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

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SOPHIA infusion substudy (NCT02492711)

Background

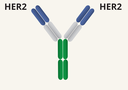
- Margetuximab is an investigational Fc-engineered anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody that shares the same antigen recognition domain as trastuzumab and exerts similar antiproliferative effects[1] (**Table 1**)
- Compared with trastuzumab, margetuximab has higher affinity for both the 158V (high-binding) and 158F (low-binding) allotypes of the activating Fc receptor CD16A[1,2] (**Table 1**)

Table 1. Monoclonal Antibodies in the Phase 3 SOPHIA Study

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[1,2]

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 Binding to FcγR Variants[1]				
Receptor Type	Receptor	Allelic Variant	Relative Binding of Alleles	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6 × ↑
		158V	Higher	4.7 × ↑
	CD32A	131R	Lower	6.1 × ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4 × ↓

FcγR, Fc gamma receptor; IgG, immunoglobulin G.

- Margetuximab enhances innate immunity, including CD16A–mediated antibody-dependent cellular cytotoxicity, more effectively than trastuzumab in vitro[1]
- Based on ex vivo experiments with cells collected from patients pre- and post-treatment, margetuximab induces adaptive immunity, including enhanced T-cell clonality and induction of HER2–specific T- and B-cell responses[3]
- The SOPHIA trial (NCT02492711), conducted in pretreated patients with HER2+ metastatic breast cancer (MBC), showed a statistically significant progression-free survival (PFS) benefit with margetuximab + chemotherapy (CTX) versus trastuzumab + CTX (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.59–0.98; *P*=.033; median PFS, 5.8 vs 4.9 months), with comparable safety (updated data presented at SABCS 2019, oral presentation, program number GS1-02, abstract 752)[4]
- Margetuximab was previously studied at 15 mg/kg every 3 weeks with infusions over 120 minutes (min) at every cycle, which can pose a significant, potentially burdensome time commitment relative to infusions over 30 min
- The SOPHIA infusion substudy was conducted to determine whether infusion duration, from Cycle 2 (C2) onward, could be safely reduced from 120 to 30 min

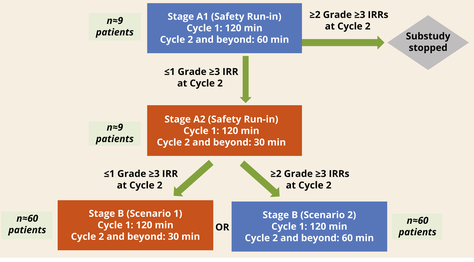
Methods

Objectives

- This substudy of SOPHIA evaluated safety and tolerability of sequentially reduced infusion durations of margetuximab from C2 and beyond (**Figure 1**)
  - Primary objective: Incidence of grade ≥3 infusion-related reactions (IRRs) by the end of C2
  - Secondary objective: Incidence of all grade IRRs

