Abstract Number: 523

Updated findings of a first-in-human phase 1 study of margetuximab, an Fc-optimized chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors

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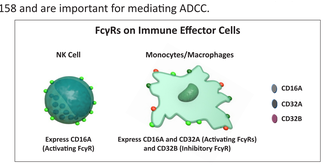
Background

- Signaling through HER2 is an important mechanism in the progression of cancers which overexpress HER2.
- In addition to blocking signaling through HER2, trastuzumab, the prototypical anti-HER2 agent, also mediates antibody-dependent cell-mediated cytotoxicity (ADCC), which may be an important mechanism for efficacy.
- Two isoforms of the CD16A (FcγRIIIA) stimulatory receptor found on natural killer (NK) cells and macrophages differ by one amino acid at codon 158 and are important for mediating ADCC.



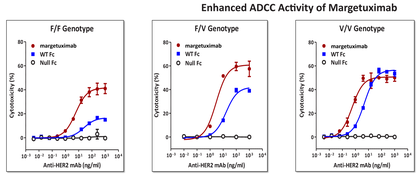
- The high affinity 158 V/V homodimer of CD16A is present on approximately 20% of the population and the lower affinity F/F homodimer and F/V heterodimer are present in the remaining 80% [1].
- A retrospective analysis of patients with metastatic breast cancer receiving trastuzumab plus taxane therapy [2] demonstrated superior outcomes in patients who were homozygous for the high affinity 158 V/V homodimer of CD16A compared to patients with lower affinity F/V heterodimers or F/F homodimers.
- Margetuximab (MGAH22) is a next-generation, molecular-engineered, Fc-optimized monoclonal antibody derived from 4D5, the parent antibody of trastuzumab. Margetuximab and trastuzumab both bind the same epitope of HER2 with similar high affinities.
- The Fc domain of of margetuximab has been engineered to substantially increase binding to both the low- and high-affinity isoforms of CD16A and substantially reduce binding to the inhibitory FcγR, CD32B [3].

Optimized FcγR Binding Properties of Margetuximab

	CD16A (FcγRIIIA) Allelic Forms		CD32A (FcγRIIA) Allelic Forms		
Antibody	F^{158} (Low Binder)	V^{158} (High Binder)	H^{131} (High Binder)	R^{131} (Low Binder)	CD32B FcγRIIB
Wild Type Fc	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

- Margetuximab and trastuzumab exhibit similar tumor-directed, effector cell-independent, anti-proliferative activity in breast cancer cells in vitro in the absence of immune effectors [3].
- In ADCC assays using effector cells from normal human subjects, margetuximab was more potent and produced greater maximum cytotoxicity than did a trastuzumab surrogate with a wild-type Fc domain [3].

Enhanced ADCC Activity of Margetuximab



Margetuximab counterparts:
- WT Fc: Wild Type Fc
- Null Fc: Fc inactivated by point mutation

Target Cells: JIMT-1 human breast cancer cell line

Effector Cells: NK cells from healthy human donors with different CD16A genotypes

E:T ratio = 3:1

Incubation Time: 24 hr

Target cell cytotoxicity: % increase in LDH release

- In transgenic mice expressing the human CD16A 158F/F low affinity FcγR, margetuximab produced superior tumor growth suppression of JIMT-1 cells, a line insensitive to growth inhibition by anti-HER2 antibodies, compared to the trastuzumab surrogate with a wild-type Fc [3].
- It is hypothesized that the enhanced ADCC activity of margetuximab could mediate greater antitumor activity compared to monoclonal antibodies with wild-type Fc domains such as trastuzumab.

References

1. Lehrnbecher T, Foster CB et al. Blood. 1999;94:4220–32
2. Musolino A, Naldi N et al. J Clin Oncol. 2008;26:1789–96.
3. Nordstrom JL, Gorlatov S et al. Breast Cancer Res. 2011 13:R123

Methods

Study Objectives

Primary Objective:

- To evaluate safety of margetuximab using two dosing regimens.

Secondary Objectives:

- To determine the maximum tolerated dose (MTD) of margetuximab.
- To characterize the pharmacokinetics (PK) and immunogenicity of margetuximab.
- To describe preliminary evidence of anti-tumor activity of margetuximab in patients with HER2+ tumors, including breast and gastric cancer.

