JAMA Oncology | Original Investigation

Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer
A Phase 3 Randomized Clinical Trial

Hope S. Rugo, MD; Seock-Ah Im, MD, PhD; Fatima Cardoso, MD; Javier Cortés, MD, PhD; Giuseppe Curigliano, MD, PhD; Antonino Musolino, MD, PhD, MSc; Mark D. Pegram, MD; Gail S. Wright, MD; Cristina Saura, MD, PhD; Santiago Escrivá-de-Romaní, MD; Michelino De Laurentiis, MD, PhD; Christelle Levy, MD; Ursa Brown-Glaberman, MD; Jean-Marc Ferrero, MD; Maaike de Boer, MD, PhD; Sung-Bae Kim, MD, PhD; Katarína Petráková, MD, PhD; Denise A. Yardley, MD; Orit Freedman, MD, MSc; Erik H. Jakobsen, MD; Bella Kaufman, MD; Rinat Yerushalmi, MD; Peter A. Fasching, MD; Jeffrey L. Nordstrom, PhD; Ezio Bonvini, MD; Scott Koenig, MD, PhD; Sutton Edlich, MS, PA; Shengyan Hong, PhD; Edwin P. Rock, MD, PhD; William J. Gradishar, MD; for the SOPHIA Study Group

IMPORTANCE ERRB2 (formerly HER2)–positive advanced breast cancer (ABC) remains typically incurable with optimal treatment undefined in later lines of therapy. The chimeric antibody margetuximab shares ERBB2 specificity with trastuzumab but incorporates an engineered Fc region to increase immune activation.

OBJECTIVE To compare the clinical efficacy of margetuximab vs trastuzumab, each with chemotherapy, in patients with pretreated ERBB2-positive ABC.

DESIGN, SETTING, AND PARTICIPANTS The SOPHIA phase 3 randomized open-label trial of margetuximab plus chemotherapy vs trastuzumab plus chemotherapy enrolled 536 patients from August 26, 2015, to October 10, 2018, at 166 sites in 17 countries. Eligible patients had disease progression on 2 or more prior anti-ERBB2 therapies and 1 to 3 lines of therapy for metastatic disease. Data were analyzed from February 2019 to October 2019.

INTERVENTIONS Investigators selected chemotherapy before 1:1 randomization to margetuximab, 15 mg/kg, or trastuzumab, 6 mg/kg (loading dose, 8 mg/kg), each in 3-week cycles. Stratification factors were metastatic sites (≤2, >2), lines of therapy (≤2, >2), and chemotherapy choice.

MAIN OUTCOMES AND MEASURES Sequential primary end points were progression-free survival (PFS) by central blinded analysis and overall survival (OS). All α was allocated to PFS, followed by OS. Secondary end points were investigator-assessed PFS and objective response rate by central blinded analysis.

RESULTS A total of 536 patients were randomized to receive margetuximab (n = 266) or trastuzumab (n = 270). The median age was 56 (27-86) years; 266 (100%) women were in the margetuximab group, while 267 (98.9%) women were in the trastuzumab group. Groups were balanced. All but 1 patient had received prior pertuzumab, and 489 (91.2%) had received prior ado-trastuzumab emtansine. Margetuximab improved primary PFS over trastuzumab with 24% relative risk reduction (hazard ratio [HR], 0.76; 95% CI, 0.59-0.98; *P* = .03; median, 5.8 [95% CI, 5.5-7.0] months vs 4.9 [95% CI, 4.2-5.6] months; October 10, 2018). After the second planned interim analysis of 270 deaths, median OS was 21.6 months with margetuximab vs 19.8 months with trastuzumab (HR, 0.89; 95% CI, 0.69-1.13; *P* = .33; September 10, 2019), and investigator-assessed PFS showed 29% relative risk reduction favoring margetuximab (HR, 0.71; 95% CI, 0.58-0.86; *P* < .001; median, 5.7 vs 4.4 months; September 10, 2019). Margetuximab improved objective response rate over trastuzumab: 22% vs 16% (*P* = .06; October 10, 2018), and 25% vs 14% (*P* < .001; September 10, 2019). Incidence of infusion-related reactions, mostly in cycle 1, was higher with margetuximab (35 [13.3%] vs 9 [3.4%]); otherwise, safety was comparable.

CONCLUSIONS AND RELEVANCE In this phase 3 randomized clinical trial, margetuximab plus chemotherapy had acceptable safety and a statistically significant improvement in PFS compared with trastuzumab plus chemotherapy in ERBB2-positive ABC after progression on 2 or more prior anti-ERBB2 therapies. Final OS analysis is expected in 2021.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02492711

JAMA Oncol. doi:10.1001/jamaoncol.2020.7932
Published online January 22, 2021.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The SOPHIA Study Group members appear at the end of the article.

Corresponding Author: Hope S. Rugo, MD, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, 1825 Fourth St, 3rd Floor, PO Box 1710, San Francisco, CA 94158 (hope.rugo@ucsf.edu).

Addition of ERBB2 (formerly HER2)–targeting monoclonal antibodies to chemotherapy improves progression-free survival (PFS) and overall survival (OS) in patients with ERBB2-positive advanced breast cancer (ABC).[1-4] Generally, patients with ERBB2-positive metastatic breast cancer (BC) receive multiple lines of therapy, yet with rare exceptions, ERBB2-positive metastatic BC remains incurable.[5,6]

Margetuximab is a chimeric, Fc-engineered, immune-activating anti-ERBB2 immunoglobulin G1 (IgG1) monoclonal antibody that shares epitope specificity and Fc-independent antiproliferative effects with trastuzumab. Fc engineering of margetuximab alters 5 amino acids from wild-type IgG1 to increase affinity for activating Fcγ receptor (FcγR) CD16A (FcγRIIIa) and to decrease affinity for inhibitory FcγR CD32B (FcγRIIb).[6,7] These effects are proposed to increase activation of innate and adaptive anti-ERBB2 immune responses, relative to trastuzumab.

Three FcγRs (CD16A, CD32A, and CD32B) expressed on immune effector cells regulate cellular activation by antibodies.[8] CD16A can trigger antibody-dependent cellular cytotoxicity (ADCC) by innate immune cells.[9,10] Two CD16A polymorphisms at amino acid 158 bind IgG1 with higher (valine [V]) or lower (phenylalanine [F]) affinity.[11] Clinical benefit of therapeutic antibodies, including trastuzumab,[11-15] appears greater for patients with the high-affinity VV genotype compared with the lower-affinity FV and FF genotypes (CD16A-158F carriers), although not all studies observed this effect.[16,17] Notably, most people (approximately 85%) are CD16A-158F allele carriers.[11,12] A key feature of margetuximab's engineered Fc domain is increased binding to all CD16A-158 V/F variants, relative to wild-type IgG1.

In a phase 1 study[18] of margetuximab monotherapy in 66 patients with pretreated ERBB2-positive carcinomas, 4 of 24 (17%) evaluable patients with ABC had a confirmed partial response. Three patients continued margetuximab monotherapy for 4 or more years.[19] Here we report initial results of a phase 3 randomized clinical trial of margetuximab vs trastuzumab, each combined with single-agent chemotherapy, in pretreated patients with ERBB2-positive ABC. In addition, we present an exploratory analysis of PFS and OS by FcγR genotype.

Key Points

Question Does margetuximab plus chemotherapy prolong progression-free survival and/or overall survival of patients with pretreated ERBB2-positive advanced breast cancer, relative to trastuzumab plus chemotherapy?

Findings In the SOPHIA phase 3 randomized clinical trial of 536 patients with pretreated ERBB2-positive advanced breast cancer, margetuximab plus chemotherapy generated a statistically significant 24% relative risk reduction in the hazard of progression vs trastuzumab plus chemotherapy. After the second planned interim analysis of 270 deaths, median OS was 21.6 months with margetuximab vs 19.8 months with trastuzumab, and final analysis of OS will be reported subsequently.

Meaning This trial demonstrates a head-to-head advantage of margetuximab (an Fc-engineered ERBB2-targeted antibody) compared with trastuzumab in a pretreated ERBB2-positive advanced breast cancer population.

Methods

Study Design and Participants

This international, randomized, open-label, phase 3 study (SOPHIA; MacroGenics study protocol No. CP-MGAH22-04) enrolled patients at 166 centers in 17 countries. Eligible patients were aged 18 years or older with confirmed ERBB2-positive ABC by local or optional central testing of the most recent biopsy, following 2013 American Society of Clinical Oncology testing recommendations.[20] Patients must have had progressive disease after 2 or more lines of prior ERBB2-targeted therapy, including pertuzumab, and 1 to 3 lines of nonhormonal metastatic BC therapy. Prior brain metastases were allowed if treated and stable. Trial conduct was in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. An independent ethics committee approved the protocol at each participating site. All patients provided written informed consent. The trial protocol and statistical analysis plan are available online (Supplement 1). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Randomization and Masking

Investigators chose 1 of 4 chemotherapies (capecitabine, eribulin, gemcitabine, or vinorelbine) for each eligible patient before 1:1 randomization by a permuted-blocks procedure. Stratification factors were metastatic sites (≤2, >2), lines of therapy for metastatic disease (≤2, >2), and chemotherapy choice. The trial was open label for patients and investigators but sponsor blinded with central blinded analysis (CBA) of PFS to prevent observer bias.

Procedures

Margetuximab was given intravenously at 15 mg/kg over 120 minutes on day 1 of each 21-day cycle. Trastuzumab was given intravenously at 6 mg/kg (over 30-90 minutes) on day 1 of each 21-day cycle after a loading dose of 8 mg/kg (over 90 minutes). Capecitabine was given orally at 1000 mg/m^2 twice daily for 14 days followed by 7 days off. Eribulin, gemcitabine, and vinorelbine were given intravenously before antibody infusion at 1.4 mg/m^2, 1000 mg/m^2, and 25 to 30 mg/m^2, respectively, on days 1 and 8 of each cycle. Margetuximab premedication was recommended, if not already given with chemotherapy: standard doses of acetaminophen or ibuprofen, diphenhydramine, ranitidine, and dexamethasone, or equivalents. Disease assessment was performed at baseline, every 6 weeks for the first 24 weeks of therapy, and then every 12 weeks until disease progression, adverse event (AE) necessitating discontinuation, consent withdrawal, or death. Safety was assessed at each visit, including AEs from study therapy initiation through the end-of-treatment visit, or 28 days after last administration of the study drug. Investigators assessed both event severity, using Common Terminology Criteria for Adverse Events, version 4.03, and causality. Left ventricular ejection fraction (LVEF) was monitored every 6 weeks

for 24 weeks and then every 12 weeks thereafter. Optional CD16A, CD32A, and CD32B genotyping was performed by polymerase chain reaction amplification of blood DNA, followed by DNA sequencing.