Study Design

Figure 1. Study Design of the Margetuximab Infusion Substudy



- Patients who enrolled in this single-arm, nonrandomized substudy participated separately from the randomized phase 3 SOPHIA trial population
- Eligible patients had HER2+ MBC and ≥4 lines of prior therapy in the metastatic setting
- Patients must have received prior trastuzumab, pertuzumab, and ado-trastuzumab emtansine
- Enrolled patients received a 120-min margetuximab infusion, with or without CTX, at Cycle 1 (C1), then 60- or 30-min infusions at C2 and beyond
- The choice of backbone CTX was made by the treating physician based on best judgment and patients' comorbidities
- There were 2 safety run-in groups: Stage A1 and Stage A2 (**Figure 1**)
  - In Stage A1, ≈9 patients received a 120-min margetuximab infusion (±CTX) at C1, so that ≥6 patients could receive 60-min infusions at C2 and beyond
  - If ≤1 patient experienced grade ≥3 IRRs in Stage A1, an additional cohort of ≈9 patients was enrolled in Stage A2 to receive a 120-min margetuximab infusion at C1, so that ≥6 patients could receive 30-min infusions at C2 and beyond
  - Premedication for margetuximab within 30 minutes of administration was recommended, if not already given with chemotherapy, including acetaminophen (650–1000 mg PO) or ibuprofen (400 mg PO); diphenhydramine (50 mg PO or IV) or equivalent H_1 antagonist; ranitidine (300 mg PO or IV) or equivalent H_2 antagonist; and dexamethasone (10 mg IV) or equivalent
- After safety data were reviewed for patients in Stages A1 and A2, an expansion cohort (Stage B) was opened for ≈60 patients to receive a 120-min margetuximab infusion at C1, followed by the fastest safe infusion time at C2 and beyond, either 30 min (Scenario 1) or 60 min (Scenario 2)
- Incidence of IRRs by grade and cycle for margetuximab given as monotherapy or in combination with CTX were calculated by summary statistics
- Adverse events (AEs) were graded according to the investigator's assessment using Common Terminology Criteria for Adverse Events v4.03

Results

- Results are provided as of June 17, 2019
- Among 88 patients enrolled, 69 received margetuximab + CTX, and 19 received margetuximab alone (**Table 2**)
- Mean age was 55 years; 99% of patients were female, and 71% were white (**Table 2**)

Table 2. Patient Demographics in the Safety Population (N=88)

	Margetuximab + CTX[a] (n=69)	Margetuximab Alone[b] (n=19)	Total Margetuximab[c] (N=88)
Age, median (range), years	54 (29–87)	56 (33–82)	55 (29–87)
Female, n (%)	68 (99)	19 (100)	87 (99)
Race, n (%)			
White	51 (74)	11 (58)	62 (71)
Asian	7 (10)	2 (11)	9 (10)
Black/African American	6 (9)	2 (11)	8 (9)
Other	5 (7)	4 (21)	9 (10)
ECOG PS, n (%)			
0	27 (39)	6 (32)	33 (38)
1	42 (61)	13 (68)	55 (63)

[a]CTX included capecitabine (given as 1000 mg/m^2 orally twice daily for 14 days in a 21-day cycle), eribulin (given as 1.4 mg/m^2 IV on days 1 and 8 in a 21-day cycle), gemcitabine (given as 1000 mg/mg^2 IV on days 1 and 8 of a 21-day cycle), or vinorelbine (given as 25–30 mg/m^2 IV on days 1 and 8 in a 21-day cycle); [b]Single-agent margetuximab 15 mg/kg every 3 weeks; [c]Includes all patients treated with margetuximab, either with CTX or as monotherapy.
ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; SD, standard deviation.

- Median number of margetuximab cycles received was 3 (range, 1–17)
- As of June 17, 2019, 37 (42%) patients remained on study therapy
- Eight patients enrolled in Stage A1, 9 in Stage A2, and 71 in Stage B1 (**Table 3**)

