SOPHIA: A Phase 3, Randomized Study of Margetuximab (M) Plus Chemotherapy (CTX) vs Trastuzumab (T) Plus CTX in the Treatment of Patients with HER2+ Metastatic Breast Cancer (MBC)

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Background

Margetuximab Acts Against HER2+ Tumors by a Combination of Potential Mechanisms

- Modulation of HER2 signaling, resulting in growth retardation or induction of apoptosis
- ADCC and improved binding to immune cells to enhance destruction of HER2+ tumor cells
- Presentation of tumor antigens by cells such as macrophages that take up and display the antigens to other cells of immune system, including T cells

Enhanced Binding to Immune Cells May Potentiate Antitumor Activity

- Fc-receptor CD16A exists in two isoforms with differing ability to activate ADCC
- Retrospective analysis of MBC patients treated with trastuzumab showed enhanced PFS for patients with high-affinity isoform of CD16A[1]
- Most patients (approximately 80%) have low affinity CD16A isoform
- Margetuximab binds with high affinity to both low- and high-affinity isoforms of CD16A, potentially enhancing ADCC activity

Antibody	CD16A (FcγRIIIA) Allelic Forms		CD32A (FcγRIIA*) Allelic Forms		CD32B FcγRIIB*
	F158 (Low Binder)	V158 (High Binder)	H131 (High Binder)	R131 (Low Binder)	
Wild Type	1059 nM	415 nM	39 nM	36 nM	52 nM
Margetuximab	161 nM	89 nM	34 nM	218 nM	437 nM
Relative change	↑ 6.6x	↑ 4.7x	↔	↓	↓ 8.4x

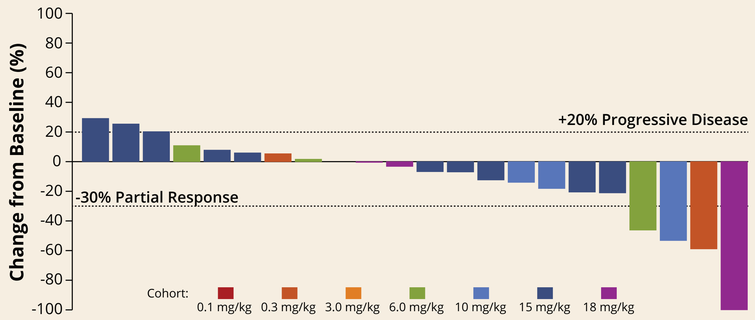
*Nordstrom JL, et al. Breast Cancer Research 13:R123, 2011

Rationale

Margetuximab Demonstrated Single Agent Activity in a Phase 1 Study

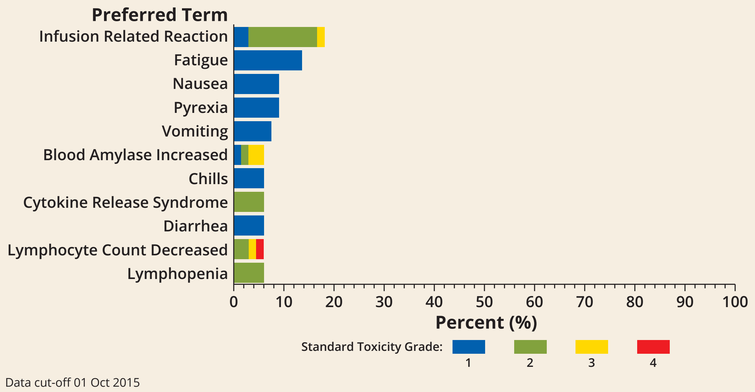
- Margetuximab was evaluated in a dose escalation and expansion study in patients with HER2+ tumors
- Margetuximab was well tolerated with mild to moderate infusion-related reaction or cytokine release syndrome the most common related adverse event
- Single agent activity was observed in patients with breast or gastric cancer
- Safety and activity profile of margetuximab was deemed acceptable to proceed with randomized study in patients with HER2+ MBC

Single-agent Activity in Phase 1 (MBC)



Data cutoff 01 Oct 2015

Related Adverse Events: All That Occured in ≥10% of All Patients



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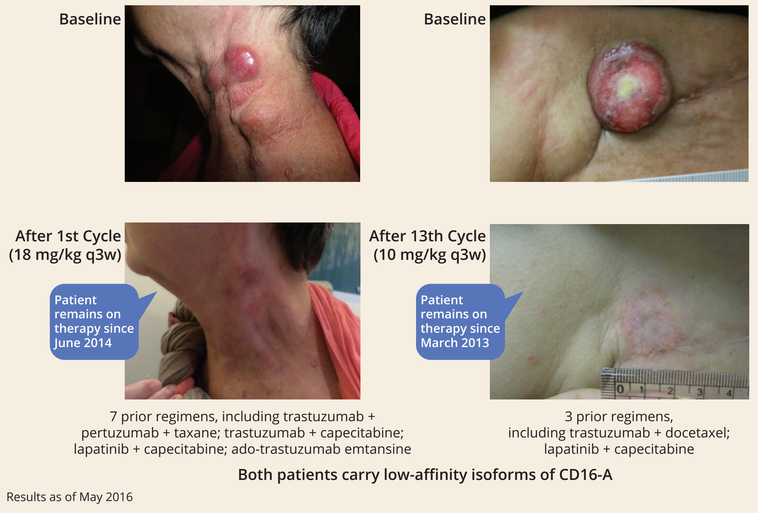
Outcomes in Heavily Pre-treated Patients