Outcomes

Primary end points were PFS by CBA, with the α entirely allocated to PFS, and OS. The PFS was defined as time from randomization to disease progression or death from any cause. Secondary end points included investigator-assessed PFS and CBA-assessed objective response rate (ORR). The PFS and ORR were assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1. Additional end points included safety, clinical benefit rate (CBR; ORR plus stable disease lasting at least 6 months), investigator-assessed ORR, response duration, antidrug antibodies, and exploratory evaluation of FcγR allelic variation on efficacy.

Statistical Analysis

For 90% power to detect median PFS improvement from 4 to 6 months (hazard ratio [HR], 0.67) at a 2-sided .05 significance level, 257 PFS events were needed. Primary PFS by CBA occurred after 257 PFS events or all patients were randomized, whichever occurred last. The OS was time from randomization to death from any cause and was to be assessed only if PFS was positive. For 80% power to detect a median OS improvement from 12 to 16 months (HR, 0.75) at a 2-sided .05 significance level, 385 OS events were needed. Three OS analyses were planned: first interim coincident with primary PFS analysis, second interim after 270 deaths, and final analysis after 385 events. All α was allocated to PFS, tested at a 2-sided .05 significance level. If PFS passed the test, then OS would be tested at the same significance level of 2-sided .05. The O'Brien-Fleming type Lan-DeMets α-spending function was applied for α allocation to each interim OS analysis.

The PFS and OS were assessed in the randomized, intention-to-treat population. Patients were censored at the last tumor assessment date for PFS and at the last time known to be alive for OS. The ORR and CBR were assessed in randomized patients with baseline measurable disease (response-evaluable population). For ORR analysis, if a patient's response was missing, the patient was classified as not available. Safety and antidrug antibodies were assessed in randomized patients after any study treatment (safety population).

Kaplan-Meier methods were used to estimate median PFS, OS, and 95% CIs for each treatment group. The stratified log-rank test was used to compare time-to-event end points between groups. A stratified Cox proportional hazards model, with treatment as the only covariate, was used to estimate PFS and OS HRs and 95% CIs.

Prespecified PFS and OS subgroup analyses included chemotherapy choice, metastatic sites, lines of prior metastatic therapy, prior ado-trastuzumab emtansine use, hormone receptor status, ERBB2 status, Eastern Cooperative Oncology Group performance status, region, age, and race, as well as *FCGR3A* (FcγRIIIa/CD16A), *FCGR2A* (FcγRIIa/CD32A), and *FCGR2B* (FcγRIIb/CD32B) genotype. The HRs and 95% CIs for PFS in each subgroup were assessed using an unstratified Cox proportional hazards model with treatment as the only covariate.

If the primary PFS and OS were each positive, then secondary PFS and ORR end points were to be tested using the Hochberg step-up procedure for multiplicity adjustment. Investigator-assessed PFS was analyzed using the same methods as the primary PFS end point. The ORR was compared between groups by the stratified Mantel-Haenszel test. Data were analyzed from February 2019 to October 2019. Analyses were performed using SAS, version 9.4 (SAS Institute).

Results

Study Population

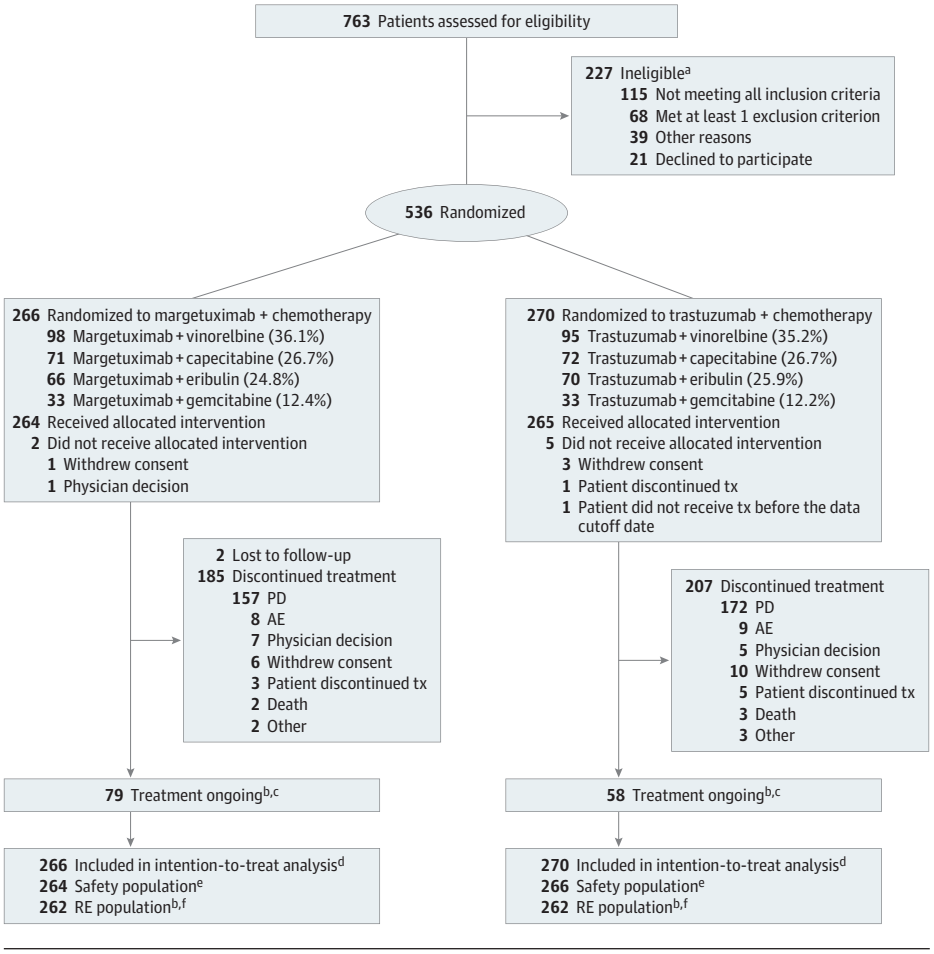
From July 2015 through October 2018, a total of 536 patients were enrolled at 166 centers in 17 countries and randomized to receive margetuximab plus chemotherapy (margetuximab group, n = 266) or trastuzumab plus chemotherapy (trastuzumab group, n = 270; **Figure 1**). The median age was 56 (27-86) years (55.0 [29-83] years for patients in the margetuximab group and 56.0 [27-86] years in the trastuzumab group); 266 (100%) women were in the margetuximab group, while 267 (98.9%) women were in the trastuzumab group. Investigator-selected chemotherapy choices were vinorelbine (n = 191, 35.6%), capecitabine (n = 143, 26.7%), eribulin (n = 136, 25.4%), and gemcitabine (n = 66, 12.3%). Patients received a median of 6 cycles of margetuximab vs 5 cycles of trastuzumab.

Baseline characteristics were balanced across groups (**Table 1**). All patients had received prior trastuzumab; all but 1 had received prior pertuzumab, and 489 (91.2%) had received prior ado-trastuzumab emtansine. One-third of patients in both groups received 3 or more prior therapies for metastatic BC (margetuximab, 92 of 266 [34.6%]; vs trastuzumab, 87 of 270 [32.2%]).

Efficacy

Primary PFS analysis was triggered by last randomization (October 10, 2018), after 265 PFS events. On that date, 79 (30%) vs 58 (22%) patients remained on margetuximab vs trastuzumab, respectively, including 13 (5%) and 5 (2%) remaining exclusively on margetuximab vs trastuzumab. Margetuximab plus chemotherapy prolonged centrally assessed PFS (HR, 0.76; 95% CI, 0.59-0.98; *P* = .03; median PFS, 5.8 [95% CI, 5.5-7.0] months vs 4.9 [95% CI, 4.2-5.6] months; **Figure 2**A), with a 24% PFS relative risk reduction over trastuzumab plus chemotherapy, meeting the primary end point of the study. The test of proportional hazards assumption indicated that the proportional hazards assumption was not violated. Investigator-assessed PFS based on 337 events was also greater with margetuximab than with trastuzumab (HR, 0.70; 95% CI, 0.56-0.87; *P* = .001; median, 5.6 vs 4.2 months; Figure 2B), with a 30% PFS relative risk reduction over trastuzumab. Coincident with the second interim OS analysis, updated investigator-assessed PFS based on 430 PFS events showed increased statistical significance in favor of margetuximab with a similar HR (HR, 0.71; 95% CI, 0.58-0.86; *P* < .001; median, 5.7 vs 4.4 months; Figure 2C).

Figure 1. Patient Flow/Patient Disposition



All randomized patients were included in the intention-to-treat population; randomized patients who received at least 1 dose of study treatment were included in the safety population; randomized patients with baseline measurable disease were included in the RE population.
AE indicates adverse event; PD, progressive disease; RE, response evaluable; tx, treatment.

[a] A patient may have more than 1 reason for screening failure.

[b] As of the October 10, 2018, cutoff.

[c] As of the April 10, 2019, cutoff, 37 patients remained on margetuximab therapy vs 20 on trastuzumab therapy.

[d] As of the October 10, 2018, cutoff and the September 10, 2019, cutoff.

[e] As of the April 10, 2019, cutoff.

[f] As of the September 10, 2019, cutoff, there were 266 margetuximab-treated patients and 270 trastuzumab-treated patients in the RE population.

The OS analysis after 270 deaths (70% of 385 final required events) occurred on September 10, 2019, after 131 (49.2%) and 139 (51.5%) OS events in the margetuximab and trastuzumab groups, respectively. Median OS was 21.6 months with margetuximab and 19.8 months with trastuzumab (HR, 0.89; 95% CI, 0.69-1.13; $P = .33$; **Figure 3**). The stopping threshold was not reached; final OS analysis will occur after 385 deaths (anticipated in 2021).

Among 524 response-evaluable patients, margetuximab recipients had higher blinded ORR (22% vs 16%; $P = .06$) and CBR (37% vs 25%; $P = .003$) than trastuzumab recipients (eTable 1 in Supplement 2). These rates were similar at the September 2019 cutoff when investigator-assessed ORR and CBR were 25% vs 14% ($P < .001$) and 48% vs 36% ($P = .003$), respectively (eTable 1 in Supplement 2). Median response duration was similar between treatment groups: 6.1 vs 6.0 months (October 10, 2018, CBA) and 6.9 vs 7.0 months (September 10, 2019, investigator assessed).

