessed) Clinical benefit rate, duration of response Safety profile, antidrug antibody Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

FIG A1. SOPHIA study design. CBA, central blinded analysis; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

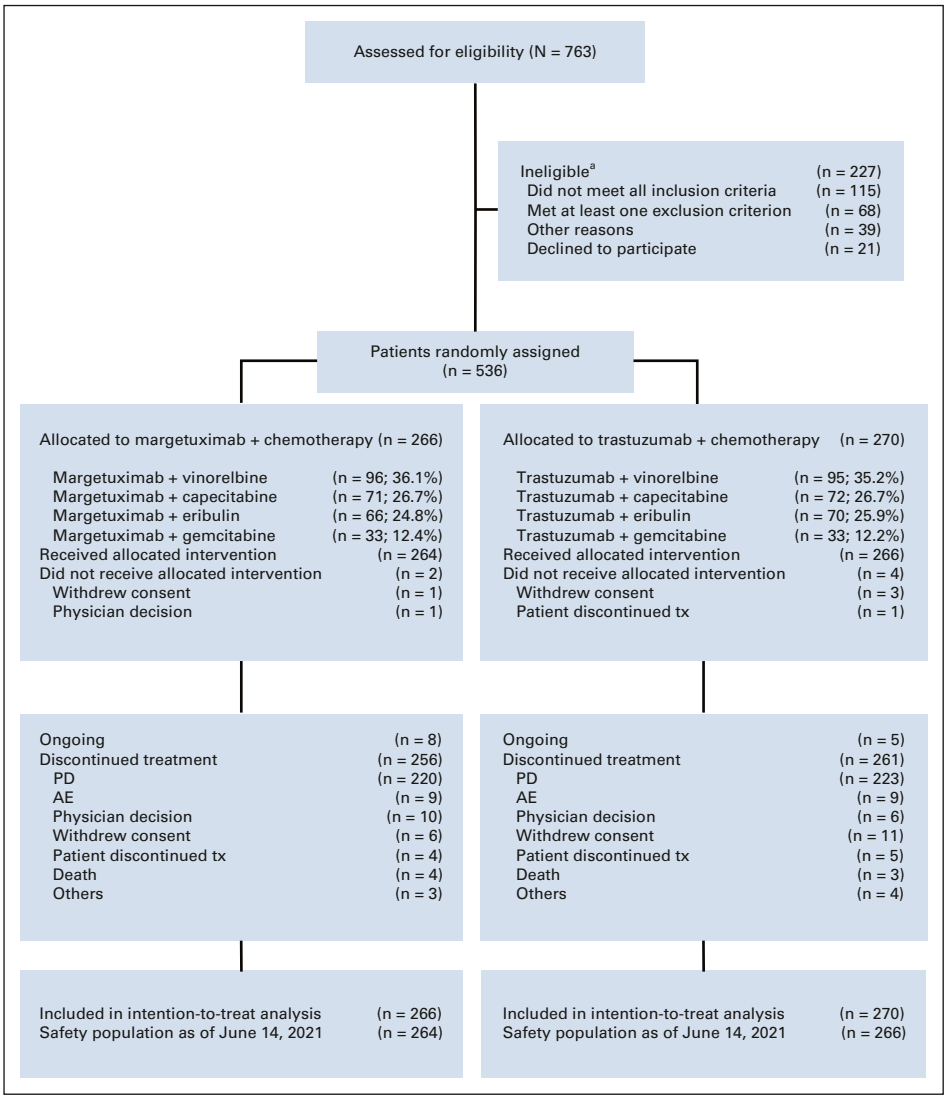


FIG A2. CONSORT diagram. All randomly assigned patients were included in the intention-to-treat population; randomly assigned patients who received at least one dose of study treatment were included in the safety population. Reasons for withdrawals are shown. [a]A patient may have more than one reason for screening failure. AE, adverse event; PD, progressive disease; tx, treatment.

