A Phase 1b/2, Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesophageal (GEJ) Junction or Gastric Cancer

Abstract TPS219

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Background

- Prognosis for advanced HER2+ GEJ and gastric cancers remains 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
- Margetuximab is an Fc-enhanced anti-HER2 monoclonal antibody (mAb) that is modified to enhance antibody-dependent cellular cytotoxicity (ADCC). It recognizes the same epitope, and binds with similar affinity as trastuzumab

Margetuximab Combines Distinct Mechanisms of Action to Mediate Antitumor Activity

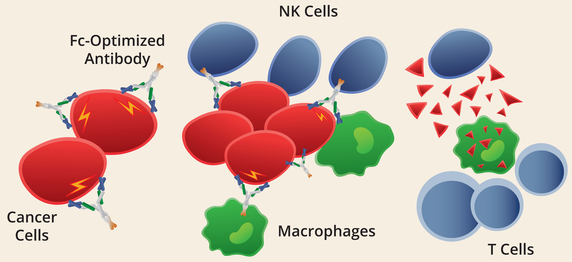
- Fc domain modifications enhance NK cell and macrophage activation in vitro[1]
  - Fc receptors occurs in two allelic forms with different ability to activate ADCC
  - Most patients (~80%) have low affinity isoform (V/F, F/F)
  - Enhanced binding to low affinity variants of activating Fcγ receptor, CD16A
  - Diminished binding to inhibitory Fcγ receptor, CD32B

Margetuximab vs Wild-type Anti-HER2 Antibody

Antibody	CD16A (FcγRIIIA) Allelic Forms		CD32A (FcγRIIA[1]) Allelic Forms		CD32B FcγRIIB[1]
	F158 (Low Binder)	V158 (High Binder)	H131 (High Binder)	R131 (Low Binder)	
Wild Type	1059 nM	415 nM	39 nM	36 nM	52 nM
Margetuximab	161 nM	89 nM	34 nM	218 nM	437 nM
Relative change	↑ 6.6x	↑ 4.7x	↔	↓	↓ 8.4x

[1]Nordstrom JL, et al. Breast Cancer Research 13:R123, 2011

Mechanism of Action

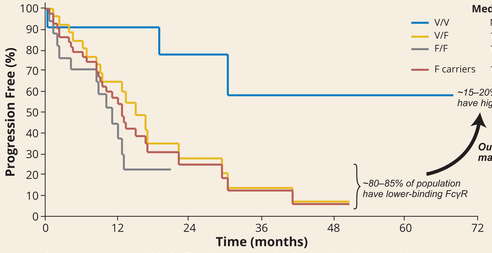


Anti-proliferative Activity (Same as trastuzumab)

Superior Engagement of Effector Cells and ADCC (Enhanced CD16A Binding, Reduced CD32B Binding)

Tumor Antigen Capture and Presentation to T Cells

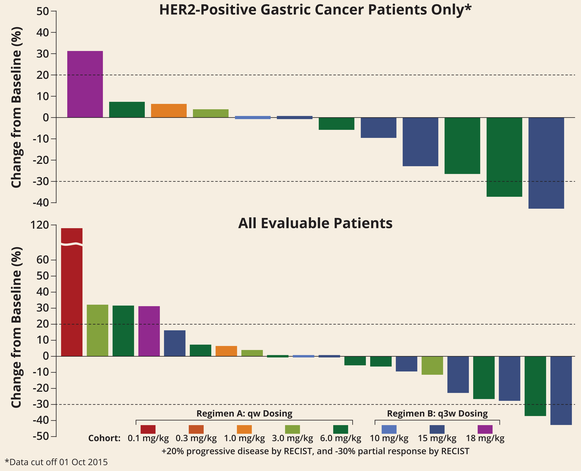
Progression Free Survival by FcgRIIIA (CD16A) Genotype[2]



[2]Metastatic breast cancer patients with high affinity Fc receptors had prolonged PFS with trastuzumab

- Preliminary data shows that margetuximab monotherapy has clinical activity against HER2+ tumors in GEJ and gastric cancer patients previously treated with trastuzumab or other anti-HER2 agents
- Pembrolizumab is a mAb that blocks the interaction of the immune checkpoint molecule PD-1, with its ligands, facilitating tumor cell elimination by releasing tumor-associated T cells from exhaustion
- Monotherapy pembrolizumab has demonstrated durable clinical activity in a Phase I study
- Safety profiles of margetuximab and pembrolizumab are acceptable and non-overlapping

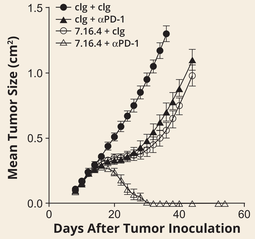
Margetuximab Single Agent Phase 1 Activity in Patients with Pre-treated Gastric Cancer



