Abstract #1040

SOPHIA Analysis by Chemotherapy (Ctx) Choice: A Phase 3 (P3) Study of Margetuximab (M) + Ctx vs Trastuzumab (T) + Ctx in Patients (pts) with Pretreated HER2+ Metastatic (met) Breast Cancer (MBC)

Santiago Escriva-de-Romani, MD[1], Seock-Ah Im, MD, PhD[2], Fatima Cardoso, MD[3], Javier Cortes, MD, PhD[4], Giuseppe Curigliano, MD, PhD[5], William J. Gradishar, MD, FASCO, FACP[6], Mark D. Pegram, MD[7], Gail S. Wright, MD, FACP, FCCP[8], Christelle Levy, MD[9], Michelino De Laurentiis, MD, PhD[10], Jean-Marc Ferrero, MD[11], Shakeela W. Bahadur, MD[12], Sung-Bae Kim, MD[13], Katarína Petráková, MD, PhD[14], David A. Riseberg, MD[15], Denise Yardley, MD[16], Sutton Edlich[17], Shengyan Hong, PhD[17], Edwin Rock, MD, PhD[17], Hope S. Rugo, MD[18], on behalf of the SOPHIA Study Group

[1]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]Seoul National University Hospital, Cancer Research Institute, and College of Medicine, Seoul, Korea; [3]Champalimaud Clinical Center/Champalimaud Foundation, Breast Unit, Lisbon, Portugal; [4]IOB Institute of Oncology, Quironsalud Group, Madrid, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [5]University of Milano, European Institute of Oncology, IRCSS, Division of Early Drug Development, Milan, Italy; [6]Northwestern University, Division of Hematology/Oncology, Chicago, Illinois, USA; [7]Stanford Women's Cancer Center, Breast Cancer Oncology Program, Palo Alto, California, USA; [8]Florida Cancer Specialists & Research Institute, New Port Richey, FL, USA; [9]Centre François Baclesse, Institut Normand du Sein, Caen, France; [10]National Cancer Institute "Fondazione Pascale," Department of Breast and Thoracic Oncology, Naples, Italy; [11]Centre Antoine Lacassagne, Department of Medical Oncology, Nice, France; [12]Bannerer MD Anderson Cancer Center, Breast Cancer Program, Gilbert, Arizona, USA; [13]Asan Medical Center, Department of Oncology, Seoul, Korea; [14]Masaryk Memorial Cancer Institute, Department of Comprehensive Cancer Care, Brno, Czech Republic; [15]Mercy Medical Center, Division of Medical Oncology and Hematology, Baltimore, Maryland, USA; [16]Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, TN, USA; [17]MacroGenics, Inc., Rockville, Maryland, USA; [18]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

rocke@macrogenics.com

Background/Methods

- Despite advances, pretreated HER2+ MBC remains incurable with ongoing need for new therapies. Investigational M has similar HER2 binding and antiproliferative effects as T. Relative to T, M Fc engineering increases binding affinity for both variants of activating Fc receptor (FcR) CD16A and decreases affinity for inhibitory FcR CD32B, coordinately activating innate and adaptive immunity
- SOPHIA (NCT02492711), an open-label P3 trial, enrolled pts with HER2+ MBC after pertuzumab and 1–3 lines of prior treatment (Tx) for MBC. Randomization was 1:1 to M (15 mg/kg IV q3w + Ctx) or T (6 [8 for loading dose] mg/kg IV q3w + Ctx), stratified by met sites (≤2, >2), Tx lines for met disease (≤2, >2), and Ctx choice, including capecitabine (Cap), eribulin (Eri), gemcitabine (Gem), or vinorelbine (Vin). Primary endpoints were central blinded PFS and OS, assessed sequentially using the stratified log-rank test
- M + Ctx prolonged PFS over T + Ctx (Table 1). Second interim OS results from Sept 2019 favor M without significance (hazard ratio [HR], 0.89; 95% CI 0.69–1.13; nominal P=0.326)

Results

- Investigator chemotherapy choices, PFS hazard ratios (HRs), and safety results by chemotherapy are shown in **Table 1** and **Figure 1**
- Patients receiving Eri and Gem had the lowest PFS HRs, favoring M over T, although no statistical significance of individual Ctx subgroups was seen
- **Table 1:** There was variable toxicity among Ctx subgroups. Fewer subjects receiving Cap had Ctx related ≥Grade 3 Adverse Events (AEs)
- In this unblinded study, more pts on M than T in all subgroups discontinued Ctx alone due to AE; 8 on M and 7 on T also discontinued antibody
- **Table 2:** AEs leading to chemotherapy discontinuation were diverse; 3 such AEs were considered probably or definitely related to antibody therapy, including 2 on M (seroma, IRR) and 1 on T (pneumonia)

Table 1. PFS and Safety Results by Chemotherapy

Population[1]	PFS, 265 events HR (95% CI)[1]	≥ Grade 3 Ctx Related AEs[2]	AEs Leading to Ctx Discontinuation[2]
Intent-To-Treat (N=536)	0.76 (0.59-0.98)	41.7% M vs 40.6% T	11% M vs 6.4% T
Capecitabine (n=143)	0.77 (0.47-1.26)	25% M vs 28% T	11.8% M vs 8.5% T
Eribulin (n=136)	0.66 (0.42-1.05)	45.5% M vs 48.5% T	13.6% M vs 5.9% T
Gemcitabine (n=66)	0.58 (0.29-1.18)	40% M vs 53.1% T	17.1% M vs 15.6% T
Vinorelbine (n=191)	0.90 (0.60-1.35)	51.6% M vs 40% T	6.3% M vs 2.1% T

[1]Primary PFS data cutoff 10-Oct-2018: 536 Intent-To-Treat subjects.
[2]Safety data cutoff 10-Apr-2019: 530 subjects who received any study therapy.

