Margetuximab Combines Distinct Mechanisms of Action to Mediate TPS219

### Background

- **Prospective for advanced HER2+ disease,** gastric cancers remain poor with median survival just beyond one year. Trastuzumab in combination with chemotherapy is the initial treatment of choice, but therapeutic options targeting HER2 beyond trastuzumab are poorly defined just beyond one year. Trastuzumab in combination with chemotherapy is the initial treatment of choice, but therapeutic options targeting HER2 beyond trastuzumab are poorly defined.
- Diminished binding to inhibitory Fc receptor, CD32B
- Enhanced binding to low affinity versions of activating Fc receptor, CD16A

### Objective

- **Margetuximab vs Wild-type Anti-HER2 Antibody**
- **Mechanism of Action**
  - Enhanced killing by NK cell and macrophage activation in vitro
  - Fc receptors occur in two allelic forms with different abilities to activate ADC

### Methods

- **Study Design**
  - This study evaluates a chemotherapy free-combination of margetuximab + pembrolizumab in patients with HER2+ gastric and GEJ cancers.
- **Patients and Treatment**
  - From patients with HER2+ gastric and GEJ cancers who have failed previous trastuzumab therapy were enrolled in this study.
  - Patients were randomized into two cohorts based on FcgRIIIA (CD16A) genotype.

### Results

- **Progression Free Survival by FcgRIIIA (CD16A) Genotype**
- **Key Study Objectives**
  - **Primary Objective**
    - Investigate preliminary anti-tumor activity by objective response rate (ORR) and response duration
  - **Secondary Objectives**
    - Investigate preliminary OS and PFS
    - Characterize pharmacodynamic activity of combination
    - Characterize pharmacokinetics and immunogenicity of combination

### References

- Stagg et al. Anti–ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti–PD-1 or anti-CD137 mAb therapy. PNAS 2011 108 (17) 7142-7.

### Conclusions

- **Key Inclusion and Exclusion Criteria**
  - **Inclusion Criteria**
    - Metastatic breast cancer patients with high affinity Fc receptors had prolonged PFS with trastuzumab
  - **Exclusion Criteria**
    - Active infection within 7 days of study initiation
    - Clinically significant cardiovascular disease and GI disorders
    - History of autoimmune disease [except vitiligo]
    - Symptomatic CNS metastases

### References