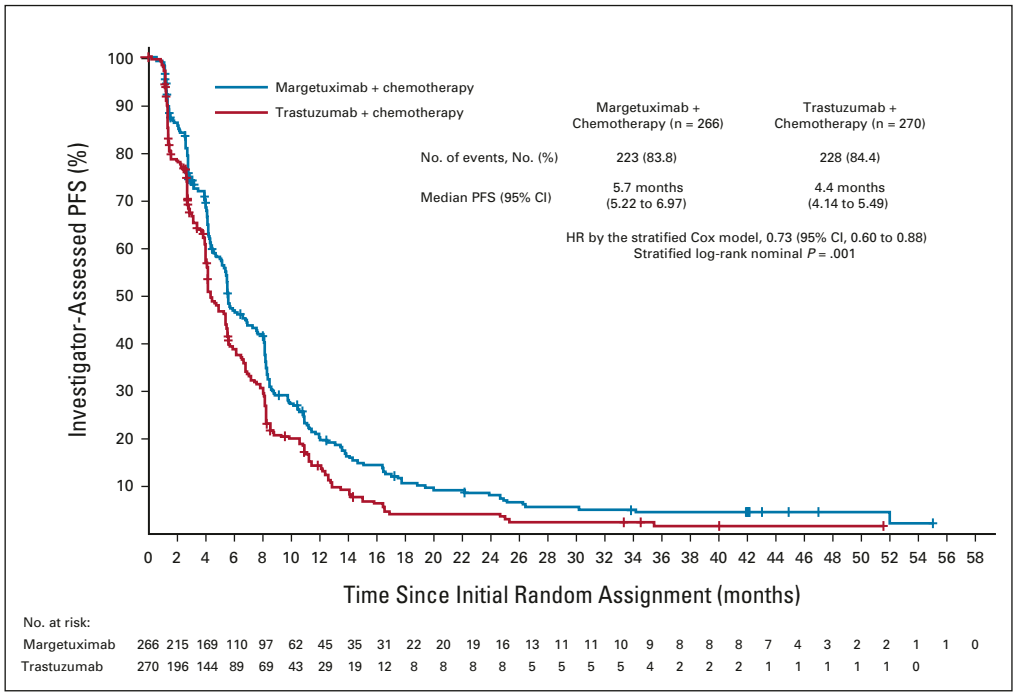


FIG A3. PFS assessed by the investigator in the intention-to-treat population (cutoff, June 14, 2021; n = 536). HR, hazard ratio; PFS, progression-free survival.

TABLE A1. Investigator-Assessed ORR by CD16A

	Response Evaluable Population (n = 536)		CD16A-158F Carriers (F/F and F/V; n = 437)		CD16A-158F Homozygotes (F/F; n = 192)		CD16A-158F/V Heterozygotes (n = 245)		CD16A-158V Homozygotes (V/V; n = 69)	
Responses	**M + CTX (n = 266)**	**T + CTX (n = 270)**	**M + CTX (n = 221)**	**T + CTX (n = 216)**	**M + CTX (n = 102)**	**T + CTX (n = 90)**	**M + CTX (n = 119)**	**T + CTX (n = 126)**	**M + CTX (n = 37)**	**T + CTX (n = 32)**
BOR, No. (%)										
CR	6 (2.3)	4 (1.5)	6 (2.7)	2 (0.9)	4 (3.9)	2 (2.2)	2 (1.7)	0	0	2 (6.3)
PR	62 (23.3)	33 (12.2)	56 (25.3)	27 (12.5)	24 (23.5)	13 (14.4)	32 (26.9)	14 (11.1)	6 (16.2)	5 (15.6)
SD	142 (53.4)	158 (58.5)	121 (54.8)	131 (60.6)	61 (59.8)	48 (53.3)	60 (50.4)	83 (65.9)	18 (48.6)	15 (46.9)
PD	40 (15.0)	57 (21.1)	30 (13.6)	45 (20.8)	11 (10.8)	21 (23.3)	19 (16.0)	24 (19.0)	9 (24.3)	9 (28.1)
NE/NA	16 (6.0)	18 (6.7)	8 (3.6)	11 (5.1)	2 (2.0)	6 (6.7)	6 (5.0)	5 (4.0)	4 (10.8)	1 (3.1)
ORR, No. (%)	68 (25.6)	37 (13.7)	62 (28.1)	29 (13.4)	28 (27.5)	15 (16.7)	34 (28.6)	14 (11.1)	6 (16.2)	7 (21.9)

Abbreviations: BOR, best overall response; CR, complete response; CTX, chemotherapy; F/F, CD16A-158FF homozygotes; F/V, CD16A-158FV heterozygotes; M, margetuximab; NA, not available; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T, trastuzumab; V/V, CD16A-158VV homozygotes.

