**Phase 1b/2 Study of Margetuximab Plus Pembrolizumab in Advanced HER2+ Gastroesophageal Junction or Gastric Adenocarcinoma**

**Background**
- Trastuzumab + chemotherapy is standard treatment in 1st line advanced HER2+ gastrointestinal adenocarcinoma (GEA).
- Margetuximab: anti-HER2 monoclonal antibody with an extended Fc domain that allows for the activating FcγRIα (CD16A) receptor on NK cells and decreases affinity for the inhibitory CD32β (FcyRIIB) receptor.
- Designed to mediate antibody-dependent cellular cytotoxicity (ADCC) against HER2-positive tumors.
- Outcomes for trastuzumab-treated breast cancer patients who carry lower-affinity CD16A-FcγR3A receptor on NK cells/monocytes and R2B (CD16A) receptor are inferior compared to those with high affinity for the activating FcγR1A.
- Loss of HER2 amplification may occur after trastuzumab failure in a subset of GEA patients.
- Outcomes for trastuzumab-treated breast cancer patients who carry lower-affinity CD16A-FcγR3A receptor on NK cells/monocytes and R2B (CD16A) receptor are inferior compared to those with high affinity for the activating FcγR1A.
- Pembrolizumab and nivolumab approved for 3rd-line treatment of recurrent PD-L1+ gastric (GC) and gastroesophageal junction or gastric cancer (GEJ) post trastuzumab failure.
- Preclinical studies suggest that engagement of innate and adaptive immunity with the combination of anti-HER2 antibodies and PD-1/PD-L1 checkpoint inhibition could advance greater antitumor activity than either agent alone.
- Goal: Develop a chemotherapy-free approach for the treatment of gastroesophageal cancer.

**Objectives**
- Patient Population: 2nd line HER2+ gastric cancer (GC) post trastuzumab failure.
- Cohort Expansion evaluated safety and ORR by RECIST v1.1 in 2nd line patients with gastroesophageal junction or gastric cancer (GEJ) post trastuzumab failure.
- Pembrolizumab and nivolumab approved for 3rd-line treatment of recurrent PD-L1+ gastric (GC) and gastroesophageal junction or gastric cancer (GEJ) post trastuzumab failure.
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**Methods**
- Dose escalation evaluated 10 mg/kg and 20 mg/kg and 200 mg pembrolizumab (pembro) for 2nd line or higher.
- Cohort expansion evaluated safety and ORR by RECIST v1.1 in 2nd line patients.
- Disease control rate (DCR) = proportion of patients with complete response (CR) + partial response (PR) + stable disease (SD).
- Combination given 21 days every 28 days; response assessed every 6 weeks.
- ctDNA analyzed in a subset of patients by plasma circulating tumor (ct)DNA analysis prior to Cycle 1.

**Results**
- Pembrolizumab 200 mg + Marge 15 mg/kg (Dose Level 2) was well-tolerated overall.
- 55% of patients experienced a treatment related AE (TRAE), most ≤ Grade 2.
- Most common TRAEs: nausea, vomiting, diarrhea, and fatigue.
- No clear association between response and CD16A genotype observed.
- Response rate higher and PFS longer in gastric vs GEJ cancer, particularly in patients with HER2 3+ at time of diagnosis.
- Gastric cancer compared to GEJ tumors has a higher rate of retention of HER2 3+ at time of diagnosis.
- Retained HER2 3+ at time of diagnosis.
- Margetuximab + pembrolizumab is a well-tolerated, chemotherapy-free combination that has shown previous antitumor activity in 2nd line patients with advanced/hyperprogressive gastric or gastroesophageal junction adenocarcinoma.

**Conclusion**
- Margetuximab + pembrolizumab is a well-tolerated, chemotherapy-free combination that has shown previous antitumor activity in 2nd line patients with advanced/hyperprogressive gastric or gastroesophageal junction adenocarcinoma.
- Response rate higher and PFS longer in gastric vs GEJ cancer, particularly in patients with HER2 3+ at time of diagnosis.
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