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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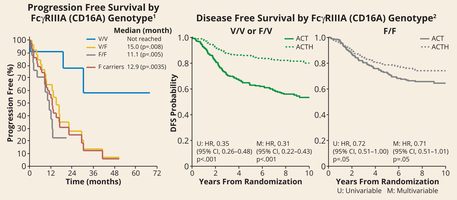
Background

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

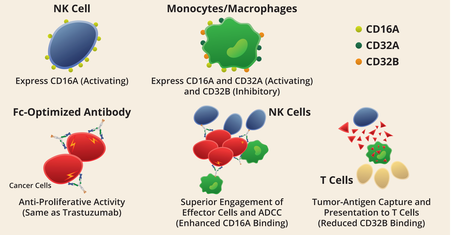
- Margetuximab derived from 4D5 and has modified IgG1 Fc domain
- Margetuximab & trastuzumab bind to same HER2 epitope with high affinity resulting in growth retardation or induction of apoptosis
- Increased ADCC activity with patient effector cells to enhance destruction of HER2+ tumor cells

Trastuzumab Activity May Differ by FcγRIIIA (CD16A) Genotype



- Fc-receptor CD16A exists in two isoforms with differing ability to activate ADCC
- Retrospective analysis of breast cancer patients treated with trastuzumab showed enhanced progression-free survival (PFS) and disease-free survival (DFS) for patients with high affinity isoform of CD16A
- Most patients (~ 80%) have low affinity CD16A isoforms (V/F, F/F)
- Margetuximab binds with high affinity to both low- and high-affinity isoforms of CD16A, potentially enhancing ADCC activity

Enhanced Binding to Immune Cells May Potentiate Antitumor Activity



Margetuximab vs. Wild Type

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

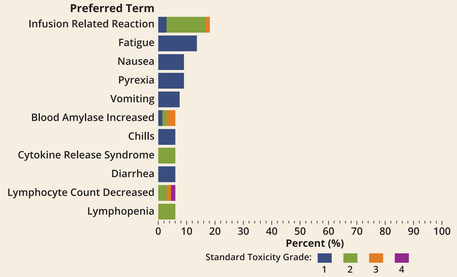
*Nordstrom JL, et al. Breast Cancer Research 13:R123, 2011

Phase 1 Study Results

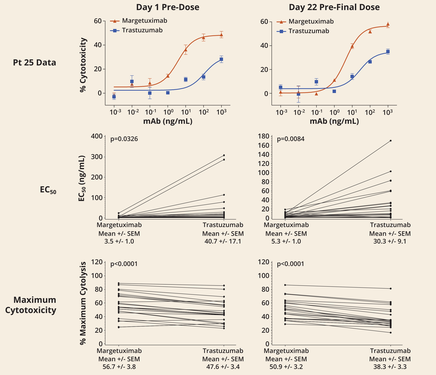
Margetuximab Demonstrated Single Agent Activity

- 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, managed well with pre-medications
- Monotherapy margetuximab activity was observed in heavily pre-treated refractory patients with breast, gastric and other HER2+ solid cancers

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



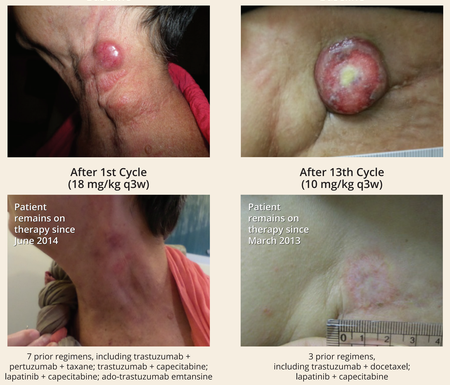
Phase 1 Ex Vivo ADCC Activity Mediated by Patient PBMCs



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 as monotherapy given weekly and Q3 Weekly

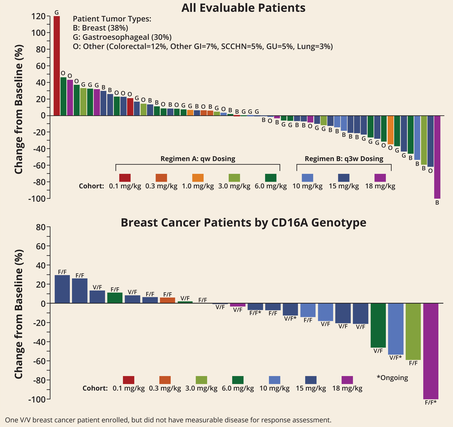
Outcomes in Heavily Pre-treated Patients



Both patients carry low-affinity isoforms of CD16A

Single Agent Activity in Heavily Pre-treated Population

Phase 1 Data

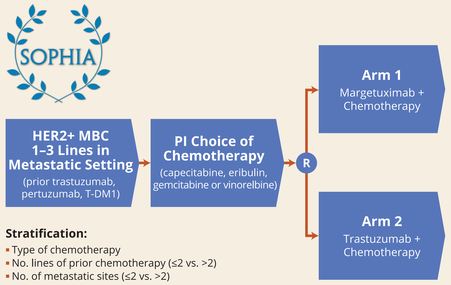


One V/V breast cancer patient enrolled, but did not have measurable disease for response assessment.

Ongoing Phase 3 Study

SOPHIA Study to Establish Superiority to Trastuzumab

Phase 3 – Randomized Global Study (n=530)



Stratification:

- Type of chemotherapy
- No. lines of prior chemotherapy (≤2 vs. >2)
- No. of metastatic sites (≤2 vs. >2)

Sequential Primary Endpoints — Progression-Free Survival and Overall Survival:

- PFS (D=257, HR=0.67, α=0.05, power=90%)
- OS (D=358, HR=0.75, α=0.05, power=80%)

Key Study Objectives

- Evaluate efficacy, as measured by 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

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 highly 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, ~200 Sites

Austria	Israel
Belgium	Italy
Canada	Netherlands
Czech Republic	Portugal
Denmark	Republic of Korea
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.

2. Gavin PG 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 Oncology. Published online November 3, 2016.

Acknowledgments

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http://ir.macrogenics.com/events.cfm