TABLE A2. Summary of AEs in the Safety Population (cutoff, June 14, 2021)

Incidence	Margetuximab + Chemotherapy (n = 264), No. (%)	Trastuzumab + Chemotherapy (n = 266), No. (%)
Any-grade AE	260 (98.5)	261 (98.1)
HER2-targeted treatment-related AE of any grade	163 (61.7)	133 (50.0)
Chemotherapy-related AEs of any grade	238 (90.2)	239 (89.8)
Any-grade infusion-related AEs	36 (13.6)	9 (3.4)
Grade ≥ 3 infusion-related AEs	5 (1.9)	0
Any-grade LVEF dysfunction	8 (3.0)	8 (3.0)
Grade ≥ 3 LVEF dysfunction	3 (1.1)	1 (0.4)
Grade ≥ 3 AE	146 (55.3)	141 (53.0)
HER2-targeted treatment-related grade ≥ 3 AE	37 (14.0)	22 (8.3)
Chemotherapy-related grade ≥ 3 AE	113 (42.8)	108 (40.6)
Any SAE	47 (17.8)	51 (19.2)
HER2-targeted treatment-related SAE	4 (1.5)	4 (1.5)
Chemotherapy-related SAE	15 (5.7)	24 (9.0)
AE leading to treatment discontinuation from combined antibody plus chemotherapy	11 (4.2)	8 (3.0)
AE leading to chemotherapy discontinuation	35 (13.3)	17 (6.4)
AE leading to discontinuation from the study	10 (3.8)	10 (3.8)
Discontinuation of HER2-targeted treatment because of IRRs	3 (1.1)	0
LVEF dysfunction leading to dose delay or discontinuation	4 (1.5)	7 (2.6)
AE resulting in deaths	4 (1.5)[a]	2 (0.8)[b]
HER2-targeted treatment-related AE resulting in deaths	0	0

Abbreviations: AE, adverse event; HER2, human epidermal growth factor receptor 2; IRR, infusion-related reaction; LVEF, left ventricular ejection fraction; SAE, serious AE.

[a]Two patients had pneumonia, one had pneumonia aspiration, and one had coronavirus infection.

[b]One patient had pneumonia, and the other had acute kidney injury.

TABLE A3. AEs in the Safety Population, Regardless of Causality (cutoff, June 14, 2021)

