Phase 3 SOPHIA Study of Margetuximab + Chemotherapy Versus Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies: Final Overall Survival Analysis

Poster #2484

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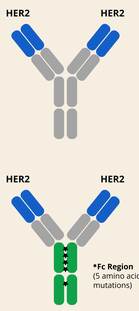
SOPHIA (NCT02492711)

Introduction

- The current standard of care for human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (MBC) is dual HER2 antibody therapy with pertuzumab/trastuzumab plus a taxane as first-line treatment, followed by TDM-1 as second-line treatment[1,2]
  - Resistance to anti-HER2 therapy remains a major therapeutic challenge
  - Treatment options for third-line treatment and beyond include chemotherapy with trastuzumab or lapatinib, and the combination of trastuzumab with lapatinib[1,2]
    - With these established regimens, the median overall survival (OS) ranges from 11.8 months to 18.8 months[3–7]
  - More recently, novel anti-HER2 agents (trastuzumab deruxtecan, neratinib, tucatinib, and margetuximab) have become available in this setting[1,2,8,9]
    - With these new agents, the median OS ranges from 21.6 months to 24.6 months[10-13]
- Margetuximab is an Fc-engineered anti-HER2 immunoglobulin G monoclonal antibody that targets the same epitope as trastuzumab, with similar antiproliferative effects (**Figure 1**)[14,15]
  - Compared with trastuzumab, margetuximab displays increased binding affinity (in vitro) for both polymorphic variants (158 V or F) of activating Fc gamma receptor (FcγR) CD16A (FcγRIIIa) and decreased binding affinity for inhibitory FcγR CD32B (FcγRIIb)[14-16]
  - Margetuximab enhances innate immunity, including CD16A-mediated antibody-dependent cellular cytotoxicity, more effectively than trastuzumab[14-16,17]
  - Margetuximab may also potentiate adaptive immunity in treated patients, as shown by enhanced clonality of the T-cell repertoire, induction of HER2-specific T-cell responses, and increased levels of HER2-specific antibodies compared with pretreatment samples[14,18]

Figure 1. Margetuximab: Fc Engineering Alters Fc Receptor Affinities



TRASTUZUMAB

Fab

- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival

Fc

- Wild-type IgG immune effector domains
- Binds and activates immune cells

MARGETUXIMAB

Fab

- Same specificity and affinity as trastuzumab
- Similarly disrupts signaling as trastuzumab

Fc Engineering

- ↑Affinity for activating FcγRIIIA (CD16A)
- ↓Affinity for inhibitory FcγRIIB (CD32B)

Margetuximab vs Trastuzumab Fcγ Receptor Affinities

Receptor type	Fcγ receptor	Allelic variant	Relative FcγR binding to antibody	Affinity change (M to T)
Activating	CD16A	158F	↓	↑
		158V	↑	↑
	CD32A	131R	↓	↓
		131H	↑	↔
Inhibitory	CD32B	232I/T	↔	↓

FcγR, Fc gamma receptor; HER2, human epidermal growth factor receptor 2; IgG, immunoglobulin G; M, margetuximab; T, trastuzumab.

- The phase 3 SOPHIA study (NCT02492711) demonstrated the clinical benefit of margetuximab versus trastuzumab, both with chemotherapy, in patients with HER2+ MBC[12]
  - Margetuximab plus chemotherapy improved progression-free survival (PFS) over trastuzumab plus chemotherapy, with a 24% relative risk reduction (hazard ratio [HR], 0.76 [95% CI, 0.59-0.98]; *P*=0.033; median, 5.8 [95% CI, 5.5-7.0] months vs 4.9 [95% CI, 4.2-5.6] months; October 10, 2018)[12]
  - Median OS after 270 deaths (interim analysis) was 21.6 months with margetuximab versus 19.8 months with trastuzumab (HR, 0.89; 95% CI, 0.69-1.13; *P*=0.33; September 10, 2019)[12]
- These results led to the US Food and Drug Administration (FDA) approval of margetuximab-cmkb with chemotherapy in patients with HER2+ MBC who have received ≥2 prior anti-HER2 regimens, at least one of which was for metastatic disease[8]

Objective

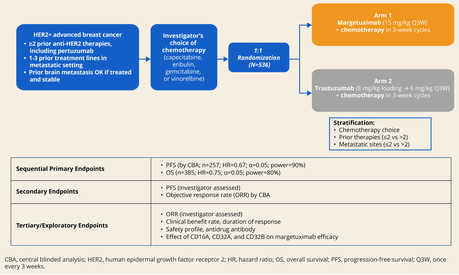
- The primary objective is to report the final OS analysis after 385 deaths, as well as updated safety

