# High Frequency of HER2-specific Immunity Observed in Patients (pts) with HER2<sup>+</sup> Cancers Treated with Margetuximab (M), An Fc-enhanced Anti-HER2 Monoclonal Antibody (mAb)

# **Abstract #1030**

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### Abstract

- •Background: Previous studies have shown that 44–71% of trastuzumab (T)-treated pts develop HER2-specific immunity<sup>2,3,4</sup>. M is an Fc-engineered mAb that shares similar HER2 binding and antiproliferative activity as T. The Fc region of M has been engineered for increased affinity to the activating FcyRIIIA (CD16A) and lower binding to the inhibitory FcyRIIB (CD32B), attributes that may enhance the mAb's immune function, such as antigen presentation.
- Methods: HER2<sup>+</sup> cancer pts who progressed on prior therapy received M (0.1–6 mg/kg QW for 3 of every 4 weeks [N = 34]; or 10–18 mg/kg Q3W [N = 32]) in phase 1 trial NCT01148849. PBMC and plasma were collected pre-dose and 50 days post-dose for 46 pts and >4 years for 3 pts on long-term treatment. Response to HER2 or control antigens (Ag) was assessed by IFNγ ELISpot and antibody (Ab) ELISA. In 14 pts, T-cell repertoire was assessed by immunosequencing the TCR beta locus.
- Results: Following M treatment, mean frequencies of IFNy-producing T cells specific for intra- or extracellular fragments of HER2 increased by 2.5 to 6-fold (p <0.0027, paired t test). Most (95%) of subjects responded to ≥2 of 6 (median = 4) HER2 Ag. Mean HER2-specific Ab concentration increased by 19–54% (p <0.0001), with all subjects responding to  $\geq 2$  (median = 4) of the 6 Ag. A small 1.6-fold increase in IFNy response to control CMV/EBV/Flu (but not tetanus or cyclin D1) peptides was observed; no increase in Ab response to control Ag was noted. Subsets of HER2-specific T-cell and Ab responses persisted during long-term treatment. Median T-cell clonality increased by 54% (p = 0.003), with an average of 138 clones expanding and 181 clones contracting.
- Conclusions: Treatment of HER2<sup>+</sup> cancer with M was associated in this analysis with enhanced HER2-specific T-cell and Ab responses together with increased T-cell clonality, indicative of a more focused T-cell repertoire. The high frequency of HER2-specific immunity in M-treated patients (>94%) is consistent with its enhanced Fc region contributing to linkage of innate and adaptive immune responses.

# Introduction

### Margetuximab

- HER2 binding and Fc-independent (e.g., antiproliferative) activities *in vitro* are similar to those of trastuzumab • Fc region was engineered to increase binding to CD16A (activating FcyR) and reduce binding to CD32B
- Engineered Fc region enhances ADCC and NK cell activation/proliferation in vitro, and may also enhance immune function, such as antigen presentation

### Study CP-MGAH22-01

- Phase 1 trial enrolled subjects with relapsed/refractory HER2<sup>+</sup> carcinomas
- Single-agent margetuximab was administered at 0.1–6 mg/kg for 3 of every 4 weeks (Regimen A) or 10–18 mg/kg once every 3 weeks (Regimen B)
- Of 60 evaluable patients: confirmed PR in 7 (11.7%), SD in 31 (51.7%)
- *Ex vivo* assays with PBMCs collected from study subjects show that margetuximab exhibits greater ADCC potency than trastuzumab (Refer to ADCC data below)
- To assess margetuximab's ability to enhance adaptive immunity, paired pre- and post-treatment samples were evaluated for changes in T-cell repertoire (TCR beta immunosequencing), antigen-specific T-cell responses (ELISpot), and antigen-specific antibody concentrations (ELISA)

### **Characteristics of Subjects in CP-MGAH22-01**

Characteristic	Regimen A N=34	Regimen B N=32	Total N=66
Tumor Type, n (%)			
Breast	10 (29%)	17 (53%)	27 (41%)
Gastroesophageal	12 (35%)	8 (25%)	20 (30%)
Colorectal	5 (15%)	0	5 (8%)
Gall Bladder	0	2 (11%)	2 (3%)
Lung	2 (6%)	0	2 (3%)
Other*	5 (15%)	5 (28%)	10 (15%)
Number of Prior Chemotherapy Regimens			
Median (Range)	3 (1–7)	3 (1–7)	3 (1–7)
Prior Anti-HER2 Therapy, n (%)			
Any	19 (56%)	26 (81%)	45 (68%)
Trastuzumab	15 (44%)	25 (78%)	40 (61%)
Lapatinib	13 (38%)	15 (47%)	28 (42%)
Other	7 (21%)	6 (19%)	15 (23%)

\*Other tumors: rectal, sigmoid colon, ampulla of Vater, bladder, endometrial cancer, esophageal-squamous cell carcinoma, malignant tumor of lacrimal gland, salivary duct cancer, submandibular gland cancer, and transitional cell carcinoma of the renal pelvis.