	Margetuximab + Chemotherapy (n = 264)		Trastuzumab + Chemotherapy (n = 266)	
Preferred Term	**All Grade[a]**	**Grade ≥ 3[b]**	**All Grade[a]**	**Grade ≥ 3[b]**
Nonhematologic AEs, No. (%)				
Fatigue[c]	112 (42.4)	14 (5.3)	95 (35.7)	8 (3.0)
Nausea	88 (33.3)	3 (1.1)	87 (32.7)	1 (0.4)
Diarrhea	69 (26.1)	6 (2.3)	67 (25.2)	6 (2.3)
Vomiting[d]	55 (20.8)	2 (0.8)	38 (14.3)	4 (1.5)
Pyrexia	52 (19.7)	1 (0.4)	37 (13.9)	1 (0.4)
Constipation	51 (19.3)	2 (0.8)	45 (16.9)	2 (0.8)
Headache	50 (18.9)	0	44 (16.5)	0
Asthenia	49 (18.6)	6 (2.3)	33 (12.4)	5 (1.9)
Alopecia	47 (17.8)	0	39 (14.7)	0
Cough	42 (15.9)	1 (0.4)	32 (12.0)	0
Decreased appetite	38 (14.4)	1 (0.4)	38 (14.3)	1 (0.4)
Infusion-related reaction[e,f]	36 (13.6)	5 (1.9)	9 (3.4)	0
Dyspnea	34 (12.9)	3 (1.1)	30 (11.3)	6 (2.3)
PPE syndrome	33 (12.5)	1 (0.4)	43 (16.2)	8 (3.0)
Pain in extremity	32 (12.1)	3 (1.1)	24 (9.0)	0
Arthralgia	28 (10.6)	0	23 (8.6)	1 (0.4)
Stomatitis	28 (10.6)	2 (0.8)	21 (7.9)	0
Abdominal pain	26 (9.8)	4 (1.5)	37 (13.9)	3 (1.1)
Urinary tract infection	26 (9.8)	2 (0.8)	28 (10.5)	3 (1.1)
Peripheral neuropathy	26 (9.8)	1 (0.4)	28 (10.5)	3 (1.1)
Dizziness	26 (9.8)	1 (0.4)	17 (6.4)	0
Mucosal inflammation[g]	26 (9.8)	0	8 (3.0)	1 (0.4)
Back pain	24 (9.1)	1 (0.4)	27 (10.2)	3 (1.1)
Hypokalemia	17 (6.4)	5 (1.9)	21 (7.9)	4 (1.5)
Hypertension	14 (5.3)	5 (1.9)	8 (3.0)	2 (0.8)
Pneumonia	9 (3.4)	5 (1.9)	11 (4.1)	9 (3.4)
Pleural effusion	8 (3.0)	2 (0.8)	13 (4.9)	4 (1.5)
Syncope	4 (1.5)	4 (1.5)	0	0
Hematologic AEs, No. (%)				
Neutropenia[h]	76 (28.8)	54 (20.5)	55 (20.7)	33 (12.4)
Anemia[i]	50 (18.9)	13 (4.9)	63 (23.7)	17 (6.4)
Neutrophil count decreased	33 (12.5)	23 (8.7)	39 (14.7)	28 (10.5)
ALT increased	26 (9.8)	5 (1.9)	26 (9.8)	4 (1.5)
AST increased	22 (8.3)	7 (2.7)	34 (12.8)	3 (1.1)
WBC decreased	20 (7.6)	7 (2.7)	26 (9.8)	8 (3.0)
Leukopenia	14 (5.3)	4 (1.5)	10 (3.8)	1 (0.4)
Febrile neutropenia[j]	8 (3.0)	8 (3.0)	13 (4.9)	13 (4.9)

Abbreviations: AE, adverse event; PPE, palmar-plantar erythrodysesthesia.

[a]All-grade AEs with an incidence of 10% or more in either treatment group.

[b]Grade ≥ 3 with an incidence of at least 2% in either treatment group.

[c]Exact test *P* value for nonprespecified comparison of all-grade fatigue between treatment groups (42.4% *v* 35.7%): $P = .1301$. Exact test *P* value for nonprespecified comparison of grade ≥ 3 fatigue between treatment groups (5.3% *v* 3.0%): $P = .1991$.

[d]Exact test *P* value for nonprespecified comparison of all-grade vomiting between treatment groups (20.8% *v* 14.3%): $P = .0525$.

[e]Infusion-related reactions include hypersensitivity/anaphylactic/anaphylactoid reactions.

[f]Exact test *P* value for nonprespecified comparison of all-grade infusion-related reaction between treatment groups (13.6% *v* 3.4%): $P < .0001$.

[g]Exact test *P* value for nonprespecified comparison of all-grade mucosal inflammation between treatment groups (9.8% *v* 3.0%): $P = .0013$.

[h]Exact test *P* value for nonprespecified comparison of all-grade neutropenia between treatment groups (28.8% *v* 20.7%): $P = .0345$. Exact test *P* value for nonprespecified comparison of grade ≥ 3 neutropenia between treatment groups (20.5% *v* 12.4%): $P = .0138$.

[i]Exact test *P* value for nonprespecified comparison of all-grade anemia between treatment groups (18.9% *v* 23.7%): $P = .2035$.

[j]Exact test *P* value for nonprespecified comparison of grade ≥ 3 febrile neutropenia between treatment groups (3.0% *v* 4.9%): $P = .3737$.