Materials and Methods

Study Design and Participants

- SOPHIA was an international, randomized, open-label, phase 3 study (**Figure 2**)
- Eligible patients were adults with confirmed HER2+ advanced breast cancer
  - Patients must have had progressive disease after ≥2 lines of prior HER2-targeted therapy, including pertuzumab, and 1-3 lines of nonhormonal MBC therapy

Figure 2. SOPHIA Study Design



Sequential Primary Endpoints	• PFS (by CBA; n=257; HR=0.67; α=0.05; power=90%) • OS (n=385; HR=0.75; α=0.05; power=80%)
Secondary Endpoints	• PFS (investigator assessed) • Objective response rate (ORR) by CBA
Tertiary/Exploratory Endpoints	• ORR (investigator assessed) • Clinical benefit rate, duration of response • Safety profile, antidrug antibody • Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

CBA, central blinded analysis; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks.

- Patients randomly assigned received either margetuximab at a dose of 15 mg/kg intravenously (IV) on day 1 of each 21-day cycle or trastuzumab at a dose of 6 mg/kg IV on day 1 of each 21-day cycle after a loading dose of 8 mg/kg
- Stratification factors were metastatic sites (≤2 vs >2), lines of therapy for metastatic disease (≤2 vs >2), and chemotherapy choice
- Sequential primary endpoints were PFS by central blinded analysis and OS

Statistical Analysis

- For 80% power to detect a median OS improvement from 12 to 16 months (HR, 0.75) at a 2-sided 0.05 significance level, 385 OS events were needed
- The following 3 OS analyses were planned: first interim coincident with primary PFS analysis (which occurred on October 10, 2018), second interim after 270 deaths (which occurred on September 10, 2019), and final analysis after 385 events (which occurred on June 14, 2021, and is reported here)

Results

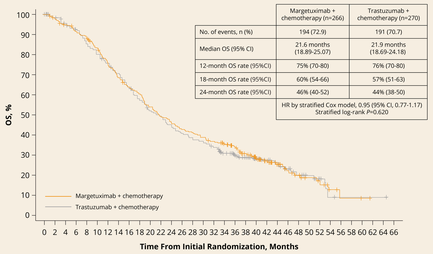
Patients

- A total of 536 patients (intention-to-treat [ITT] population) were enrolled and randomly assigned to receive margetuximab plus chemotherapy (margetuximab group, n=266) or trastuzumab plus chemotherapy (trastuzumab group, n=270)
- Baseline characteristics have been previously published and were balanced between treatment groups[12]
  - All patients had received prior trastuzumab; all but 1 had received prior pertuzumab and 489 (91.2%) had received prior ado-trastuzumab emtansine[12]
- At the median follow-up of 20.2 months among all ITT patients, patients received a median of 7 cycles of margetuximab plus chemotherapy versus 6 cycles of trastuzumab plus chemotherapy

Efficacy

- The data cutoff was June 14, 2021, when the 385th death had occurred (194 [73%] in the margetuximab group vs 191 [71%] in the trastuzumab group)
- The median OS in the ITT population was not statistically different between the 2 treatment groups: 21.6 months with margetuximab versus 21.9 months with trastuzumab (HR, 0.95 [95% CI, 0.77-1.17]; *P*=0.620; **Figure 3**)

Figure 3. Final Overall Survival (OS) in the Intention-to-Treat Population (June 14, 2021 Cutoff)



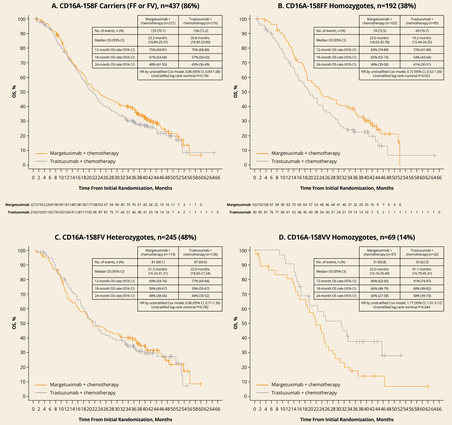
	Margetuximab + chemotherapy (n=266)	Trastuzumab + chemotherapy (n=270)
No. of events, n (%)	194 (72.9)	191 (70.7)
Median OS (95% CI)	21.6 months (18.89-25.07)	21.9 months (18.89-24.18)
12-month OS rate (95%CI)	75% (70-80)	76% (70-80)
18-month OS rate (95%CI)	60% (54-66)	57% (51-63)
24-month OS rate (95%CI)	46% (40-52)	44% (38-50)
	HR by stratified Cox model, 0.95 (95% CI, 0.77-1.17) Stratified log-rank *P*=0.620	