Prespecified exploratory subgroup analyses of primary PFS (October 10, 2018, cutoff) and second interim OS (September 10, 2019, cutoff) by CD16A genotype are shown in eFigures 1 and 2 in Supplement 2, respectively. Genotyping was available for 506 patients (94%). Study groups were in Hardy-Weinberg equilibrium for all 3 *FCGR* genotypes (eTable 2 in Supplement 2). Baseline characteristics of patients assigned to margetuximab vs trastuzumab by FcγR genotype are shown in eTable 3 in Supplement 2. The interim OS per treatment group by CD16A genotype is shown in eFigure 3 in Supplement 2. Efficacy outcomes by CD32A and CD32B are shown in eFigure 4 and eFigure 5 in Supplement 2.

Safety

As of April 10, 2019, which provided 6 additional months of safety follow-up after the primary PFS analysis, the safety population included 264 margetuximab and 266 trastuzumab recipients. Common AEs (≥20% of patients), regardless of causality, included fatigue, nausea, diarrhea, and neutropenia in both groups (**Table 2**), as well as vomiting (margetuximab group) and anemia (trastuzumab group). Grade 3 or greater AEs in at least 5% of patients included neutropenia and anemia in both groups, as well as fatigue in the margetuximab group and febrile neutropenia in the trastuzumab group. Discontinuations owing to AEs were similar (margetuximab, 8 of 266 [3.0%]; trastuzumab, 7 of 270 [2.6%]; eTable 4 in Supplement 2). Adverse events leading to death were reported in 5 patients (margetuximab, n = 3 [1.1%]; trastuzumab, n = 2 [0.8%]; eTable 4 in Supplement 2); none were considered treatment related.

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

Characteristic	No. (%)	
	Margetuximab plus chemotherapy (n = 266)	Trastuzumab plus chemotherapy (n = 270)
Female sex	266 (100)	267 (98.9)
Age, median (range), y	55.0 (29-83)	56.0 (27-86)
Race		
Asian	20 (7.5)	14 (5.2)
Black or African American	16 (6.0)	12 (4.4)
White	205 (77.1)	222 (82.2)
Other	25 (9.4)	22 (8.1)
Region		
Europe	152 (57.1)	138 (51.1)
North America	85 (32.0)	102 (37.8)
Other	29 (10.9)	30 (11.1)
ECOG performance status		
0	149 (56.0)	161 (59.6)
1	117 (44.0)	109 (40.4)
Disease extent at screening		
Metastatic	260 (97.7)	264 (97.8)
Locally advanced, unresectable	6 (2.3)	6 (2.2)
Measurable disease	262 (98.5)	262 (97.0)
No. of metastatic sites		
≤2	138 (51.9)	144 (53.3)
>2	128 (48.1)	126 (46.7)
Common sites of metastases (≥10% of patients) at study entry		
Bone	153 (57.5)	155 (57.4)
Lymph node	140 (52.6)	151 (55.9)
Lung	124 (46.6)	126 (46.7)
Liver	93 (35.0)	95 (35.2)
Breast	44 (16.5)	37 (13.7)
Skin	41 (15.4)	32 (11.9)
Brain	37 (13.9)	34 (12.6)
Combined ER and PR status		
ER positive, PR positive, or both	164 (61.7)	170 (63.0)
ER negative and PR negative	102 (38.4)	98 (36.3)
Settings of prior systemic/hormonal therapy		
Adjuvant and/or neoadjuvant	158 (59.4)	145 (53.7)
Metastatic only	108 (40.6)	125 (46.3)
No. of prior lines of therapy in the metastatic setting		
≤2	175 (65.8)	180 (66.7)
>2	91 (34.2)	90 (33.3)
Prior systemic therapy in early and metastatic settings		
Chemotherapy		
Taxane	252 (94.7)	249 (92.2)
Anthracycline	118 (44.4)	110 (40.7)
Platinum	34 (12.8)	40 (14.8)
ERBB2-targeted therapy		
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	6 (2.3)	6 (2.2)
Endocrine therapy	126 (47.4)	133 (49.3)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.

Adverse events of special interest included infusion-related reactions (IRRs) and left ventricular (LV) dysfunction. All-grade IRRs were more common with margetuximab than with trastuzumab (35 [13.3%] vs 9 [3.4%], respectively; Table 2). Most IRRs were grade 1 or 2, occurred on cycle 1, day 1, and resolved within 24 hours. Grade 3 IRRs on cycle 1, day 1 were reported in 4 (1.5%) margetuximab-treated patients. Of these 4 patients, 2 (0.8%) continued therapy for 5 or more cycles and 2 (0.8%) discontinued owing to IRRs (eTable 4 in Supplement 2). No trastuzumab recipients had grade 3 IRRs. Adverse events of LV dysfunction occurred in 7 patients (3%) in each treatment group (eTable 4 in Supplement 2). Grade 3 LV dysfunction AEs were observed in 3 margetuximab recipients (1.1%) and 1 trastuzumab recipient (0.4%). Monitoring of LVEF led to dose delay or discontinuation in 4 margetuximab-treated (1.5%) vs 6 trastuzumab-treated patients (2.3%). All LVEF reductions detected by monitoring were asymptomatic. Reductions in LVEF were reversible for all patients with complete follow-up.

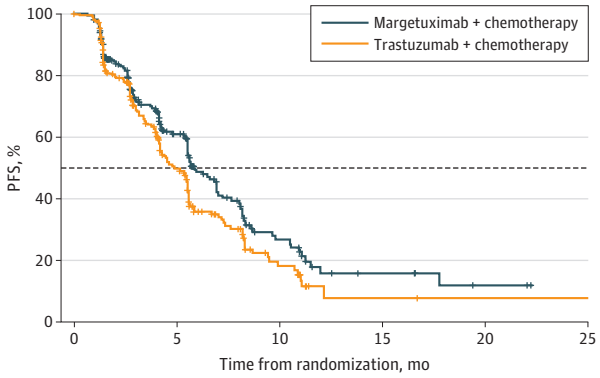
Discussion

The phase 3 SOPHIA trial compared margetuximab, a novel chimeric Fc-engineered anti-ERBB2 antibody, to trastuzumab, each with chemotherapy, in patients with pretreated ERBB2-positive ABC. This randomized clinical trial was positive for its PFS primary end point. Margetuximab plus chemotherapy led to an independently assessed PFS benefit vs trastuzumab plus chemotherapy, with a 24% relative risk reduction. Investigator-assessed PFS complemented primary blinded PFS with a 29% relative risk reduction. No conclusion can be drawn at this time about OS based on the 2 OS interim analyses conducted after 40% and 70% of target OS events (immature data); final analysis of the effect of margetuximab vs trastuzumab on survival will occur after 385 deaths (anticipated in 2021).

Margetuximab plus chemotherapy had acceptable safety, comparable with control trastuzumab plus chemotherapy. Although IRRs were increased with margetuximab, almost all occurred during the first infusion only, and the observed margetuximab IRR rate aligns with that in published literature on

Figure 2. Progression-Free Survival (PFS) in the Intention-to-Treat Population

A PFS by CBA, October 2018 cutoff



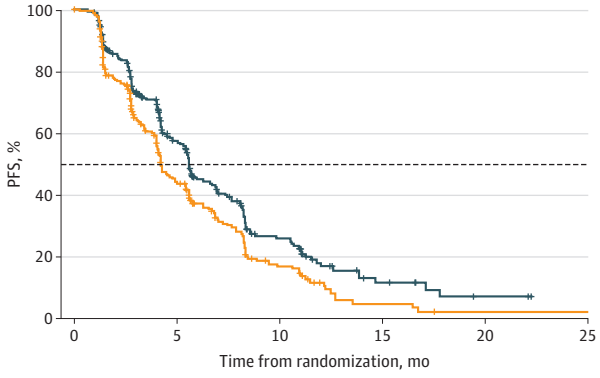
No. at risk

Margetuximab	266	174	94	45	21	8	6	4	2	0	
Trastuzumab	270	158	74	33	13	2	2	1	1	1	1

	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	130	135
Median PFS (95% CI)	5.8 mo (5.52-6.97)	4.9 mo (4.17-5.59)
3-mo PFS rate	72% (65%-77%)	70% (63%-76%)
6-mo PFS rate	48% (41%-56%)	36% (28%-44%)
9-mo PFS rate	30% (22%-38%)	22% (15%-30%)

HR by stratified Cox model, 0.76 (95% CI, 0.59-0.98)
Stratified log-rank *P* = .03
24% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

B PFS by investigator, October 2018 cutoff



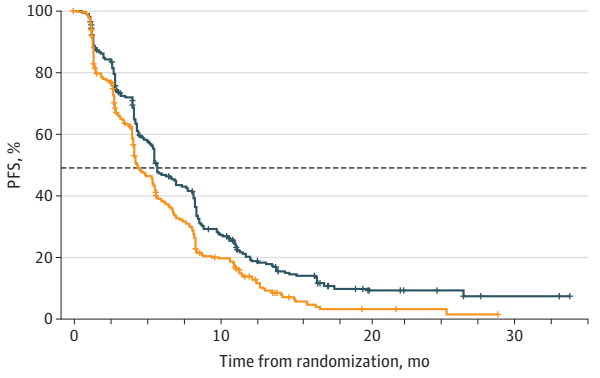
No. at risk

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	0

	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	160	177
Median PFS (95% CI)	5.6 mo (5.06-6.67)	4.2 mo (3.98-5.39)
3-mo PFS rate	73% (67%-78%)	65% (58%-71%)
6-mo PFS rate	45% (38%-52%)	37% (31%-44%)
9-mo PFS rate	27% (20%-34%)	19% (13%-25%)

HR by stratified Cox model, 0.70 (95% CI, 0.56-0.87)
Stratified log-rank *P* = .001
30% Risk reduction of disease progression[a]
Median follow-up, 2.8 mo

C PFS by investigator, September 2019 cutoff



No. at risk

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		

	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	208	222
Median PFS (95% CI)	5.7 mo (5.22-6.97)	4.4 mo (4.14-5.45)
3-mo PFS rate	74% (68%-79%)	67% (61%-72%)
6-mo PFS rate	47% (41%-53%)	38% (32%-45%)
9-mo PFS rate	29% (24%-35%)	20% (16%-26%)

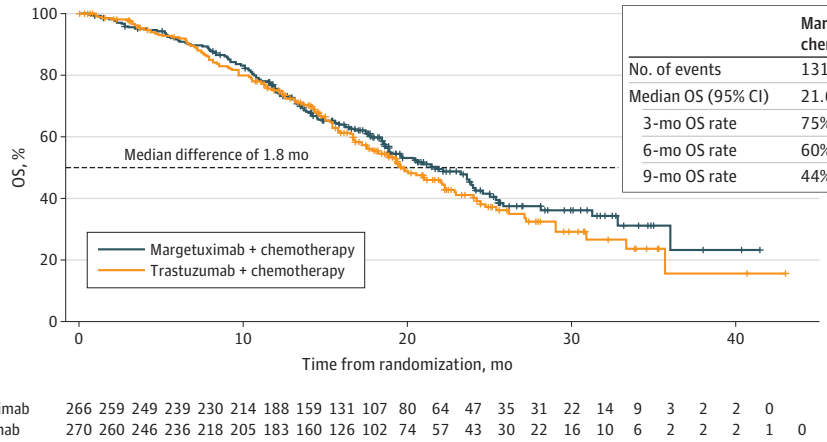
HR by stratified Cox model, 0.71 (95% CI, 0.58-0.86)
Stratified log-rank *P* <.001
29% Risk reduction of disease progression[b]

A, Kaplan-Meier estimates of PFS in the intention-to-treat population by central blinded analysis (CBA), based on the October 2018 cutoff. B, Kaplan-Meier estimates of PFS in the intention-to-treat population by investigator assessment, based on the October 2018 cutoff. C, Kaplan-Meier estimates of PFS in the intention-to-treat population by investigator assessment, based on the September 2019 cutoff. The dashed line indicates 50% (median PFS); plus signs, censored data. HR indicates hazard ratio.

