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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Abstract 1375

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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 all allotypes of activating CD16A Fcγ receptors on NK cells and decreased affinity for inhibitory CD32B Fcγ receptors, compared to trastuzumab
- Margetuximab was well tolerated at all doses in a Phase 1 montherapy 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%)[1]
- Ex-vivo analyses of patient peripheral blood 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/cytologically-confirmed carcinoma with documented HER2 overexpression by IHC (2+ or 3+) and disease 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%
- Margetuximab was given by IV at 0.1–6.0 mg/kg for 3 of every 4 weeks or once every 3 weeks (10–18 mg/kg)
- Anti-HER2 immune responses were evaluated with PBMC or plasma samples collected at Day 1 (prior to dosing) and Day 50 (post-dosing)
- HER2-specific T-cell responses: ELISPOT
  - After incubation of PBMCs (250,000 per well) with antigens (HER2 or control peptides), the number of cells making IFN-γ was quantitated
  - 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, then detected with HRP-conjugated anti-human IgG
  - Data are expressed as plasma concentration (μg/mL) of antigen-specific antibodies
- HER2-specific protein/peptides: HER2 ECD fragment (aa 22-122), HER2 p59 class II peptide (aa 59-73), HER2 p88 class II peptide (aa 85-99), HER2 p422 class II peptide (aa 422-436), HER2 ICD protein (aa 676-1255), HER2 p885 class II peptide (aa 885-899)
- Control peptides: Pan class II binding cyclin D1 peptide (aa 40-54), Tetanus toxoid (TT), and CMV/EBV/Influenza (CEF) – mixture of 9mers

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 treatment-related adverse events thus far during long 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

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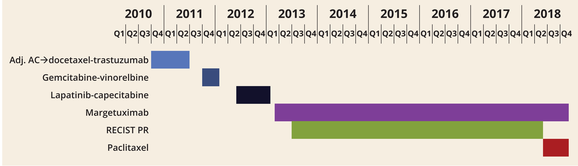
Results

Patient 035

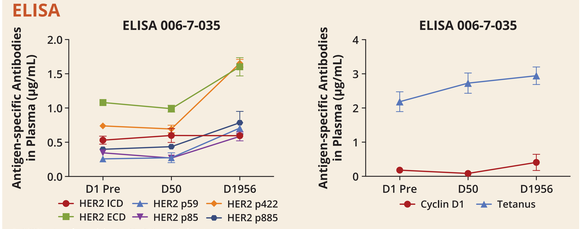
CD16 158^{VF}

Past Medical History	▪ 47-year-old woman with coronary artery disease and advanced ER-PR-HER2+ (IHC 3+) breast cancer ▪ Baseline: neuropathy, G1 anemia, G1 bradycardia, left arm edema
Cancer Disease History	▪ L breast cancer (IDC) pT2pN3M0 → L MRM with ALND (level 3) on 21 Oct 2010 ▪ Adjuvant AC #4 → docetaxel + trastuzumab #4 followed by adjuvant trastuzumab (Nov 2010 – Jun 2011) & adjuvant radiotherapy of L chest wall and L breast Feb-Mar 2011
Study Therapy	▪ **10 mg/kg single-agent margetuximab started Mar 2013,** 95 cycles to date ▪ After disease progression observed in Jun 2018, paclitaxel added; combination ongoing
Margetuximab-related AEs	▪ G1 dermatits acneiform Jan 2014, G2 increased amylase Feb 2015



- Endogenous anti-HER2 antibodies
  - Pre-existing Abs were 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

ELISA

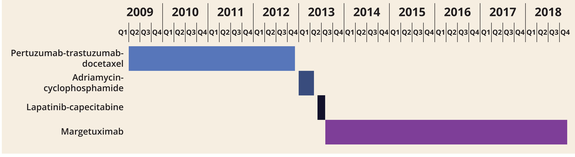


ELISPOT not performed due to D1–D50 sample loss in transit.