Results as of May 2016

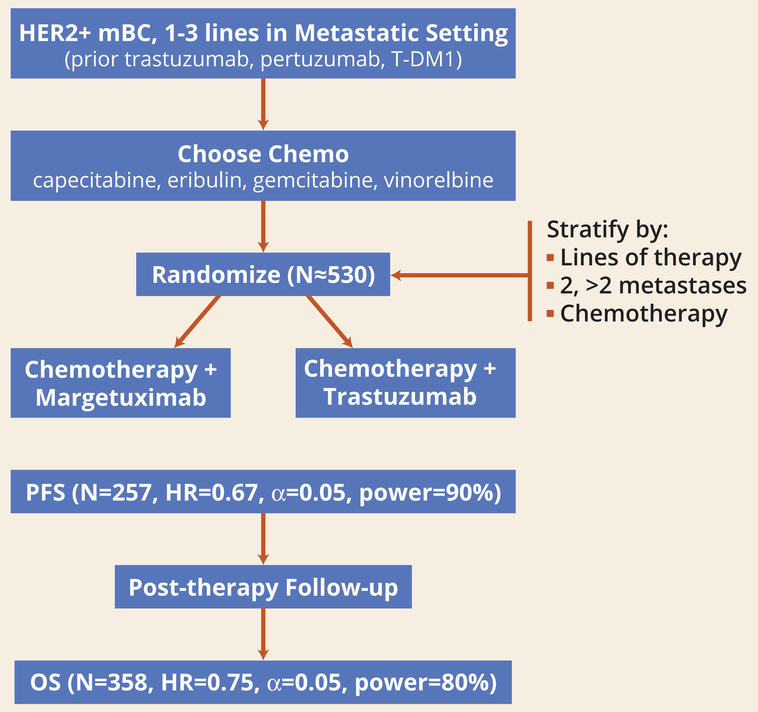
Summary

- Fc optimization leads to enhanced binding to CD16A and augmented activity in effector cell-dependent ADCC assays
- Activity is independent of FcγR isoforms
- Single-agent activity seen in heavily pre-treated HER2+ MBC patients
- Well tolerated in Phase 1 study
- There is no standard therapy for patients with HER2+ MBC who have received trastuzumab, pertuzumab and ado-trastuzumab emtansine

Key Study Objectives

- Evaluate efficacy, as measured by progression-free survival (PFS) assessed by independent review, and overall survival (OS), of margetuximab plus chemotherapy compared to trastuzumab plus chemotherapy in patients with advanced HER2+ breast cancer
- To evaluate PFS, as assessed by study investigators, of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy
- To evaluate by independent review the objective response rate (ORR) of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy
- Evaluate health-related quality of life (HRQoL), as assessed using Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI) -16 and EQ-5D-5L
- Characterize safety profile of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy

Study Schema



Study Design

- Phase 3, randomized, open-label, comparator-controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy
- Patients randomized 1:1 to receive either margetuximab or trastuzumab in combination with chemotherapy of the investigator's choice to be chosen from capecitabine, eribulin, gemcitabine, or vinorelbine
- N = 530 patients based on hazard ratio for OS of 0.75 with power of 80%
- Randomization stratified by number of metastatic sites (≤2, >2), number of lines of therapy in metastatic setting (≤2, >2), and choice of chemotherapy
- Independent radiologic review to determine PFS and ORR

Entry Criteria

Key Inclusion Criteria

- Histologically-proven metastatic or locally-advanced relapsed/refractory HER2+ breast cancer based on most recently available tumor biopsy collected from the patient. Tumors may be estrogen receptor (ER)/progesterone receptor (PR) positive or negative
- Prior treatment with pertuzumab, trastuzumab, and ado-trastuzumab emtansine in neoadjuvant, adjuvant, or metastatic setting. Prior radiotherapy, hormonal therapies, and other anti-HER2 therapies are allowed
- Prior treatment for at least one, **and no more than three**, lines of therapy in the metastatic setting. Patients must have progressed on or following, most recent line of therapy
- Resolution of all chemotherapy or radiation-related toxicities to ≤ Grade 1
- Acceptable laboratory parameters
- Negative pregnancy test and effective contraception

Key Exclusion Criteria

- Known, untreated brain metastasis. Patients with signs or symptoms of brain metastasis must have a CT or MRI performed within 4 weeks prior to randomization to specifically exclude the presence of radiographically-detected brain metastases
- History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation
- History of clinically significant cardiovascular disease
- Clinically-significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation
- Any condition that would be a contraindication to receiving trastuzumab as described in the approved local label or a condition that would prevent treatment with the physician's choice of chemotherapy

Study Status

Ongoing; 16 Countries, 192 Sites	
Austria	Israel
Belgium	Italy
Canada	Korea
Czech Republic	Netherlands
Denmark	Portugal
Finland	Spain
France	United Kingdom
Germany	United States

References

1. Musolino A, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER2/neu-positive metastatic breast cancer. J Clin Oncol. 2008;26:1789-96.

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