Methods

- Patients were enrolled at 3 sites, two in the US and one in Korea using two dosing regimens.
- Regimen A: 3+3 design with sequential cohorts of 0.1, 0.3, 1.0, 3.0, and 6.0 mg/kg administered on Weeks 1, 2, 3, and 4 for the first cycle and then 3 of every 4 weeks for subsequent cycles.
- Regimen B: 6+6 design with sequential cohorts of 10, 15, and 18 mg/kg administered once every 3 weeks.
- Margetuximab was administered intravenously over 120 minutes with pre-medication.
- MTD was defined as the highest dose evaluated at which <33% of patients in the cohort experience DLT.
- Tumor response was evaluated by CT scan every 6 weeks using RECIST v1.1. Patients who did not demonstrate disease progression and otherwise tolerated margetuximab were allowed to remain on study.
- Cardiac function was monitored by multi-gated acquisition vetriculography (MUGA) or echocardiograms performed at baseline and at the end of every other treatment cycle.
- Blood samples for pharmacokinetics were collected prior to and at 1, 2, 4, 6, ~24, ~72, and ~96 hours after infusion of the first dose of margetuximab and at regular intervals thereafter.
- A quantitative sandwich enzyme-linked immunosorbent assay (ELISA) was used to measure margetuximab concentration in serum.
- A 2-compartment model with parallel linear and Michaelis-Menten elimination and allometric scaling of all clearance and volume parameters was used to describe the observed data. Standard errors were obtained from the NONMEM covariance step.
- The study protocol was reviewed and approved by relevant institutional review boards or ethics committees and informed consent obtained from all patients.
- The study was registered with clinicaltrials.gov (NCT01148849).

Key Inclusion Criteria

- Histologically- or cytologically-confirmed carcinoma that overexpressed HER2 by immunohistochemistry (IHC) (2+ or 3+) by local laboratory testing;
- Disease progression during or following the last treatment regimen;
- Age ≥18 years and had life expectancy ≥3 months;
- Eastern Cooperative Oncology Group performance status score ≤1;
- Measurable disease by RECIST 1.1 criteria;
- Adequate bone marrow, renal, and hepatic function;
- Left ventricular ejection fraction (LVEF) ≥50%; and
- Completion of immunosuppressive medications, antineoplastic therapies, or vaccinations prior to enrollment.

Key Exclusion Criteria

- Pregnant or breastfeeding women;
- Lifetime anthracycline exposure >360 mg/m2 of doxorubicin or equivalent;
- Heart disease corresponding to New York Heart Association class III or IV;
- Significant pulmonary compromise; or
- Treatment with radiotherapy and/or chemotherapy within 4 weeks, or monoclonal antibodies within 3 half-lives, prior to study entry.

Patient Demographics

Characteristic	MBC (N= 23)	All (N= 60)
Age (years):		
N	23	60
Median (Range)	55.0 (36.0 - 72.0)	59.5 (36.0 - 83.0)
Gender [n/N (%)]:		
Female	23/23 (100)	33/60 (55.0)
Male	0	27/60 (45.0)
Race [n/N (%)]:		
Asian	17/23 (73.9)	40/60 (66.7)
Black	1/23 (4.3)	3/60 (5.0)
White	5/23 (21.7)	17/60 (28.3)
Prior HER2 Therapy	22/23 (95.7)	39/60 (65.0)
Prior Lines of Therapy	4 (3-7)	3 (1-7)

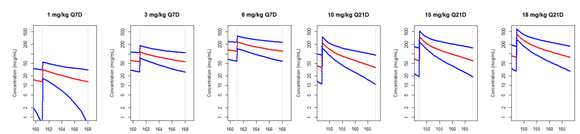
Cancer Type	N (%)
Breast	23 (38.3)
Gastroesophageal	18 (30.0)
Colorectal	7 (11.7)
Other Gastrointestinal	4 (6.7)
Head and Neck SCC	3 (5.0)
Genitourinary	3 (5.0)
Lung	2 (3.3)

