Long-Term Responders to Single-Agent Margetuximab, an Fc-Modified Anti-HER2 Monoclonal Antibody, in Metastatic HER2+ Breast Cancer Patients with Prior Anti-HER2 Therapy

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The San Antonio Breast Cancer Symposium® December 4–8, 2018, San Antonio, TX

Background

- Margetuximab is an investigational Fc-engineered anti-HER2 antibody that recognizes the same epitope as trastuzumab
- The engineered Fc domain of margetuximab confers increased affinity in vitro for allotypes of activating CD16A Fc receptors on NK cells and decreased affinity for inhibitory CD32B Fc receptors, compared to trastuzumab
- Margetuximab was well tolerated at all doses in a Phase 1 monotherapy study of 66 patients with relapsed or metastatic HER2+ cancer across multiple indications
- Among 24 breast cancer patients evaluable for response, all previously treated with at least one HER2-targeted therapy (11.48% experienced tumor reduction, with confirmed partial responses in 4/17)
- Ex-vivo analyses of NK cells from margetuximab treated patients showed increased mononuclear cell (PBMC) samples confirmed margetuximab’s ability to enhance antibody dependent cell-mediated cytotoxicity (ADCC) over that of trastuzumab
- We report on 3 breast cancer patients enrolled after anti-HER2 therapy failure with durable (≥3.5 years) SD (1) or PR (2) on margetuximab

Methods

- Enrolled patients had histologically or cytologically confirmed carcinoma with documented HER2 overexpression by IHC (2+ or 3+)
- Patients evaluated for HER2 progression during following last therapy
- Eligibility included life expectancy ≥3 months; PS ≤1, measurable disease by RECIST 1.1; adequate bone marrow, renal, hepatic function; and LVEF ≥50%
- Anti-HER2 immune responses were evaluated with PBMC or plasma samples collected at Day 1 (prior to dosing) and Day 30 (post-dosing)
- HER2-specific T-cell responses: ELISPOT
  - After incubation of PBMCs (25,000 per well) with antigens (HER2 or control peptides), the numbers of cells making IFN-γ were quantified
  - Data are expressed as number of antigen-specific T-cells per million PBMC
- HER2-specific endogenous antibody responses: ELISA
  - Antibodies were captured by wells coated with HER2 or control antigens
  - Pre-existing Abs were present in plasma (0.2 to 0.8 µg/mL)
  - Control peptide responses stable
  - Endogenous anti-HER2 antibodies
  - Pre-existing Abs present in plasma (0.3 to 1.1 µg/mL)
  - Levels generally increased after margetuximab treatment
  - Greatest increases were for HER2 p422 and HER2 ECD antibodies

Conclusions

- Single-agent margetuximab was well-tolerated, including in long-term responders with HER2+ metastatic breast cancer up to 5.25 years
- There were no cardiac toxicities or grade 3 treatments-related adverse events thus far during term follow-up for these 3 patients
- Durable responses of pre-treated metastatic breast cancer patients were seen
- Margetuximab induced significant increases in HER2-specific T-cell responses and more modest increases in the levels of pre-existing HER2-specific antibody responses in these patients

Results

Patient 035

- 47-year-old woman with coronary artery disease and advanced ER/PR-HER2+ (HR+) breast cancer
- Baseline: neutropenia, G1 anemia, G1 bradycardia, left arm edema
- Margetuximab induced significant increases in HER2-specific T-cell responses and decreased affinity for inhibitory CD32B Fc receptors, compared to trastuzumab
- Antibody concentrations in plasma (µg/mL)

<table>
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<th>Antigen-specific Antibodies</th>
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<th>D1 Pre</th>
<th>D50</th>
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Acknowledgments

Our gratitude to participating patients and their families, ELISA and ELISPOT assays, immunologic analysis, and People of Immunology and Courtney Clark, Department of Immunology, Mayo Clinic, Jacksonville, Florida.

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