*Data cut off 01 Oct 2015

Anti-HER2 and Anti-PD-1

- HER2 is validated target in gastric cancer; trastuzumab is a component of 1L SoC
- No HER2 SoC after 1L; existing therapy (chemo, ramucirumab) is sub-optimal
- Negative GATSBY trial with T-DM1 in 2L gastric cancer may highlight importance of immune-mediated mechanisms in clinical activity of anti-HER2 agents
- Checkpoint inhibitors are clinically active in patients with gastric cancer (ORR, OS)
- Clear non-clinical rationale for combining anti-HER2 directed therapy and I-O agents
- Synergistic antitumor activity using combination of anti-HER2 and anti-PD-1 antibodies in HER2+ murine mammary adenocarcinoma model[3]

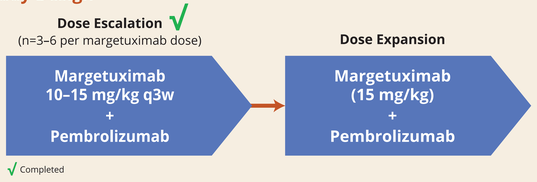


[3]Stagg, et al. PNAS, 2011

Methods

This study evaluates a chemotherapy free-combination of margetuximab + pembrolizumab for advanced HER2+ GEJ and gastric cancer patients. Enrolled patients will have relapsed/refractory HER2+ GEJ or gastric adenocarcinoma with measurable disease that has progressed on trastuzumab plus first line chemotherapy. HER2+ (IHC 3+ or ISH+) will be confirmed by central lab. Two dose levels of margetuximab (10 mg/kg and 15 mg/kg) and a fixed dose of pembrolizumab (200 mg) were evaluated for safety and tolerability. Patients will receive the combination once every 21 days for up to 24 months, until confirmed disease progression or intolerable toxicity. Dose expansion will enroll up to 60 patients at 15 mg/kg of margetuximab, with 20 undergoing pre- and on-treatment biopsy. Response will be assessed every 6 weeks for the first 6 months and every 12 weeks thereafter per RECIST v1.1 and IR RECIST to account for response patterns observed with immunotherapies. Primary endpoint is ORR and duration of response, and secondary endpoints include PFS and OS. The study was initiated January 2016 and is ongoing in North America and Asia.

Study Design



Entry Criteria

Key Study Objectives

Primary Objective

- Characterize safety, tolerability and maximum tolerated dose (MTD) of combination
- 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

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Histologically proven GEJ/gastric adenocarcinoma 3+ by IHC or ISH-amplified
- Unresectable locally advanced or metastatic
- Have received prior trastuzumab
- Have received one or more line of cytotoxic chemotherapy
  - If relapsed within 6 months of completion of adjuvant therapy, will be considered one line of treatment for metastatic disease
  - For **Dose Expansion**: ONLY one line prior treatment, including trastuzumab, is allowed
- Prior immune checkpoint inhibitor treatment allowed, but toxicities related to treatment need to be resolved to ≤ Grade 1 or baseline
- Age ≥18 years, ECOG 0 or 1 and life expectancy ≥12 weeks
- Measurable disease as per RECIST 1.1 criteria
- Available formalin-fixed paraffin embedded tumor specimen or unstained slides for determination of HER-2 and PD-L1 expression
- Lab Parameters:
  - Plts ≥100K, ANC ≥1.5 (w/o GCSF/GMCSF w/in 2 weeks of study start), Hgb ≥9
  - ALT/AST ≤3x ULN (≤5x ULN with liver mets), Tbili ≤1.5x ULN, Cr <2 or CrCL >50

Exclusion Criteria

- Symptomatic CNS metastases
  - No concurrent treatment (surgery, RT, or steroids ≥10 mg/day of Prednisone or equivalent)
  - No progression of CNS mets on MRI/CT for at least 21 days after last day of treatment
  - No cord compression/leptomeningeal disease
- Prior checkpoint inhibitor therapy related toxicity:
  - ≥ Gr 3 ocular AE
  - Met Hy's Law criteria [>3x ULN ALT/AST with concurrent >2x ULN Tbili without other cause]
  - ≥ Gr 3 neurologic toxicity
  - ≥ Gr 3 colitis or pneumonitis
- History of autoimmune disease [except vitiligo]
- Radiation treatment with 3 weeks of treatment initiation
- Clinically significant cardiovascular disease and GI disorders
- Clinically significant pulmonary compromise and/or active pneumonitis
- Vaccination with live virus vaccine within 4 weeks prior to study initiation
- Known positive HIV or history of Hep B (Core Ag, Surface Ag) and Hep C (PCR)
- Active infection within 7 days of study initiation
- Pregnancy and/or breastfeeding

Study Status

- Escalation is completed*
- Expansion is ongoing in North America and Asia

*As of Jan 2017

References

1. Nordstrom JL, et al. Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fcy receptor binding properties. Breast Cancer Res. 2011;13(6):R123.

2. Musolino A, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER2/neu-positive metastatic breast cancer. J Clin Oncol. 2008;26:1789-96.

3. 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.

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