Patient 044

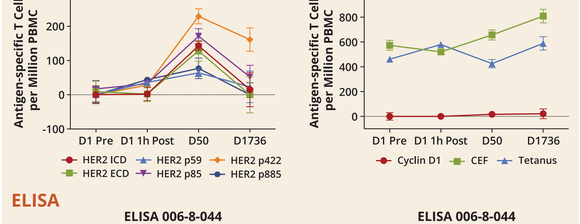
CD16 158^{FF}

Past Medical History	▪ 59-year-old woman with metastatic ER-PR-HER2+ (IHC 3+) breast cancer ▪ Baseline: G1 neuropathy
Cancer Disease History	▪ L breast cancer (IDC) cT4cN3M1(lung), metastatic breast cancer diagnosed 20 Mar 2009
Study Therapy	▪ **15 mg/kg single-agent margetuximab started Nov 2013,** 85 cycles to date, ongoing
Margetuximab-related AEs	▪ G2 lymphopenia Feb 2014

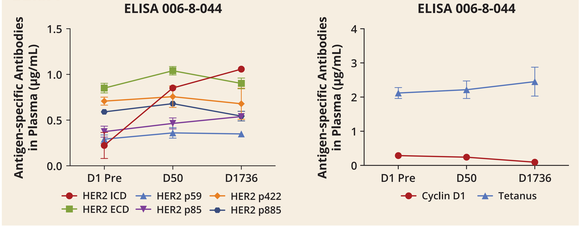


- Anti-HER2 T-cell responses
  - Significant increases at Day 50 that decline over time. Highest response for HER2 p422
  - No response to Cyclin D1 negative control peptide and stable CEF/tetanus responses
- Endogenous anti-HER2 antibodies
  - Pre-existing Abs present (0.2–0.9 μg/mL)
  - HER2 p85 antibodies increased slightly after margetuximab
  - HER2 ICD antibodies increased 5-fold after margetuximab
  - Tetanus antibodies were stable, and anti-Cyclin D1 declined

ELISPOT



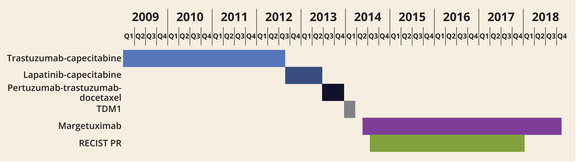
ELISA



Patient 050

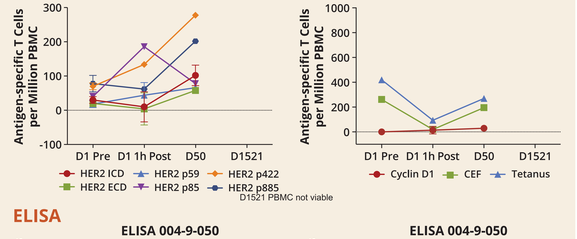
CD16 158^{FF}

Past Medical History	▪ 63-year-old woman with hypothyroidism and advanced HER2+ (IHC 3+) breast cancer ▪ Baseline: hand/foot syndrome, mucositis, systolic murmur
Cancer Disease History	▪ T1N0MX (L posterior triangle) breast cancer diagnosed **May 2000** → R lumpectomy, adjuvant CMF ▪ Jul 2003 local recurrence → R mastectomy, adjuvant anastrazole, Aug 2004 R mastectomy
Study Therapy	▪ **18 mg/kg single-agent margetuximab started Jun 2014,** 70 cycles to date, ongoing
Margetuximab-related AEs	▪ G1 AST/ALT increased Jun 2014



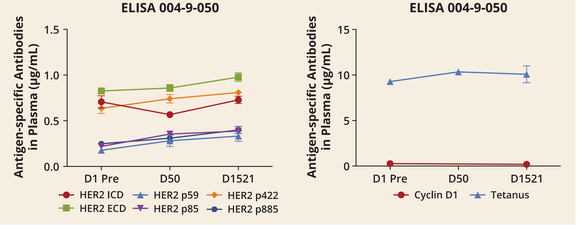
- Anti-HER2 T-cell responses
  - Measurable responses at baseline, increased 2–3 fold at Day 50, highest for p422 and p885
  - Control peptide responses stable
- Endogenous anti-HER2 antibodies
  - Pre-existing Abs present in plasma (0.2 to 0.8 μg/mL)
  - Levels increased slightly after margetuximab

ELISPOT



D1521 PBMC not viable

ELISA



Reference

1. Y. J. Bang, Annals of Oncology, Volume 28, Issue 4, 1 April 2017.

Acknowledgments

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