### Margetuximab Mediates ADCC with Greater Potency than Trastuzumab in *Ex Vivo* Assays with PBMCs from CP-MGAH22-01 Subjects



C with significantly greater potency (lower EC<sub>50</sub> values) than trastuzumab in ex vivo assays utilizing PBMC effector cells from subjects collected before (Day 1) or after margetuximab treatment (Day 22)

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181 contracted clones at Day 50





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# **T-cell Repertoire Responses**

A: T-cell clonality scores at Day 1 (pre-treatment) and Day 50 (post-treatment) are presented. Columns show the mean scores and lines track the changes individual subjects. The p value for the paired comparison (Mann-Whitney U test) is provided. **B:** Numbers of expanded T-cell clones at Day 50. **C:** Numbers of contracted T-cell clones at Day 50. Bar represents the mean value.

T-cell clonality increased significantly by an average of 54%

Increases in T-cell clonality occurred in 12 of 14 subjects, with an average of 138 expanded clones and

Expanded and contracted T-cell clones are evident in all subjects treated with margetuximab



ubiect (N = 41). P values for the paired comparisons (Wilcoxon matched pairs ranked sum test) for each antigen are shown • Frequencies of T cells specific to the different HER2 antigens increased significantly in response to treatment with margetuximab

## HER2-specific Antibody Responses are Enhanced Following Margetuximab Treatment



Concentrations of antibodies specific to HER2 or control antigens were determined by ELISA (conducted by Post responses for each subject (N = 48). P values for the paired comparisons for each antigen are shown. • Antibodies specific to the different HER2 antigens increased significantly in response to treatment with margetuximab

# **Antigen Descriptions** HER2 Antigen HER2 ECD Fragment HER2 ICD HER2 p59 HER2 p85 HER2 p422 HER2 p885 **Control Antigen** Cyclin D1 (control) CEA (carcinoembryonic antigen) TT (tetanus toxoid) CEF (CMV/EBV/Influenza pool)

HER2 protein domains: ECD (23-652), transmembrane (653-675), ICD (676-1255). The HER2 p59, HER2 p85, HER2 p422, HER2 p885, Cyclin D1 peptides are degenerate HLA-DR binding T cell epitopes

# HER2-specific Immune Responses



### High Frequency of Enhanced HER2-specific Antibody Responses Following Margetuximab Treatment

![](_page_0_Figure_51.jpeg)

HER2 antigens (median = 4)

94% of subjects exhibited enhanced antibody responses to at least one HER2 antigen

Antibody responses were defined as positive if the concentration of HER2-specific antibodies in the in the post-treatment sample increased by  $\geq$  2-fold compared to the pre-treatment baseline sample. post-treatment sample increased by  $\geq$  25% compared to the pre-treatment baseline sample<sup>2</sup>.

![](_page_0_Picture_55.jpeg)

![](_page_0_Figure_64.jpeg)

cell and antibody responses specific to HER2 or cor Days 1 and 50 due to sample loss in transit.

HER2-specific T-cell responses generally declined at long-term times compared to Day 50, but some remained elevated or showed increases: 4 of 6 HER2 antigens (Subj 035); HER2 p422 (Subj 044); HER2 ICD, ECD and p59 (Subj 050)

ol antigens are shown. Data are mean ± SEM. For Subject 035, T-cell responses were not determined

HER2-specific antibody responses were maintained at the long-term times, generally at increased levels, particularly for HER2 ECD and p422 (Subj 035) and HER2 ICD (Subj 044)

### Subjects on Long-term Margetuximab Treatment

Subject 035

- ER<sup>-</sup> PR<sup>-</sup> HER2<sup>+</sup> (IHC3<sup>+</sup>) breast cancer; CD16A-158 VF genotype – 10 mg/kg margetuximab for 102 cycles (6 years) as of March 2019; ongoing – Paclitaxel added at cycle 90
- PR continues through cycle 100
- Subject 044
- ER<sup>-</sup> PR<sup>-</sup> HER2<sup>+</sup> (IHC3<sup>+</sup>) breast cancer; CD16A-158 FF genotype
- 15 mg/kg margetuximab for 94 cycles (5.4 years) as of April 2019; ongoing - SD continues through cycle 92
- Subject 050
- HER2<sup>+</sup> (IHC3<sup>+</sup>) breast cancer; CD16A-158 FF genotype
- 18 mg/kg margetuximab for 78 cycles (4.8 years) as of March 2019; ongoing
- PR continues through cycle 73

# Conclusions

- Relapsed/refractory HER2<sup>+</sup> cancer subjects treated with margetuximab exhibited significant increases in: - HER2-specific T-cell responses
- HER2-specific antibody responses
- T-cell clonality related to T-cell clone expansion and contraction
- Subsets of the HER2-specific T-cell and antibody responses persisted in 3 subjects that received long-term (4.8–6 years) treatment with margetuximab
- The high frequency (≥94%) of enhanced HER2-specific immunity in patients treated with margetuximab s nominally higher that that previously reported for patients treated with trastuzumab (44–71%)<sup>2,3,4</sup> These data are consistent with margetuximab contributing to activation of both innate and adaptive immune responses, ostensibly via enhanced Fcy receptor binding by its engineered Fc domain

### References

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