Margetuximab 266 259 249 239 230 214 193 176 163 154 138 126 117 109 105 99 93 85 75 61 45 37 27 21 17 12 8 4 2 2 1 0
Trastuzumab 270 261 248 238 220 207 194 180 161 146 131 124 111 103 95 91 84 72 61 52 41 32 25 19 13 10 5 2 1 1 1 1 1 0

CI, confidence interval; HR, hazard ratio.

- Prespecified non–α-allocated subgroup analyses of OS by CD16A genotype are shown in **Figure 4**
  - Genotyping was available for 506 patients (94%)
  - Among 437 patients (86%) who carried the CD16A-158F low-affinity allele (F carriers), margetuximab prolonged OS by 2.5 months compared with trastuzumab (**Figure 4A**)
    - The median OS was 23.3 months with margetuximab versus 20.8 months with trastuzumab (HR, 0.86 [95% CI, 0.69-1.08]; nominal *P*=0.19; **Figure 4A**)
  - Among 192 patients (38%) homozygous for the F allele, margetuximab prolonged OS by 4.4 months compared with trastuzumab
    - The median OS was 23.6 months with margetuximab versus 19.2 months with trastuzumab (HR, 0.72 [95% CI, 0.52-1.00]; nominal *P*=0.05; **Figure 4B**)
  - By contrast, in the 69 (14%) VV homozygotes, median OS was 22.0 months with margetuximab versus 31.1 months with trastuzumab (HR, 1.77 [95% CI, 1.01-3.12]; nominal *P*=0.04; **Figure 4D**)
  - The treatment by CD16A interaction test for OS (F carrier vs VV) was nominally significant (*P*=0.0293)

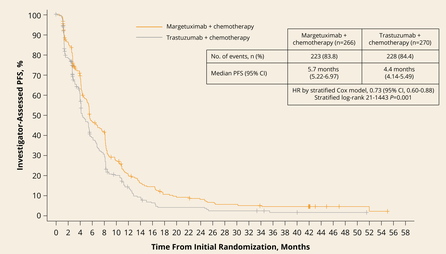
Figure 4. Prespecified Exploratory OS Analysis, per CD16A Genotype by Treatment Group (June 14, 2021 Cutoff)[a]



[a]A total of 506 out of 536 ITT patients genotyped (94%). Treatment by CD16A genotype (F carrier vs VV) interaction *P*=0.0293.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NA, not available (because cannot be calculated).

- The median PFS assessed by the investigator in the ITT population was nominally statistically different between the 2 treatment groups: 5.7 months with margetuximab versus 4.4 months with trastuzumab (HR, 0.73 [95% CI, 0.60-0.88]; *P*=0.001; **Figure 5**)

Figure 5. Progression-Free Survival (PFS) Assessed by the Investigator in the Intention-to-Treat Population (June 14, 2021 Cutoff)



	Margetuximab + chemotherapy (n=266)	Trastuzumab + chemotherapy (n=270)
No. of events, n (%)	223 (83.8)	228 (84.4)
Median PFS (95% CI)	5.7 months (5.22-6.97)	4.4 months (4.14-5.49)
	HR by stratified Cox model, 0.73 (95% CI, 0.60-0.88) Stratified log-rank *P*=0.001	

Margetuximab 266 215 169 110 97 62 45 35 31 22 20 19 16 13 11 11 10 9 8 8 8 7 4 3 2 2 1 1 0
Trastuzumab 270 196 144 89 69 43 29 19 12 8 8 8 8 5 5 5 5 4 2 2 2 1 1 1 1 1 1 0

CI, confidence interval; HR, hazard ratio.