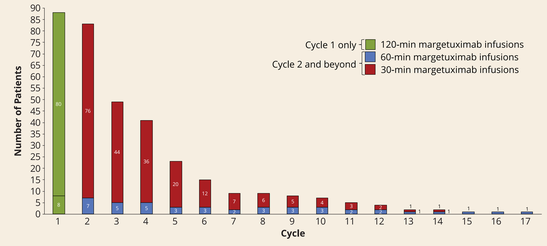
Table 3. Patient Disposition

Treated Patients, n (%)	Margetuximab + CTX[a] (n=69)	Margetuximab Alone (n=19)	Total Margetuximab[b] (N=88)
Enrolled in Stage A1	6 (9)	2 (11)	8 (9)
Enrolled in Stage A2	9 (13)	0	9 (10)
Enrolled in Stage B1	54 (78)	17 (90)	71 (81)
Discontinued from CTX only[c]	1 (1)	NA	1 (1)
Discontinued from margetuximab and CTX	40 (58)	11 (58)	51 (58)
Reason for discontinuation			
Radiologic PD	28 (41)	8 (42)	36 (41)
Nonradiologic PD	3 (4)	1 (5)	4 (5)
AE	2 (3)	0	2 (2)
Physician decision	3 (4)	0	3 (3)
Patient decision	2 (3)	0	2 (2)
Withdrew consent	1 (1)	1 (5)	2 (2)
Lost to follow-up	1 (1)	0	1 (1)
Unknown	0	1 (5)	1 (1)
End of study status			
Alive	19 (28)	3 (16)	22 (25)
Dead	11 (16)	3 (16)	14 (16)
Ongoing	29 (42)	8 (42)	37 (42)
Off treatment and missing status	10 (15)	5 (26)	15 (17)

[a]CTX included capecitabine, eribulin, gemcitabine, or vinorelbine; [b]Includes all patients treated with margetuximab, either with CTX or as monotherapy; [c]Reason for discontinuation was PD per Response Evaluation Criteria in Solid Tumors.
NA, not applicable; PD, progressive disease.

- Overall, 7 patients received 60-min margetuximab infusions starting at C2 (range, 1–17 cycles), and 76 patients received 30-min margetuximab infusions starting at C2 (range, 1–14 cycles; **Figure 2**). Five patients did not receive C2 treatment due to nonradiologic progressive disease, unrelated AE, patient or physician decision, or loss to follow-up
- No grade ≥3 IRRs occurred in any stage

Figure 2. Extent of Exposure by Duration of Infusion



- The overall rate of IRRs was 21% (18/88) (**Table 4**)
  - The rate of IRRs in premedicated and non-premedicated patients was 21% (17/80) and 13% (1/8), respectively
- Of 18 patients with IRRs, 2 (11%) were grade 1 and 16 (89%) were grade 2 (none had grade ≥3)
  - 17/18 (94%) of patients with IRRs received premedication in C1 to prevent IRR
  - 10/18 (56%) of patients with IRRs received treatment for IRR in C1

Table 4. Premedications or Treatments for IRRs

Patients With an IRR, n (%)	Margetuximab + CTX[a] (n=15)	Margetuximab Alone (n=3)	Total Margetuximab[b] (N=18)
Patients with an IRR who received premedication or treatment	15 (100)	3 (100)	18 (100)
Premedication for IRR	14 (93)	3 (100)	17 (94)
Antihistamine	14 (93)	3 (100)	17 (94)
Steroid	10 (67)	3 (100)	13 (72)
Antipyretic	7 (47)	1 (33)	8 (44)
Other[c]	8 (53)	0	8 (44)
Treatment for IRR	9 (60)	1 (33)	10 (56)

Patients Without an IRR, n (%)	Margetuximab + CTX[a] (n=54)	Margetuximab Alone (n=16)	Total Margetuximab[b] (N=70)
Patients without an IRR who received premedication	49 (91)	14 (88)	63 (90)
Antihistamine	47 (87)	14 (88)	61 (87)
Steroid	40 (74)	10 (63)	50 (71)
Antipyretic	34 (63)	13 (81)	47 (67)
Other[c]	30 (56)	3 (19)	33 (47)

[a]CTX included capecitabine, eribulin, gemcitabine, or vinorelbine; [b]Includes all patients treated with margetuximab, either with CTX or as monotherapy; [c]Includes antiemetic, proton-pump inhibitors, and anti-inflammatory agents.