Figure 1. Progression-Free Survival Results by Chemotherapy

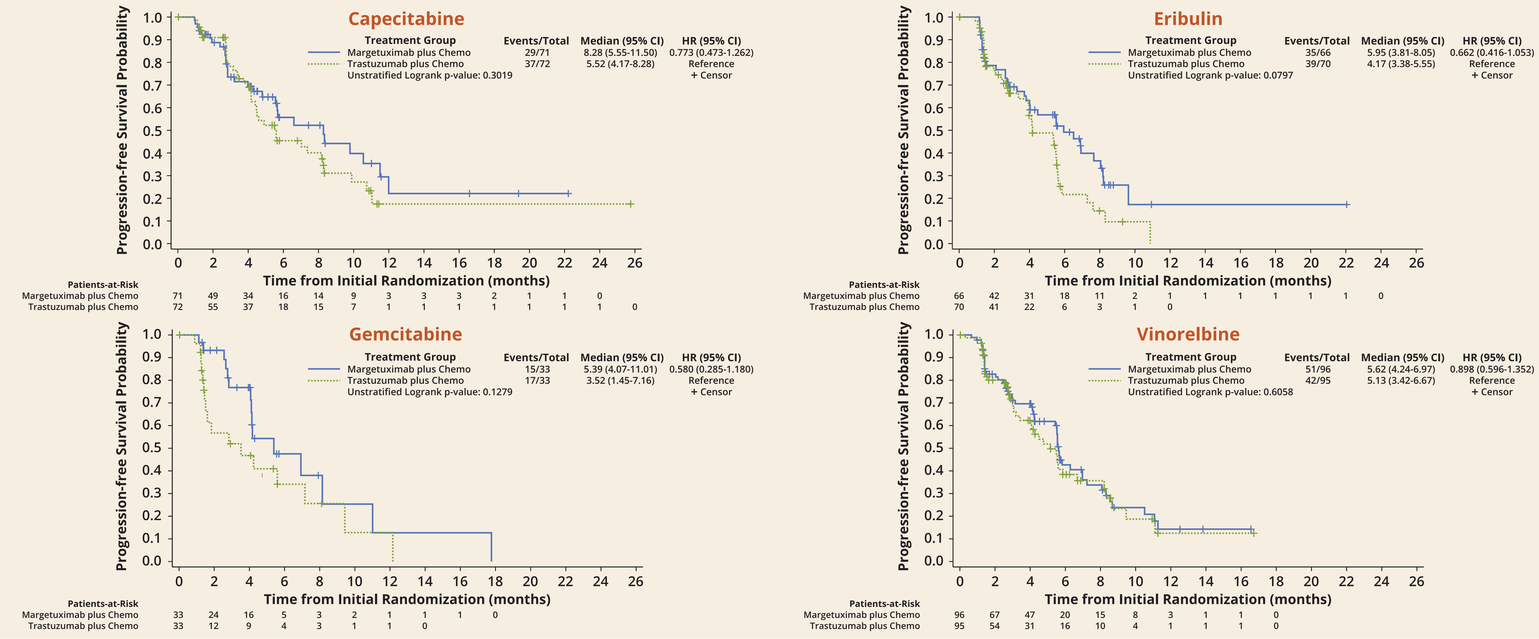

Table 2. Adverse Events Leading to Chemotherapy Discontinuation

Population[1]	Total	Grade (G)					≥ Grade 3 Adverse Events
		G5	G4	G3	G2	G1	
M + Ctx (n=264)	**29**	**1**	**1**	**13**	**11**	**3**	
Cap (n=68)	8	1	1	2	4	–	Aspiration pneumonia (G5), septic shock (G4), hydronephrosis (G3), colitis (G3)
Eri (n=66)	9	–	–	5	3	1	Left ventricular (LV) dysfunction, neuropathy, neutropenia, **seroma[3]**, spondylolisthesis
Gem (n=35)[2]	6	–	–	4	1	1	Asthenia, edema, stress, vasculitis
Vin (n=95)	6	–	–	2	3	1	Abdominal pain, **infusion related reaction (IRR)[3]**
T + Ctx (n=266)	**17**	**–**	**–**	**7**	**1**	**1**	
Cap (n=71)	6	–	–	5	1	-	Fatigue, GI toxicity, leukemia, neuropathy, palmar-plantar erythrodysesthesia
Eri (n=68)	4	–	–	3	1	-	Intracranial hemorrhage, neuralgia, transaminase elevations
Gem (n=32)	5	–	–	3	1	1	Clostridium difficile infection, osteonecrosis of jaw, bilirubin elevation
Vin (n=95)	2	–	–	2	-	-	Intestinal obstruction, **pneumonia[3]**

[1]Safety data cutoff 10-Apr-2019: 530 subjects who received any study therapy. [2]2 subjects had capecitabine selected but received gemcitabine. [3]Considered probably or definitely related to antibody study therapy.

Conclusions

- Margetuximab improved PFS over trastuzumab across all chemotherapy subgroups
- Hazard ratio differences among chemotherapy subgroups may be driven by selection bias and/or tumor sensitivity to individual chemotherapies
- Safety was acceptable and manageable in all chemotherapy subgroups

We thank the patients who consented to this research and study teams at all participating study sites.