[a] PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred.

[b] PFS analysis performed as of September 10, 2019, after 430 PFS events occurred.

Figure 3. Overall Survival (OS) in the Intention-to-Treat Population (September 2019 Cutoff)[a]



	Margetuximab + chemotherapy (n = 266)	Trastuzumab + chemotherapy (n = 270)
No. of events	131	139
Median OS (95% CI)	21.6 mo (18.86-24.05)	19.8 mo (17.54-22.28)
3-mo OS rate	75% (70%-80%)	75% (70%-80%)
6-mo OS rate	60% (53%-66%)	56% (49%-62%)
9-mo OS rate	44% (36%-51%)	40% (33%-48%)

HR by stratified Cox model, 0.89 (95% CI, 0.69-1.13)
Stratified log-rank *P* = .33
Median follow-up, 15.6 mo

No. at risk

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

Kaplan-Meier estimates of OS in the intention-to-treat population, based on the September 2019 cutoff. The dashed line indicates 50% (median OS); plus signs, censored data. HR indicates hazard ratio.

[a] OS analysis performed as of September 10, 2019, data cutoff, after 270 of 385 (70%) events needed for final OS analysis had occurred.

trastuzumab first exposure (16%).[21] In a nonrandomized infusion safety substudy, margetuximab was administered over 30 minutes from cycle 2 onward and appeared well tolerated with no increase in IRR risk, supporting 30-minute margetuximab infusions after cycle 1.[22] There was no increase in cardiac toxic effects with margetuximab compared with trastuzumab.

The SOPHIA study also tested the hypothesis that altering Fc-FcγR interactions can drive clinical benefit. Trastuzumab triggers ADCC[23] via activation of FcγRIIIa (CD16A).[8] Associations between efficacy and CD16A polymorphism in trastuzumab-treated patients with early and advanced BC suggest lower immune activation in CD16A-158F allele carriers compared with VV homozygotes.[10-12,14,24] Diminished clinical response to trastuzumab for these CD16A-158F carriers suggests these patients may benefit from an antibody with enhanced Fc-dependent immune activation.[11,12,24] Margetuximab Fc engineering increases affinity for both CD16A allotypes, enhances ADCC potency over trastuzumab with effector cells of all CD16A genotypes (FF, FV, VV), albeit proportionally more for CD16A-158F carriers under certain conditions, and boosts activity against ERBB2-positive BC xenografts in mice transgenic for human CD16A-158F.[6,25] Exploratory PFS analysis by CD16A genotype suggested that presence of a CD16A-158F allele may predict margetuximab benefit over trastuzumab. Early OS results showed a similar pattern. Conversely, there was no margetuximab benefit in the smaller CD16A-158VV group in this study of heavily pretreated patients. There is no clear biological explanation for the observation that margetuximab provided no clinical benefit in CD16A-158VV homozygotes compared with trastuzumab, although there was an imbalance in poor prognostic features between the 2 groups.

Increasing evidence implicates adaptive immunity in the clinical activity of anti-ERBB2 monoclonal antibodies.[26] ERBB2-specific T-cell and antibody responses were observed in 50% to 78% and 42% to 69%, respectively, of trastuzumab-treated patients with ERBB2-positive BC.[10,24,26-30] Correspondingly, increases in ERBB2-specific T-cell and antibody responses were observed in 98% and 94%, respectively, of pretreated phase 1 study patients receiving margetuximab monotherapy.[31]

This trial demonstrates a small but statistically significant PFS benefit of margetuximab plus chemotherapy over trastuzumab plus chemotherapy in patients with ERBB2-positive ABC who progressed after treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine.[1,2,4,32] Alternatives for this patient population include neratinib, tucatinib, and trastuzumab deruxtecan, which have emerged as active regimens, albeit with different levels of effectiveness, and all with notable toxic effects. Margetuximab may have a role for patients in this setting who are unable, or unwilling, to tolerate toxic effects of these novel therapies.

Limitations

Limitations of this trial include that the primary end point did not allocate α to the CD16A analysis and that patients with active brain metastases were not included. An ongoing neoadjuvant investigator-sponsored trial is comparing margetuximab vs trastuzumab in patients with the low-affinity CD16A genotype (the MARGetuximab Or Trastuzumab trial, known as MARGOT; NCT04425018). Immune-mediated therapies, such as margetuximab, may be more effective in the earlier disease setting where the immune system is relatively intact.

Conclusions

The chimeric antibody margetuximab shares ERBB2 specificity with trastuzumab but incorporates an engineered Fc region to optimize immune activation. This phase 3 randomized clinical trial demonstrates improvement in PFS of margetuximab in combination with chemotherapy vs trastuzumab plus chemotherapy in patients with pretreated ERBB2-positive ABC, which remains typically incurable.

Table 2. Adverse Events in the Safety Population, Regardless of Causality (April 2019 Cutoff)

	No. (%)			
	Margetuximab plus chemotherapy (n = 264)		Trastuzumab plus chemotherapy (n = 266)	
Adverse event	All grade[a]	Grade ≥3[b]	All grade[a]	Grade ≥3[b]
Nonhematologic				
Fatigue[c]	111 (42.0)	13 (4.9)	94 (35.3)	8 (3.0)
Nausea	86 (32.6)	3 (1.1)	86 (32.3)	1 (0.4)
Diarrhea	66 (25.0)	6 (2.3)	67 (25.2)	6 (2.3)
Constipation	51 (19.3)	2 (0.8)	44 (16.5)	2 (0.8)
Vomiting[d]	54 (20.5)	2 (0.8)	38 (14.3)	4 (1.5)
Pyrexia	50 (18.9)	1 (0.4)	37 (13.9)	1 (0.4)
Headache	47 (17.8)	0	42 (15.8)	0
Alopecia	47 (17.8)	0	39 (14.7)	0
Asthenia	47 (17.8)	6 (2.3)	33 (12.4)	5 (1.9)
Decreased appetite	38 (14.4)	1 (0.4)	36 (13.5)	1 (0.4)
Infusion-related reaction[e,f]	35 (13.3)	4 (1.5)	9 (3.4)	0
Cough	37 (14.0)	1 (0.4)	31 (11.7)	0
PPE syndrome	33 (12.5)	1 (0.4)	41 (15.4)	8 (3.0)
Dyspnea	34 (12.9)	3 (1.1)	28 (10.5)	6 (2.3)
Pain in extremity	30 (11.4)	2 (0.8)	23 (8.6)	0
Arthralgia	27 (10.2)	0	23 (8.6)	1 (0.4)
Stomatitis	27 (10.2)	2 (0.8)	21 (7.9)	0
Peripheral neuropathy	26 (9.8)	1 (0.4)	28 (10.5)	3 (1.1)
Urinary tract infection	26 (9.8)	2 (0.8)	28 (10.5)	3 (1.1)
Mucosal inflammation[g]	26 (9.8)	0	8 (3.0)	1 (0.4)
Abdominal pain	25 (9.5)	4 (1.5)	37 (13.9)	3 (1.1)
Dizziness	25 (9.5)	1 (0.4)	16 (6.0)	0
Hypokalemia	16 (6.1)	4 (1.5)	19 (7.1)	4 (1.5)
Hypertension	14 (5.3)	5 (1.9)	6 (2.3)	2 (0.8)
Pneumonia	9 (3.4)	5 (1.9)	9 (3.4)	7 (2.6)
Pleural effusion	8 (3.0)	2 (0.8)	14 (5.3)	4 (1.5)
Syncope	4 (1.5)	4 (1.5)	0	0
Hematologic				
Neutropenia[h]	75 (28.4)	52 (19.7)	55 (20.7)	33 (12.4)
Anemia[i]	49 (18.6)	13 (4.9)	62 (23.3)	17 (6.4)
Neutrophil count decreased	33 (12.5)	23 (8.7)	39 (14.7)	28 (10.5)
ALT increased	24 (9.1)	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	19 (7.2)	5 (1.9)	27 (10.2)	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: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; WBC, white blood cell.

[a] All-grade adverse events with ≥10% incidence in either treatment group.

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

[c] Exact test *P* value for nonprespecified comparison of all-grade fatigue between treatment groups (42.0% vs 35.3%): *P* = .13. Exact test *P* value for nonprespecified comparison of grade ≥3 fatigue between treatment groups (4.9% vs 3.0%): *P* = .28.

[d] Exact test *P* value for nonprespecified comparison of all-grade vomiting between treatment groups (20.5% vs 14.3%): *P* = .07.

[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 (13.3% vs 3.4%): *P* < .001.

[g] Exact test *P* value for nonprespecified comparison of all-grade mucosal inflammation between treatment groups (9.8% vs 3.0%): *P* = .001.

[h] Exact test *P* value for nonprespecified comparison of all-grade neutropenia between treatment groups (28.4% vs 20.7%): *P* = .04. Exact test *P* value for nonprespecified comparison of grade ≥3 neutropenia between treatment groups (19.7% vs 12.4%): *P* = .02.

[i] Exact test *P* value for nonprespecified comparison of all grade anemia between treatment groups (18.6% vs 23.3%): *P* = .20.