- All patients with IRRs (n=18) experienced the IRRs in C1 during the initial 120-min margetuximab infusion, except for 1 patient who had an IRR in C2 with the following history:
  - One patient had C1 premedication with an antihistamine, then eribulin, followed by intravenous margetuximab and a grade 2 IRR of chills and fever. Margetuximab was interrupted and acetaminophen given before infusion resumption and completion. In C2, she had no premedication before a target 30-min margetuximab infusion then had a grade 1 IRR of chills. Treatment was interrupted. No other therapy was offered. After C2, this patient received an additional 6 cycles of margetuximab without premedication, all with 30-min margetuximab infusions, and no further IRRs occurred

- Of 88 patients enrolled, 85 (97%) experienced a treatment-emergent AE (TEAE), and 38 (43%) had grade ≥3 TEAEs (**Table 5**)
- Fifty patients (57%) had margetuximab-related AEs, including 7 (8%) who had grade ≥3 AEs
- The most common margetuximab-related AEs (in ≥5% of patients) were IRRs (n=17 [19%]), fatigue (n=9 [10%]), diarrhea (n=5 [6%]), and aspartate aminotransferase increase (n=5 [6%]; **Table 6**)
  - No grade ≥3 IRRs were observed
  - No patient discontinued treatment due to an IRR
- Serious AEs occurred in 13 of 88 patients (15%); none were considered margetuximab-related by the investigator
- There were no margetuximab-related deaths

Table 5. Safety Summary

Patients, n (%)	Margetuximab + CTX[a] (n=69)	Margetuximab Alone (n=19)	Total Margetuximab[d] (N=88)
Any TEAE	69 (100)	16 (84)	85 (97)
Margetuximab-related AE	40 (58)	10 (53)	50 (57)
CTX-related AE	58 (84)	NA	58 (66)
Grade ≥3 TEAE	33 (48)	5 (26)	38 (43)
Grade ≥3 margetuximab-related AE	6 (9)	1 (5)	7 (8)
Grade ≥3 CTX-related AE	26 (38)	NA	26 (30)
Serious TEAE	12 (17)	1 (5)	13 (15)
Margetuximab-related serious AE	0	0	0
Discontinuation due to TEAEs	2 (3)[b]	1 (5)[c]	3 (3)
Deaths	11 (16)	3 (16)	14 (16)
Margetuximab-related deaths	0	0	0

[a]CTX included capecitabine, eribulin, gemcitabine, or vinorelbine; [b]Septic shock (n=1), general physical health deterioration (n=1); [c]Left ventricular dysfunction; [d]Includes all patients treated with margetuximab, either with CTX or as monotherapy.
NA, not applicable.

Table 6. Margetuximab-Related AEs in ≥5% of Patients

Patients, n (%)	Margetuximab + CTX[a] (n=69)	Margetuximab Alone (n=19)	Total Margetuximab[b] (N=88)
Patients with any margetuximab-related AE	40 (58)	10 (53)	50 (57)
IRR	14 (20)	3 (16)	17 (19)
Fatigue	9 (13)	0	9 (10)
Diarrhea	5 (7)	0	5 (6)
AST increased	4 (6)	1 (5)	5 (6)
Nausea	3 (4)	1 (5)	4 (5)
ALT increased	4 (6)	0	4 (5)
Anemia	3 (4)	1 (5)	4 (5)

[a]CTX included capecitabine, eribulin, gemcitabine, or vinorelbine; [b]Includes all patients treated with margetuximab, either with CTX or as monotherapy.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Conclusions

- In this study, shorter margetuximab infusion times starting from C2 appear to be well tolerated
  - 94% of IRRs occurred during C1 with the 120-minute infusion
    - One patient not premedicated in C1 (120-min infusion) had IRR and one patient not premedicated in C2 (30-min infusion) had IRR
  - Only 1 patient had 2 events of IRR: one event in C1 (120-min infusion), and the other event in C2 (30-min infusion)
  - No grade ≥3 IRRs were observed at any infusion rate
- These results show that acceptable safety and tolerability of margetuximab were maintained after target infusion time was reduced to 30-min from C2 onward
- Shorter infusion times, without increased toxicity, may reduce the burden of chronic margetuximab therapy on patients, caregivers, and clinic staff

References

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