Safety

- As of June 14, 2021, the safety population included 264 patients in the margetuximab group and 266 patients in the trastuzumab group (**Table 1**)

Table 1. Summary of AEs in the Safety Population (June 14, 2021 Cutoff)

	Margetuximab + chemotherapy n=264 n (%)	Trastuzumab + chemotherapy n=266 n (%)
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, n (%)	36 (13.6)	9 (3.4)
Grade ≥3 infusion-related AEs, n (%)	5 (1.9)	0
Any-grade LVEF dysfunction, n (%)	8 (3.0)	8 (3.0)
Grade ≥3 LVEF dysfunction, n (%)	3 (1.1)	1 (0.4)
Grade ≥3 AE, n (%)	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, n (%)	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, n (%)	11 (4.2)	8 (3.0)
AE leading to chemotherapy discontinuation, n (%)	35 (13.3)	17 (6.4)
AE leading to discontinuation from the study, n (%)	10 (3.8)	10 (3.8)
Discontinuation of HER2-targeted treatment due to IRRs, n (%)	3 (1.1)	0
LVEF dysfunction leading to dose delay or discontinuation, n (%)	4 (1.5)	7 (2.6)
AE resulting in deaths, n (%)	4 (1.5)[a]	2 (0.8)[b]
HER2-targeted treatment-related AE resulting in deaths, n (%)	0	0

[a]Two patients had pneumonia, 1 had pneumonia aspiration, and 1 had coronavirus infection. [b]One patient had pneumonia and the other had acute kidney injury.
AE, adverse event; HER2, human epidermal growth factor receptor 2; IRR, infusion-related reaction; LVEF, left ventricular ejection fraction; SAE, serious adverse event.

Table 2. AEs in the Safety Population, Regardless of Causality (June 14, 2021 Cutoff)

	Margetuximab + chemotherapy (N=264)		Trastuzumab + chemotherapy (N=266)	
	All grade[a]	Grade ≥3[b]	All grade[a]	Grade ≥3[b]
Nonhematologic AEs, n (%)				
Fatigue	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	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	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	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, n (%)				
Neutropenia	76 (28.8)	54 (20.5)	55 (20.7)	33 (12.4)
Anemia	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	8 (3.0)	8 (3.0)	13 (4.9)	13 (4.9)

[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.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; WBC, white blood cell.

- Common adverse events (AE) 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; **Table 2**)
- Grade ≥3 AEs in at least 5% of patients were neutropenia, neutrophil count decreased, and anemia in both groups, as well as fatigue (margetuximab group) and febrile neutropenia (trastuzumab group; **Table 2**)
- Discontinuations from the study due to AEs were similar in both treatment groups: 10 patients (4%) in the margetuximab group and 10 patients (4%) in the trastuzumab group (**Table 1**)
- There were 6 deaths due to AEs, none of which were considered treatment related: 4 patients (2%) in the margetuximab group and 2 patients (1%) in the trastuzumab group (**Table 1**)
- AEs of special interest included infusion-related reactions (IRR) and left ventricular (LV) dysfunction
  - All-grade IRRs were more common with margetuximab than with trastuzumab (36 [14%] vs 9 [3%], respectively; **Table 1**). Among margetuximab recipients, grade ≥3 IRRs were reported in 5 patients (2%) and IRRs leading to margetuximab discontinuation occurred in 3 patients (1.1%). No trastuzumab recipients had grade ≥3 IRRs, nor IRRs leading to discontinuation
  - AEs of LV dysfunction occurred in 8 patients (3%) in both treatment groups (**Table 1**). Grade ≥3 LV dysfunction AEs were observed in 3 margetuximab recipients (1%) and 1 trastuzumab recipient (0.4%). AEs of LV dysfunction requiring dose delay or discontinuation were experienced in 4 margetuximab-treated (2%) versus 7 trastuzumab-treated patients (3%)

Conclusions

- The final OS analysis for the ITT population did not demonstrate a statistically significant advantage for margetuximab plus chemotherapy compared with trastuzumab plus chemotherapy
- A prespecified non–α-allocated analysis of CD16A genotyping indicates a numerical OS advantage in favor of margetuximab in F homozygous patients, along with a numerical OS advantage in favor of trastuzumab in V homozygous patients
- Safety of margetuximab plus chemotherapy, comparable to trastuzumab plus chemotherapy, was similar to previous reports and consistent with the FDA-approved label for margetuximab
- Further studies of margetuximab in patients with HER2+ breast cancer with different CD16A allelic variants are warranted, including MARGOT (NCT04425018), the ongoing neoadjuvant investigator-initiated study examining the efficacy of margetuximab versus trastuzumab in patients carrying F-allelic variants of CD16A

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