[j] Exact test *P* value for nonprespecified comparison of grade ≥3 febrile neutropenia between treatment groups (3.0% vs 4.9%): *P* = .37.

ARTICLE INFORMATION

Accepted for Publication: November 18, 2020.

Published Online: January 22, 2021. doi:10.1001/jamaoncol.2020.7932

Author Affiliations: University of California San Francisco Helen Diller Family Comprehensive Cancer Center (Rugo); Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea (Im); Champalimaud Clinical Center/Champalimaud Foundation, Breast Unit, Lisbon, Portugal (Cardoso); IOB Institute of Oncology, Quironsalud Group, Madrid and Barcelona, Spain (Cortés); Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain (Cortés); European Institute of Oncology, IRCCS, Division of Early Drug Development, University of Milano, Milan, Italy (Curigliano); Department of Medicine and Surgery, University of Parma, Medical Oncology and Breast Unit, University Hospital of Parma, Parma, Italy (Musolino); Stanford Comprehensive Cancer Institute, Stanford University School of Medicine, Stanford, California (Pegram); Florida Cancer Specialists & Research Institute, New Port Richey (Wright); Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology Service, Barcelona, Spain (Saura, Escrivá-de-Romaní); Department of Breast and Thoracic Oncology, Istituto Nazionale Tumori "Fondazione Pascale", Naples, Italy (De Laurentiis); Centre François Baclesse, Institut Normand du Sein, Caen, France (Levy); Division of Hematology/Oncology, University of New Mexico Comprehensive Cancer Center, Albuquerque (Brown-Glaberman); Centre Antoine Lacassagne, Department of Medical Oncology, University Côte d'Azur, Nice, France (Ferrero); Maastricht University Medical Center, Division of Medical Oncology, Department of Internal Medicine, GROW-School of Oncology and Developmental Biology, Maastricht, the Netherlands (de Boer); Department of Oncology, Asan Medical Center, Seoul, Korea (Kim); Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic (Petráková); Sarah Cannon Research Institute, Tennessee Oncology PLLC, Nashville (Yardley); RS McLaughlin Durham Regional Cancer Centre, Lakeridge Health, Oshawa, Ontario, Canada (Freedman); Department of Oncology, Vejle Hospital, Vejle, Denmark (Jakobsen); Chaim Sheba Medical Center, Breast Oncology Institute, Ramat Gan, Israel (Kaufman); Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel (Yerushalmi); Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Department of Gynecology and Obstetrics, Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Germany (Fasching); MacroGenics, Inc, Rockville, Maryland (Nordstrom, Bonvini, Koenig, Edlich, Hong, Rock); Division of Hematology/Oncology, Northwestern University, Chicago, Illinois (Gradishar).

Author Contributions: Drs Rugo and Rock had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Rugo, Im, Cardoso, Cortés, Curigliano, Pegram, Jakobsen, Koenig.
Acquisition, analysis, or interpretation of data: Rugo, Im, Cardoso, Curigliano, Musolino, Pegram, Wright, Saura, Escrivá-de-Romaní, De Laurentiis, Levy, Brown-Glaberman, Ferrero, de Boer, Kim, Petráková, Yardley, Freedman, Kaufman, Yerushalmi, Fasching, Nordstrom, Bonvini, Koenig, Edlich, Hong, Rock, Gradishar.
Drafting of the manuscript: Rugo, Curigliano, Musolino, Pegram, Yerushalmi, Nordstrom, Bonvini, Rock, Gradishar.
Critical revision of the manuscript for important intellectual content: Rugo, Im, Cardoso, Cortés, Curigliano, Musolino, Pegram, Wright, Saura, Escrivá-de-Romaní, De Laurentiis, Levy, Brown-Glaberman, Ferrero, de Boer, Kim, Petráková, Yardley, Freedman, Jakobsen, Kaufman, Fasching, Nordstrom, Bonvini, Koenig, Edlich, Hong, Rock, Gradishar.
Statistical analysis: Curigliano, Saura, Hong.
Obtained funding: Koenig.
Administrative, technical, or material support: Rugo, Im, Curigliano, Musolino, Petráková, Yardley, Kaufman, Fasching, Edlich, Rock, Gradishar.
Supervision: Curigliano, Musolino, Wright, Saura, Freedman, Koenig, Rock.

Conflict of Interest Disclosures: Dr Rugo reported receiving grants from MacroGenics during the conduct of the study; and grants from Roche, Pfizer, Novartis, Lilly, Merck, Seattle Genetics, Odonate Therapeutics, Eisai, Sermonix Pharmaceuticals, Immunomedics, and Daiichi Sankyo and personal fees from Puma and Samsung outside the submitted work. Dr Im reported receiving grants from Daewoong Pharmaceutical; grants and personal fees from AstraZeneca, Pfizer, and Roche; and personal fees from Amgen, Eisai, Hanmi Pharmaceutical, Novartis, Lilly, and Merck Sharp & Dohme outside the submitted work. Dr Cardoso reported receiving personal fees from MacroGenics during the conduct of the study; and personal fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, MacroGenics, Medscape, Merck Sharp & Dohme, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seattle Genetics, and Teva outside the submitted work. Dr Cortés reported receiving personal fees from Roche, Celgene, AstraZeneca, Cellestia, Biothera Pharmaceuticals, Merus, Seattle Genetics, Daiichi Sankyo, Erytech Pharma, Athenex, Polyphor, Lilly, Servier, Merck Sharp & Dohme, GlaxoSmithKline, Leuko, Bioasis Technologies, Clovis Oncology, Boehringer Ingelheim, Novartis, Eisai, Pfizer, and Samsung Bioepis; honoraria from Samsung Bioepis, Pfizer, Eisai, Novartis, Roche, Celgene, Daiichi Sankyo, Lilly, Merck Sharp & Dohme; serving on advisory boards for Boehringer Ingelheim, Clovis Oncology, Bioasis, Leuko, GlaxoSmithKline, Merck Sharp & Dohme, Servier, Lilly, Polyphor, Athenex, Erytech, Daiichi Sankyo, Seattle Genetics, Merus, Biothera, Cellestia, AstraZeneca, Celgene, and Roche; and owning stock from MedSIR outside the submitted work; and travel, accommodation, and expenses from Roche, Novartis, Eisai, Pfizer, and Daiichi Sankyo. Dr Curigliano reported receiving travel grants from Roche; serving on advisory boards for Pfizer, Seattle Genetics, Novartis, AstraZeneca, Lilly, Merck Sharp & Dohme, Daiichi Sankyo, Genomic Health, and Ellipsis; and serving as a steering committee member for Bristol Myers Squibb outside the submitted work. Dr Musolino reported receiving personal fees from MacroGenics during the conduct of the study; and grants and personal fees from Roche and Eisai and personal fees from Novartis and Lilly outside the submitted work. Dr Pegram reported receiving personal fees from MacroGenics and Roche during the conduct of the study. Dr Wright reported receiving payment to Sarah Cannon Research Institute for conduct of clinical trial from MacroGenics during the conduct of the study; and payment to Sarah Cannon Research Institute for conduct of clinical trial from AbbVie, Incyte, Genentech, Novartis, Lilly, Janssen, Astellas, Celgene, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, G1 Therapeutics, Medivation, Merrimack, Pfizer, Tesaro, and Odonate Therapeutics outside the submitted work. Dr Saura reported receiving personal fees from AstraZeneca, Celgene, Daiichi Sankyo, Eisai, F. Hoffmann-La Roche Ltd, Genomic Health, Merck, Sharp and Dohme España SA, Novartis, Odonate Therapeutics, Pfizer, Philips HealthWork, Pierre Fabre, prIME Oncology, Puma, Synthon, and Sanofi Aventis outside the submitted work. Dr Escrivá-de-Romaní reported receiving grants from MacroGenics during the conduct of the study; and grants from Synthon and Zymeworks; grants, personal fees, and nonfinancial support from Roche; personal fees and nonfinancial support from Pierre Fabre; personal fees from Eisai, Kyowa Kirin, and Esteve; and nonfinancial support from Daiichi Sankyo outside the submitted work. Dr De Laurentiis reported receiving grants from MacroGenics during the conduct of the study; and grants from Daiichi Sankyo; grants and personal fees from Roche, Novartis, Pfizer, Eli Lilly, Pierre Fabre, and AstraZeneca; personal fees from Celgene, Eisai, Genomic Health, and Amgen outside the submitted work. Dr Brown-Glaberman reported receiving personal fees from Novartis, Eisai, Biotheranostics, and Seattle Genetics outside the submitted work. Dr de Boer reported receiving grants from Parexel during the conduct of the study; and grants from Novartis, Pfizer, and Eli Lilly and grants and personal fees from Roche outside the submitted work. Dr Kim reported participation as a consultant in advisory boards for Novartis, AstraZeneca, Lilly, Enzychem Lifesciences, Dae Hwa Pharmaceutical Co Ltd, ISU Abxis, and Daiichi Sankyo and receiving research funding (paid to institution) from Novartis, Sanofi-Aventis, and DongKook Pharmaceutical Co Ltd outside the submitted work. Dr Petráková reported receiving personal fees from Novartis, Roche, Merck Sharp & Dohme, and Pfizer outside the submitted work. Dr Yardley reported a consultant/advisory role (paid to institution) for Bristol Myers Squibb, Genentech/Roche, Eisai, Biotheranostics, Daiichi Sankyo/Lilly, Celgene, Novartis, NanoString Technology, and MacroGenics; research funding (paid to institution) from Daiichi Sankyo, Clovis Oncology, AstraZeneca, Genentech/Roche, InventisBio, Syndax, Lilly, MedImmune, Pfizer, Eisai, Novartis, Medivation, Tesaro, Immunomedics, AbbVie, Merck, and Oncothyreon; and participation in speakers bureaus and travel/accommodations/expenses for Novartis and Genentech/Roche outside the submitted work. Dr Jakobsen reported receiving financial support from Cascadian Therapeutics during the conduct of

the study; and grants from Cascadian Therapeutics and grants and personal fees from Roche, Novartis, Lilly, and Pfizer outside the submitted work. Dr Kaufman reported receiving personal fees from Pfizer and AstraZeneca outside the submitted work. Dr Fasching reported receiving personal fees from MacroGenics during the conduct of the study; and grants from Cepheid and personal fees from Novartis, Pfizer, Daiichi Sankyo, AstraZeneca, Eisai, Merck Sharp & Dohme, Lilly, Pierre Fabre, and Seattle Genetics outside the submitted work. Dr Bonvini reported receiving salary, stocks, and stock options from MacroGenics as compensation as a condition of employment. Dr Koenig is an employee of MacroGenics and reported holding a patent to US20180298100 pending and a patent to US20160257761 pending. Drs Nordstrom, Hong, and Rock and Mr Edlich are or were employees of MacroGenics. No other disclosures were reported.