Results

Safety

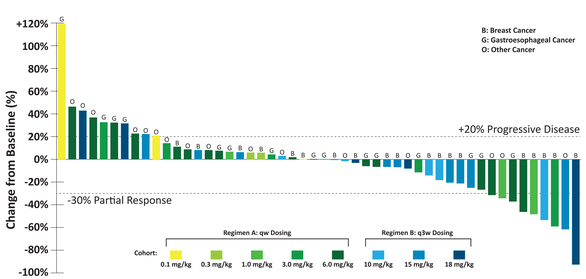
Preferred Term	All Patients	All Related	Grade 3,4	Related Grade 3,4
Hematological				
Lymphopenia/lymphocyte count decreased	17 (28)	8 (13)	10 (17)	2 (3)
Anaemia	10 (17)	2 (3)	2 (3)	.
Non-hematological				
Infusion related reaction/CRS	14 (23)	14 (23)	1 (2)	1 (2)
Nausea	12 (20)	6 (10)	.	.
Pyrexia	12 (20)	6 (10)	1 (2)	.
Diarrhoea	11 (18)	4 (7)	.	.
Decreased appetite	10 (17)	3 (5)	1 (2)	.
Fatigue	10 (17)	9 (15)	1 (2)	.
Vomiting	9 (15)	4 (7)	1 (2)	.
Alkaline phosphatase increased	7 (12)	2 (3)	1 (2)	1 (2)
Amylase increased	7 (12)	4 (7)	3 (5)	1 (2)
Cough	7 (12)	1 (2)	.	.
Lipase increased	7 (12)	3 (5)	5 (8)	1 (2)
Chills	6 (10)	4 (7)	.	.
Dizziness	6 (10)	2 (3)	.	.

Pharmacokinetics



Median (red) and 90% prediction intervals (blue) of simulated concentration-time profiles following IV administration of 1, 3, 6 mg/kg QW and 10, 15, 18 mg/kg Q3W doses. For each dosing regimen, concentrations were simulated for 1000 patients with covariate values sampled with replacement from analysis population.

% Reduction of Target Lesions: Best Reduction - Evaluable Population

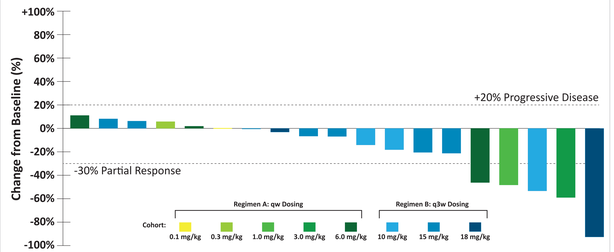


Acknowledgements

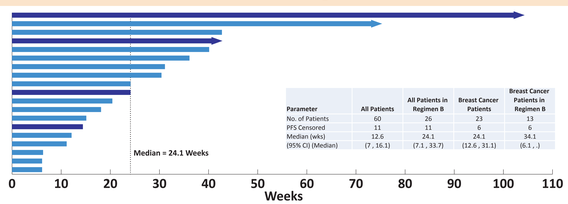
The authors thank the patients and their families who participated in this study.
Funding was provided by MacroGenics, Inc. and Green Cross.

Clinical Activity in Breast Cancer

% Reduction of Target Lesions: Best Reduction - Breast Cancer



Time to Partial Response and Progression - Breast Cancer



Parameter	All Patients	All Patients in Regimen B	Breast Cancer Patients	Breast Cancer Patients in Regimen B
No. of Patients	60	26	23	13
PFS Censored	11	11	6	6
Median (wks)	12.6	24.1	24.1	34.1
(95% CI) (Median)	(7 , 16.1)	(7.1 , 33.7)	(12.6 , 31.1)	(6.1 , .)

Includes evaluable breast cancer subjects with both baseline and post-baseline target lesion measurements. Subjects with triangle markers continued on therapy as of data extraction date (10APR2015). **Bars in dark blue indicate confirmed partial responses.** Note: all patients had received earlier HER2-directed therapy.

Conclusions

Basic Science:

- Margetuximab is a next-generation, molecularly-engineered antibody that is designed specifically to bind more effectively to all isoforms of the activating FcR and less effectively to the inhibitory FcR.
- As a result of these modifications, margetuximab demonstrates enhanced ADCC, irrespective of the FcR isoform and across tumor cell lines with HER2 expression ranging from 1+ to 3+ intensity.

Clinical Results:

- Margetuximab was well-tolerated. Infusion reactions were generally mild overall, and were well-controlled with pre-medication. No cardiac dysfunction was noted.
- Monotherapy anti-tumor activity observed across several tumor types including patients with breast, gastric, colorectal and head/neck cancer.
- Monotherapy antitumor activity in breast cancer patients despite extensive prior therapy and progression during prior HER2-directed therapy.
- Median PFS of approximately 5.5 months in patients with HER2+ MBC compares favorably to patients who received chemo+trastuzumab on TH3RESA (3.2 months).
- Pivotal Phase 3 study (SOPHIA) to start this summer will investigate margetuximab+chemotherapy vs. trastuzumab+chemotherapy.

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