Funding/Support: This study was supported by MacroGenics, Inc.

Role of the Funder/Sponsor: 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. MacroGenics, Inc, paid for medical writing support to generate the manuscript. All authors reviewed and approved manuscript submission.

Group Information for the SOPHIA Study: *Austria* – Daniel Egle, MD, Universitätsklinik Innsbruck, Innsbruck, Alois Lang, MD, and Holger Rumpold, MD, Landeskrankenhaus Rankweil, Vorarlberg; *Belgium* – Sevilay Altintas, MD, PhD, UZ Antwerpen – Oncologie, Edegem, Annelore Barbeaux, MD, CHR Verviers East Belgium, Verviers, Jean-Francois Baurain, MD, PhD, Cliniques Universitaires Saint-Luc – Oncology, Bruxelles, Marleen Borms, MD, AZ Groeninge – Campus Loofstraat, Kortrijk, Nele Claes, MD, AZ Sint-Jan Brugge – Oostende AV – Campus Sint-Jan, Brugge, Caterina Confente, MD, INDC Entité Jolimontoise – CH de Jolimont-Lobbes, Haine-Saint-Paul, Ines Deleu, MD, AZ Nikolaas – Campus Sint-Niklaas Moerland, Sint-Niklaas, Luc Dirix, MD, PhD, GZA Ziekenhuizen – Campus Sint-Augustinus, Wilrijk, Christel Fontaine, MD, UZ Brussel – Campus Jette, Bruxelles, Marie-Pascale Graas, MD, CHC MontLégia, Liège, Stephanie Henry, MD, Donatienne Taylor, MD, and Peter Vuylsteke, MD, CHU UCL Namur – Site Sainte-Elisabeth, Namur, Jeroen Mebis, MD, PhD, Jessa Ziekenhuis – Campus Virga Jesse, Hasselt, Renaud Poncin, MD, Clinique Saint Pierre Ottignies, Ottignies, Isabelle Spoormans, MD, AZ Damiaan, Oostende; *Canada* – Orit Freedman, MD, MSc, RS McLaughlin Durham Regional Cancer Centre, Lakeridge Health, Oshawa, Skander Ghedira, MD, Dr Leon Richard Oncology Centre, Moncton, Ravi Ramjeesingh, MD, PhD, The Atlantic Clinical Cancer Research Unit, Halifax; *Czech Republic* – Zdenek Kral, MD, CSc, Fakultni nemocnice Brno, Brno, Bohuslav Melichar, MD, PhD, Fakultni nemocnice Olomouc, Olomouc, Katarína Petráková, MD, PhD, Masaryk Memorial Cancer Institute, Brno, Jana Prausova, MD, PhD, MBA, Fakultni nemocnice v Motole, Praha 5; *Denmark* – Vesna Glavicic, MD, Næstved Sygehus, Næstved, Erik H Jakobsen, MD, Vejle Hospital, Vejle, Julia Kenholm, MD, Regionshospitalet Herning, Herning Centralsygehus, Herning, Sven Langkjer, MD, PhD, Aarhus Universitets Hospital, Aarhus C; *Finland* – Johanna Mattson, MD, PhD, Helsinki University Central Hospital – Meilahden Sair, Helsinki, Minna Tanner, MD, PhD, MSc, Tampere University Hospital, Tampere; *France* – Thomas Bachelot, MD, PhD, Centre Leon Berard, Lyon Cedex 08, Etienne Brain, MD, PhD, Institut Curie – Hôpital René Huguenin, Saint-Cloud, Mario Campone, MD, PhD, Centre de Lutte Contre le Cancer – Institut de Cancer, Saint Herblain, Bruno Coudert, MD, and Audrey Hennequin, MD, Centre Georges Francois Leclerc, Dijon, Veronique Dieras, MD, MSc, Centre De Lutte Contre Le Cancer – Institut Curie, Paris, Jean-Marc Ferrero, MD, University Côte d'Azur, Centre Antoine Lacassagne, Nice, Cyril Foa, MD, and Robert Herve, MD, Hôpital Privé Clairval, Marseille, Christelle Levy, MD, Centre François Baclesse, Institut Normand du Sein, Caen Cedex 5, Marie-Ange Mouret-Reynier, MD, Centre Jean Perrin, Clermont-Ferrand Cedex 1, Francesco Ricci, MD, PhD, Centre De Lutte Contre Le Cancer – Institut Curie, Paris; *Germany* – Bahriye Aktas, MD, PhD, and Oliver Hoffmann, MD, PhD, Universitaetsklinikum Essen – Klinik fuer Frauenheilkunde, Essen, Nikola Bangemann, MD, Campus Charité Mitte, Berlin, Malgorzata J Banys-Paluchowski, MD, and Gerhard Gebauer, MD, MBA, Katholisches Marienkrankenhaus gGmbH – Frauenklinik, Hamburg, Wolfgang Eiermann, MD, Interdisziplinäres Onkologisches Zentrum München, München, Peter A. Fasching, MD, Erlangen University Hospital, Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University of Erlangen-Nuremberg, Erlangen, Aristoteles Giagounidis, MD, Marien Hospital Düsseldorf, Düsseldorf, Eva-Maria Grischke, MD, Universitaetsklinikum Tuebingen, Tuebingen, John Hackmann, MD, Marien Hospital, Witten, Meinolf Karthaus, MD, Städtisches Krankenhaus München – Neuperlach, München, Anita Prechtl, MD, Praxis für Frauenheilkunde, München, Andreas Schneeweiss, MD, University Hospital Heidelberg, Heidelberg, Pauline Wimberger, MD, Medizinische Fakultät Carl Gustav Carus, Dresden; *Israel* – Noa Efrat, MD, Kaplan Medical Center, Rehovot, David Geffen, MD, and Margarita Tokar, MD, Soroka University Medical Center, Beer Sheva, Goldberg Hadassah, MD, Galilee Medical Center, Nahariya, Natalya Karminsky, MD, PhD, The Edith Wolfson Medical Center, Holon, Bella Kaufman, MD, Chaim Sheba Medical Center, Breast Oncology Institute, Ramat Gan, Iryna Kuchuk, MD, Meir Medical Center, Kfar Saba, Michelle Leviov, MD, Clalit Health Services – Lin Medical Center, Haifa, Larisa Ryvo, MD, and Ido Wolf, MD, Tel Aviv Sourasky Medical Center, Tel Aviv, Beatrice Uziely, MD, Hadassah Medical Center, Jerusalem, Rinat Yerushalmi, MD, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petah Tikva; *Italy* – Antonio Ardizzoia, MD, Presidio Ospedaliero "Alessandro Manzoni", Lecco, Rossana Berardi, MD, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, GM Lancisi, G Salesi, Ancona, Antonio Bernardo, MD, and Lorenzo Pavesi, MD, Istituti Clinici Scientifici Maugeri, Pavia, Laura Biganzoli, MD, Nuovo Ospedale di Prato Santo Stefano, Prato, Roberto Bordonaro, MD, Presidio Ospedaliero Garibaldi-Nesima, Catania, Marco Colleoni, MD, European Institute of Oncology, Milan, Giuseppe Curigliano, MD, PhD, European Institute of Oncology, University of Milano, Milan, Mauro D'Amico, MD, Ente Ospedaliero Ospedali Galliera, Genova, Bruno Daniele, MD, and Vincenza Tinessa, MD, Azienda Ospedaliera San Pio, Presidio Gaetano Rummo, Benevento, Michelino De Laurentiis, MD, PhD, Istituto Nazionale Tumori "Fondazione Pascale", Naples, Alfredo Falcone, MD, Azienda Ospedaliero-Universitaria Pisana Santa Chiara, Pisa, Gabriella Farina, MD, and Nicla Maria La Verde, MD, Azienda Ospedaliera Fatebenefratelli e Oftalmico, Milano, Guido Francini, MD, Azienda Ospedaliero Universitaria Senese, Siena, Antonio Frassoldati, MD, Azienda Ospedaliero-Universitaria "Arcispedale Sant'Anna", Ferrara, Daniele Generali, MD, Presidio Ospedaliero di Cremona, Cremona, Donatella Grasso, MD, and Paolo Pedrazoli, MD, Fondazione IRCCS Policlinico San Matteo, Pavia, Vito Lorusso, MD, Istituto Oncologico Giovanni Paolo II, Bari, Gabriele Luppi, MD, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Paolo Marchetti, MD, Azienda Ospedaliero-Universitaria Sant'Andrea, Roma, Filippo Montemurro, MD, Istituto di Candiolo, Candiolo, Antonino Musolino, MD, PhD, MSc, University of Parma – University Hospital of Parma, Parma, Andrea Rocca, MD, Istituto Scientifico Romagnolo per lo Studio e la Cura die Tumori, Meldola, Elena Rota Caremoli, MD, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Enzo Ruggeri, MD, Ospedale Belcolle, Viterbo, Armando Santoro, MD, Istituto Clinico Humanitas, Rozzano, Giuseppe Tonini, MD, Policlinico Universitario Campus Bio-Medico, Roma; *Korea* – Seock-Ah Im, MD, PhD, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Young-Hyuck Im, MD, PhD, Samsung Medical Center, Seoul, Sung-Bae Kim, MD, PhD, Asan Medical Center, Seoul, Joo Hyuk Sohn, MD, PhD, Severance Hospital, Yonsei University Health System, Seoul; *the Netherlands* – Maaike de Boer, MD, PhD, Maastricht University Medical Center, GROW-School of Oncology and Developmental Biology, Maastricht, Franciscus Erdkamp, MD, Stichting Zuyderland Medisch Centrum, Sittard-Geleen, Daniel Houtsma, MD, and Johanna Portielje, MD, PhD, Haga Ziekenhuis, Leiden, Robbert van Alphen, MD, Elisabeth-Tweesteden Ziekenhuis, Tilburg; *Poland* – Barbara Bauer-Kosinska, MD, Mazowiecki Szpital Onkologiczny, Wieliszew, Dorota Garncarek-Lange, MD, PhD, Wojewódzki Szpital Specjalistyczny we Wrocławiu, Wroclaw, Bartosz Itrych, MD, and Tomasz Sarosiek, MD, PhD, Magodent Sp. z o.o. Szpital Elblaska, Warszawa, Tomasz Jankowski, MD, PhD, Centrum Onkologii Ziemi Lubelskiej im. sw. Jana z Dukli, Lublin, Zbigniew Nowecki, MD, PhD, Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy, Warszawa, Tadeusz Pieńkowski, MD, PhD, Radomskie Centrum Onkologii, Warszawa, Piotr Wysocki, MD, PhD, Spzoz Szpital Uniwersytecki w Krakowie, Uniwersyteckie Lecznictwo Szpitalne, Krakow; *Portugal* – Miguel Abreu, MD, Instituto Português Oncologia Francisco Gentil do Porto, Porto, Fatima Cardoso, MD, and Maria Rita Dionisio, MD, Champalimaud Clinical Center – Champalimaud Foundation, Lisbon, Luis Costa, MD, PhD, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon; *Puerto Rico* – Mirelis Acosta, MD, Fundacion de Investigacion de Diego, San Juan; *Spain* – José Alés Martínez, MD, PhD, Hospital Nuestra Señora de Sonsoles, Avila, Begoña Bermejo de las Heras, MD, PhD, Hospital Clínico Universitario de Valencia, Valencia, Beatriz Cirauqui, MD, Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Badalona, Javier Cortes Castan, MD, PhD, IOB Institute of Oncology, Quironsalud Group, Madrid & Barcelona – Vall

d'Hebron Institute of Oncology, Barcelona, Joan Dorca Ribugent, MD, ICO-Hospital Universitari de Girona Dr Josep Trueta, Girona, María Fernández Abad, MD, PhD, Hospital Universitario Ramón y Cajal, Madrid, Laura García Estévez, MD, and Elena Sevillano Fernández, MD, Hospital Madrid Norte Sanchinarro, Madrid, José García Sáenz, MD, Hospital Clínico San Carlos, Madrid, Joaquin Gavilá Gregori, MD, Fundación Instituto Valenciano de Oncología, Valencia, Antonio Gonzalez Martin, MD, PhD, and Raúl Márquez Vázquez, MD, MD Anderson Center Madrid, Madrid, Santiago González Santiago, MD, Hospital San Pedro de Alcántara, Cáceres, José Juan Illarramendi Manas, MD, Hospital de Navarra, Pamplona, Mireia Melé Olivé, MD, Hospital Universitari Sant Joan de Reus, Reus, Serafín Morales Murillo, MD, Hospital Universitari Arnau de Vilanova, Lleida, Laura Palomar Abad, MD, and Ana Santaballa Bertrán, MD, Hospital Universitari i Politècnic La Fe, Valencia, José Pérez García, MD, PhD, Hospital Quirón Barcelona, Barcelona, José Ponce Lorenzo, MD, Hospital General Universitario de Alicante, Alicante, Manuel Ruiz Borrego, MD, Hospital Universitario Virgen del Rocio, Sevilla, Cristina Saura Manich, MD, PhD, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Miguel Angel Segui Palmer, MD, PhD, Hospital Universitari Parc Tauli, Sabadell, Sonia Servitja Tormo, MD, PhD, Hospital del Mar, Barcelona; *United Kingdom* – Pavel Bezecny, MD, DVM, Blackpool Victoria Hospital, Blackpool, Steve Chan, MBBS, DM, Nottingham University Hospital, Nottingham, Amandeep Dhadda, MBChB, MSc, Castle Hill Hospital, Hull, Janine Graham, MBChB, South Tees NHS Foundation Trust, Middlesbrough, Catherine Harper-Wynne, MBBS, MD, CCST, Maidstone Hospital – Kent Oncology Centre, Maidstone, Martin Hogg, MBBS, Royal Preston Hospital, Blackburn, Chiara Intrivici, MD, PhD, United Lincolnshire Hospitals NHS Trust, Boston, Janine Mansi, MBBS, MD, Guys and Saint Thomas NHS Foundation Trust, London; Christopher J. Poole, MBBChir, University Hospital Coventry, Coventry; *United States* – Apurv Agrawal, MD, New Jersey Hematology Oncology Associates, Brick, NJ, Eugene Ahn, MD, and Dennis Citrin, MBChB, PhD, Cancer Treatment Centers of America at Midwestern Regional Medical Center, Zion, IL, Sramila Aithal, MD, Eastern Regional Medical Center Inc, Philadelphia, PA, Eleni Andreopoulou, MD, and Linda Vahdat, MD, MBA, Breast Center at Weill Cornell Medicine, New York, NY, Shakeela Bahadur, MD, Banner MD Anderson Cancer Center, Gilbert, AZ, Samuel Bailey, MD, and Hassan Ghazal, MD, ARH Cancer Clinic, Hazard, KY, Reema Batra, MD, Sharp Memorial Hospital, San Diego, CA, Chiara Battelli, MD, PhD, New England Cancer Specialists, Scarborough, ME, Thaddeus Beeker, MD, and Michael Meshad, MD, Southern Cancer Center, Mobile, AL, Christiana M. Brenin, MD, University of Virginia Cancer Center, Charlottesville, VA, Ursa Brown-Glaberman, MD, University of New Mexico Comprehensive Cancer Center, Albuquerque, NM, Adam Brufsky, MD, PhD, University of Pittsburgh Medical Center, Pittsburgh, PA, Daniel Bruetman, MD, and Ebenezer Kio, MD, IU Health Goshen Center for Cancer Care, Goshen, IN, Jennifer Carney, MD, MA, Kaiser Permanente Hawaii Moanalua Medical Center, Honolulu, HI, Helen Chew, MD, UC Davis Medical Center – UC Davis Comprehensive Cancer, Sacramento, CA, Marc Citron, MD, ProHealth Care Associates, LLP, Lake Success, NY, Melody Cobleigh, MD, Rush University Medical Center, Chicago, IL, Suzanne Cole, MD, Mercy Clinic Oncology and Hematology, Oklahoma City, OK, Jessica Croley, MD, Saint Joseph Hospital, Lexington, KY, Christopher Croot, MD, Jewish Medical Center Northeast, Louisville, KY, Brooke Daniel, MD, Tennessee Oncology PLLC, Chattanooga, TN, Robert Dichmann, MD, Central Coast Medical Oncology, Santa Maria, CA, Alfred DiStefano, MD, Arlington Cancer Center, Arlington, TX, Tracy Dobbs, MD, Tennessee Cancer Specialists, PLLC, Dowell Springs, Knoxville, TN, Robert Droder, MD, and Arielle Lee, MD, HOPE Cancer Center of East Texas, Tyler, TX, Erin Ellis, MD, Swedish Cancer Institute, Seattle, WA, John Erban, MD, and Rachel Buchsbaum, MD, Tufts Medical Center Cancer Center, Boston, MA, Louis Fehrenbacher, MD, and Jennifer Suga, MD, Kaiser Permanente Medical Center, Vallejo, CA, Trevor Feinstein, MD, Piedmont Cancer Institute, PC, Atlanta, GA, Erin Fleener, MD, Saint Joseph Health Cancer Center, Bryan, TX, William Fusselman, MD, Physicians Clinic of Iowa, Cedar Rapids, IA, Nashat Gabrail, MD, Gabrail Cancer Center Research, Canton, OH, Christopher Gallagher, MD, MedStar Washington Hospital Center, Washington, DC, William J. Gradishar, MD, Northwestern University, Chicago, IL, Deena Graham, MD, Hackensack University Medical Center – John Theurer Cancer Center, Hackensack, NJ, Maria Grosse-Perdekamp, MD, Carle Cancer Center, Urbana, IL, Barbara Haley, MD, University of Texas Southwestern Medical Center, Dallas, TX, Kathleen Harnden, MD, and Mary Wilkinson, MD, Inova Schar Cancer Institute, Fairfax, VA, Lowell Hart, MD, Florida Cancer Specialists & Research Institute, Fort Myers, FL, John Hrom, MD, Hattiesburg Clinic, PA, Hattiesburg, MS, Sara Hurvitz, MD, UCLA Hematology Oncology, Ventura, Los Angeles, CA, Nicholas Iannotti, MD, Hematology/Oncology Associates of the Treasure Coast, Port Saint Lucie, FL, Sujith Kalmadi, MD, Ironwood Cancer & Research Center, Chandler, AZ, Edward Kaplan, MD, Hematology Oncology of the North Shore, Skokie, IL, Peter Kaufman, MD, and Gary Schwartz, MD, Dartmouth-Hitchcock Norris Cotton Cancer Center, Lebanon, NH, Mary Kemeny, MD, Queens Hospital Center, Jamaica, NY, Stephen Kendall, MD, Utah Cancer Specialist, Salt Lake City, UT, Elisa Krill-Jackson, MD, Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, Bradley Lash, MD, Guthrie Medical Group, PC, Corning, NY, Andrew Brown, MD, and Anna Litvak, MD, Cancer Center of Saint Barnabas Medical Center, Livingston, NJ, Philip Lowry, MD, Guthrie Medical Group, PC, Sayre, PA, Kit Lu, MD, UPMC Pinnacle Health Cancer Institute, Harrisburg, PA, Cynthia Lynch, MD, Western Regional Medical Center, Inc, Goodyear, AZ, Ajit Maniam, MD, Pacific Cancer Medical Center, Inc, Anaheim, CA, Monte Martin, MD, Flaget Cancer Center, Bardstown, KY, Samuel McCachren, MD, Suratha Murali, MD, MS, and Wenqing Zhang, MD, PhD, Thompson Cancer Survival Center, Knoxville, TN, Diana Medgyesy, MD, and Ann Stroh, DO, Poudre Valley Health Care, Inc, Fort Collins, CO, Susan Melin, MD, Wake Forest University Baptist, Winston-Salem, NC, Raul Mena, MD, East Valley Hematology and Oncology Medical Group, Burbank, CA, Kathy Miller, MD, Indiana University Health Melvin and Bren Simon Cancer Center, Indianapolis, IN, Aldemar Montero, MD, Gwinnett Medical Center – Center for Cancer Care, Lawrenceville, GA, Mahvish Muzaffar, MD, ECU – Leo W Jenkins Cancer Center, Greenville, NC, Bichlien Nguyen, MD, Long Beach Memorial Medical Center, Bakersfield, CA, Damien Hansra, MD, and Mary Ninan, MD, Southeastern Regional Medical Center, Newnan, GA, Yelena Novik, MD, New York University Clinical Cancer Center, New York, NY, Brian O'Connor, MD, Frederick Memorial Hospital, Frederick, MD, Ira Oliff, MD, Orchard Healthcare Research Inc, Skokie, IL, Raul Oyola, MD, Northwest Georgia Oncology Centers, PC, Marietta, GA, Mark D Pegram, MD, Stanford Comprehensive Cancer Institute, Stanford University School of Medicine, Stanford, CA, Alejandra Perez, MD, University of Miami Sylvester Comprehensive Cancer Center, Plantation, FL, Timothy Pluard, MD, Saint Luke's Cancer Institute, Kansas City, MO, David Riseberg, MD, Mercy Medical Center, Baltimore, MD, Angel Rodriguez, MD, Austin Cancer Center, Austin, TX, Hope S. Rugo, MD, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, Lupe Salazar, MD, University of Washington – Seattle Cancer Care Alliance, Seattle, WA, Nikita Shah, MD, UF Health Cancer Center at Orlando Health, Orlando, FL, Sagun Shrestha, MD, Southwestern Regional Medical Center Inc, Tulsa, OK, Bethany Sleckman, MD, Mercy Hospital St. Louis, St. Louis, MO, Robert Somer, MD, Cooper University Hospital, Camden, NJ, Scott Sonnier, MD, Touro Infirmary Hospital, Marrero, LA, Elizabeth Tan-Chiu, MD, Florida Cancer Research Institute, Plantation, FL, Saritha Thumma, MD, Cancer Care Northwest, PS, Spokane, WA, Michaela Tsai, MD, Virginia Piper Cancer Institute, Minneapolis, MN, Sonia Varghese, MD, MBBS, Mercy Clinic Oncology and Hematology, Dallas, TX, Sumithra Vattigunta, MD, Palm Beach Cancer Institute, West Palm Beach, FL, Pramvir Verma, MD, Fort Belvoir Community Hospital, Fort Belvoir, VA, Jeanine L Werner, MD, Anne Arundel Medical Center, Annapolis, MD, Gail S. Wright, MD, Florida Cancer Specialists & Research Institute, New Port Richey, FL, Denise A. Yardley, MD, Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, TN, Robyn Young, MD, The Center for Cancer and Blood Disorders, Fort Worth, TX, Andrew Zahalsky, MD, Monongahela Valley Hospital, Monongahela, PA.

Meeting Presentations: This study was presented at the American Society of Clinical Oncology Annual Meeting (May 31-June 4, 2019; Chicago, Illinois) and the San Antonio Breast Cancer Symposium (December 10-14, 2019; San Antonio, Texas).

Data Sharing Statement: See Supplement 3.

Additional Contributions: The authors thank all of the patients, their families, and the entire staff who participated in this trial. Professional medical writing support was provided by Francesca Balordi, PhD, and Emily Cullinan, PhD, of The Lockwood Group, Stamford, Connecticut, USA, in accordance with Good Publication Practice, GPP3 guidelines, with funding by MacroGenics, Inc, Rockville, Maryland, USA.

REFERENCES

1. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 4). *Ann Oncol*. 2018; 29(8):1634-1657. doi:10.1093/annonc/mdy192

2. Giordano SH, Temin S, Chandarlapaty S, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO clinical practice guideline

update. *J Clin Oncol*. 2018;36(26):2736-2740. doi:10.1200/JCO.2018.79.2697

3. Mendes D, Alves C, Afonso N, et al. The benefit of HER2-targeted therapies on overall survival of patients with metastatic HER2-positive breast cancer—a systematic review. *Breast Cancer Res*. 2015;17:140. doi:10.1186/s13058-015-0648-2

4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: breast cancer (v3.2020). Accessed March 13, 2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

5. Palumbo R, Sottotetti F, Riccardi A, et al. Which patients with metastatic breast cancer benefit from subsequent lines of treatment? an update for clinicians. *Ther Adv Med Oncol*. 2013;5(6):334-350. doi:10.1177/1758834013508197

6. Nordstrom JL, Gorlatov S, Zhang W, et al. Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fcγ receptor binding properties. *Breast Cancer Res*. 2011;13(6):R123. doi:10.1186/bcr3069

7. Stavenhagen JB, Gorlatov S, Tuaillon N, et al. Fc optimization of therapeutic antibodies enhances their ability to kill tumor cells in vitro and controls tumor expansion in vivo via low-affinity activating Fcgamma receptors. *Cancer Res*. 2007;67(18):8882-8890. doi:10.1158/0008-5472.CAN-07-0696

8. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. *Nat Rev Immunol*. 2008;8(1):34-47. doi:10.1038/nri2206

9. Chen X, Song X, Li K, Zhang T. FcγR-binding is an important functional attribute for immune checkpoint antibodies in cancer immunotherapy. *Front Immunol*. 2019;10:292. doi:10.3389/fimmu.2019.00292

10. Muntasell A, Cabo M, Servitja S, et al. Interplay between natural killer cells and anti-HER2 antibodies: perspectives for breast cancer immunotherapy. *Front Immunol*. 2017;8:1544. doi:10.3389/fimmu.2017.01544

11. Musolino A, Naldi N, Bortesi B, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. *J Clin Oncol*. 2008;26(11):1789-1796. doi:10.1200/JCO.2007.14.8957

12. Gavin PG, Song N, Kim SR, et al. Association of polymorphisms in *FCGR2A* and *FCGR3A* with degree of trastuzumab benefit in the adjuvant treatment of ERBB2/HER2-positive breast cancer: analysis of the NSABP B-31 Trial. *JAMA Oncol*. 2017;3(3):335-341. doi:10.1001/jamaoncol.2016.4884

13. Magnes T, Melchardt T, Hufnagl C, et al. The influence of FCGR2A and FCGR3A polymorphisms on the survival of patients with recurrent or metastatic squamous cell head and neck cancer treated with cetuximab. *Pharmacogenomics J*. 2018;18(3):474-479. doi:10.1038/tpj.2017.37

14. Musolino A, Naldi N, Dieci MV, et al. Immunoglobulin G fragment C receptor polymorphisms and efficacy of preoperative chemotherapy plus trastuzumab and lapatinib in HER2-positive breast cancer. *Pharmacogenomics J*. 2016;16(5):472-477. doi:10.1038/tpj.2016.51

15. Persky DO, Dornan D, Goldman BH, et al. Fc gamma receptor 3a genotype predicts overall survival in follicular lymphoma patients treated on SWOG trials with combined monoclonal antibody plus chemotherapy but not chemotherapy alone. *Haematologica*. 2012;97(6):937-942. doi:10.3324/haematol.2011.050419

16. Hurvitz SA, Betting DJ, Stern HM, et al. Analysis of Fcγ receptor IIIa and IIa polymorphisms: lack of correlation with outcome in trastuzumab-treated breast cancer patients. *Clin Cancer Res*. 2012;18(12):3478-3486. doi:10.1158/1078-0432.CCR-11-2294

17. Norton N, Olson RM, Pegram M, et al. Association studies of Fcγ receptor polymorphisms with outcome in HER2+ breast cancer patients treated with trastuzumab in NCCTG (Alliance) Trial N9831. *Cancer Immunol Res*. 2014;2(10):962-969. doi:10.1158/2326-6066.CIR-14-0059

18. Bang YJ, Giaccone G, Im SA, et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. *Ann Oncol*. 2017;28(4):855-861. doi:10.1093/annonc/mdx002

19. Im SA, Bang YJ, Oh DY, et al. Long-term responders to single-agent margetuximab, an Fc-modified anti-HER2 monoclonal antibody, in metastatic HER2+ breast cancer patients with prior anti-HER2 therapy. Abstract P6-18-11. *Cancer Res*. 2019;79(4)(suppl).

20. Wolff AC, Hammond ME, Hicks DG, et al; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013. doi:10.1200/JCO.2013.50.9984

21. Thompson LM, Eckmann K, Boster BL, et al. Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. *Oncologist*. 2014;19(3):228-234. doi:10.1634/theoncologist.2013-0286

22. Gradishar WJ, Im S-A, Cardoso F, et al. Phase 3 SOPHIA study of margetuximab + chemotherapy vs trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer after prior anti-HER2 therapies: infusion time substudy results. 2019 San Antonio Breast Cancer Symposium; P1-18-04.

23. Arnould L, Gelly M, Penault-Llorca F, et al. Trastuzumab-based treatment of HER2-positive breast cancer: an antibody-dependent cellular cytotoxicity mechanism? *Br J Cancer*. 2006;94(2):259-267. doi:10.1038/sj.bjc.6602930

24. Norton N, Fox N, McCarl CA, et al. Generation of HER2-specific antibody immunity during trastuzumab adjuvant therapy associates with reduced relapse in resected HER2 breast cancer. *Breast Cancer Res*. 2018;20(1):52. doi:10.1186/s13058-018-0989-8

25. Liu L, Yang Y, Burns R, et al. Margetuximab mediates greater Fc-dependent anti-tumor activities than trastuzumab or pertuzumab in vitro. Abstract 1538. *Cancer Res* 2019;79(13)(suppl).

26. Musolino A, Boggiani D, Pellegrino B, et al. Role of innate and adaptive immunity in the efficacy of anti-HER2 monoclonal antibodies for HER2-positive breast cancer. *Crit Rev Oncol Hematol*. 2020;149:102927. doi:10.1016/j.critrevonc.2020.102927

27. Disis ML, Stanton SE. Can immunity to breast cancer eliminate residual micrometastases? *Clin Cancer Res*. 2013;19(23):6398-6403. doi:10.1158/1078-0432.CCR-13-0734

28. Knutson KL, Clynes R, Shreeder B, et al. Improved survival of HER2+ breast cancer patients treated with trastuzumab and chemotherapy is associated with host antibody immunity against the HER2 intracellular domain. *Cancer Res*. 2016;76(13):3702-3710. doi:10.1158/0008-5472.CAN-15-3091

29. Muraro E, Comaro E, Talamini R, et al. Improved Natural Killer cell activity and retained anti-tumor CD8(+) T cell responses contribute to the induction of a pathological complete response in HER2-positive breast cancer patients undergoing neoadjuvant chemotherapy. *J Transl Med*. 2015;13:204. doi:10.1186/s12967-015-0567-0

30. Taylor C, Hershman D, Shah N, et al. Augmented HER-2 specific immunity during treatment with trastuzumab and chemotherapy. *Clin Cancer Res*. 2007;13(17):5133-5143. doi:10.1158/1078-0432.CCR-07-0507

31. Nordstrom JL, Muth J, Erskine CL, et al. High frequency of HER2-specific immunity observed in patients (pts) with HER2+ cancers treated with margetuximab (M), an Fc-enhanced anti-HER2 monoclonal antibody (mAb). Abstract 1030. *J Clin Oncol*. 2019;37(15)(suppl).

32. Martínez-Jañez N, Chacón I, de Juan A, et al. Anti-HER2 therapy beyond second-line for HER2-positive metastatic breast cancer: a short review and recommendations for several clinical scenarios from a Spanish expert panel. *Breast Care (Basel)*. 2016;11(2):133-138. doi:10.1159/000443601