Margetuximab Combined With Anti-PD-1 (MGA012) or Anti-PD-1/LAG3 (MGD013) ± Chemotherapy in First-line Therapy of Advanced/Metastatic HER2+ Gastroesophageal Junction or Gastric Cancer

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Abstract #P375

MAHOGANY (NCT04082364)

Qr Code Text

Background

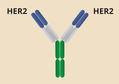
- Trastuzumab, a monoclonal antibody (mAb) targeting the human epidermal growth factor receptor 2 (HER2), plus chemotherapy (CTX) is the standard of care palliative first-line therapy for patients with advanced HER2+ gastroesophageal junction (GEJ) or gastric cancer (GC) (**Table 1**)[1,2]
- Margetuximab is an investigational Fc-engineered anti-HER2 mAb targeting the same epitope as trastuzumab (**Table 1**)[3–5]
  - Five amino acid substitutions in the immunoglobulin (Ig) G1 Fc domain of margetuximab lead to higher affinity, compared with trastuzumab, for both 158V (high binding) and 158F (low binding) alleles of the activating FcγRIIIA (CD16A) and diminished binding to inhibitory FcγRIIB (CD32B)[3,5]
  - Translational studies suggest that margetuximab may potentially modulate both innate and adaptive immunity, including antigen-specific T- and B-cell responses to HER2[3,4]
- Programmed cell death receptor 1 (PD-1) and lymphocyte-activation gene 3 (LAG3) are both T-cell checkpoint molecules that suppress T-cell function
  - According to a meta-analysis, programmed cell death ligand 1 (PD-L1) positivity is found in 63% to 72% of patients with GC[6]
  - Based on an analysis conducted by MacroGenics on 34 patients with GC, LAG3 positivity was observed in 88% of patients
- MGA012 (INCMGA00012) is a humanized, hinge-stabilized, IgG4κ anti-PD-1 mAb blocking binding of PD-L1 or PD-L2 to PD-1 (**Table 1**)[7]
- MGD013 is a humanized, Fc-bearing bispecific tetravalent DART® protein that concomitantly binds to PD-1 and LAG3, inhibiting their respective ligand-binding (**Table 1**)[8]

Table 1. Monoclonal Antibodies in MAHOGANY Phase 2/3 Study of First-line GEJ or GC

TRASTUZUMAB

Fab
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival

Fc
- Wild-type IgG immune effector domains
- Binds and activates immune cells

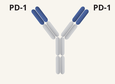


MARGETUXIMAB[3,5]

Fab
- Same specificity and affinity as trastuzumab
- Similarly disrupts signaling as trastuzumab

Fc
- ↑Affinity for activating FcγRIIIA (CD16A)
- ↓Affinity for inhibitory FcγRIIB (CD32B)

Margetuximab Binding to FcγR Variants				
Receptor Type	Receptor	Allelic Variant	Relative Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6 × ↑
		158V	Higher	4.7 × ↑
	CD32A	131R	Lower	6.1 × ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4 × ↓



MGA012[7]

Fab
- Binds PD-1 with high affinity (>4× greater than nivolumab and >6× greater than pembrolizumab)
- Blocks binding of PD-L1 or PD-L2 to PD-1

Fc
- Humanized, hinge-stabilized IgG4κ

MGD013[8]

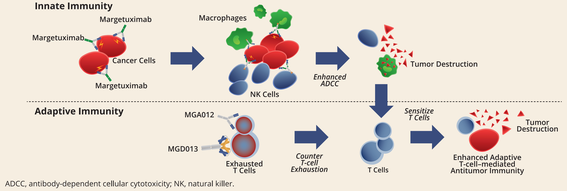
Fab
- Bispecific, tetravalent PD-1 × LAG3 co-engages both molecules (PD-1 and LAG3) for blockade
- Blocks binding of PD-L1 or PD-L2 to PD-1
- Blocks binding of MHC-II to LAG3

Fc
- Humanized, hinge-stabilized IgG4κ

FcγR, Fc gamma receptors; MHC-II, major histocompatibility complex class II.

- We hypothesize that dual blockade targeting of PD-1 and LAG3 will increase effectiveness of margetuximab by enhancing innate and adaptive immune responses against HER2-overexpressing tumor cells (**Figure 1**)

Figure 1. Hypothesized Mechanism for Potential Coordinate Engagement of Innate and Adaptive Immunity by Margetuximab, Supporting Rationale for Combination With Checkpoint Inhibitors Including MGA012 or MGD013



ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer.

- We previously reported that a CTX-free regimen consisting of margetuximab + pembrolizumab (PD-1 blockade) was well tolerated in patients with GEJ/GC and induced a favorable antitumor activity in patients with GC[9]
  - Objective response rate (ORR) was 30% (18/61) in patients with GC (2.3- to 2.7-fold greater than in historical controls with checkpoint inhibitors alone)[10–12]
  - Disease control rate (DCR) was 66% (40/61) in patients with GC
  - Biomarker analysis revealed an ORR of 52% (12/23) and a DCR of 83% (19/23) in GC patients HER2 IHC 3+ and PD-L1 + (combined positive score ≥1%, by IHC)

Study Design

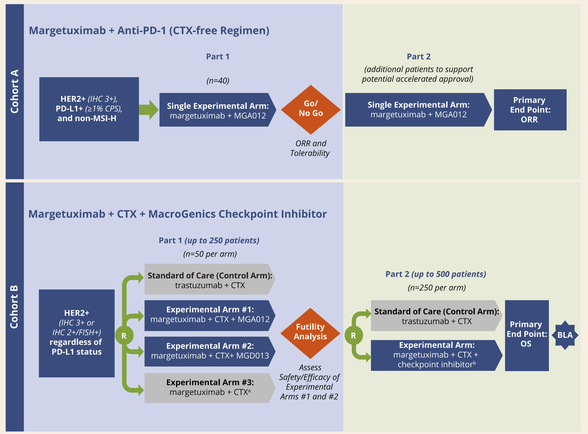
- The MAHOGANY trial (NCT04082364) described here is a phase 2/3, randomized, open-label study investigating the efficacy, safety, and tolerability of margetuximab + checkpoint inhibition (either MGA012 or MGD013) ± CTX in treatment-naïve patients with metastatic/locally advanced, HER2+ GEJ/GC (**Figure 2**)
- Key study objectives are summarized in **Table 2**
- The MAHOGANY study will be conducted in 2 cohorts (**Figure 2**)
  - Cohort A will determine efficacy/safety of margetuximab combined with MGA012 in patients who are positive for both HER2 immunohistochemistry (IHC) 3+ and PD-L1+, as well as non-microsatellite instability-high (MSI-H) status (determined by a central laboratory before enrollment)
  - Cohort B has a randomized, open-label design, with a total planned sample size of ~750, consisting of 2 parts:
    - In Cohort B, Part 1, 200 patients who are HER2+ (IHC 3+, or IHC 2+ and fluorescence in situ hybridization [FISH]+), irrespective of PD-L1 status will be randomized 1:1:1:1 to 4 arms, stratified by CTX regimen (XELOX [capecitabine and oxaliplatin] vs mFOLFOX-6 [modified folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin]) and tumor location (GEJ vs GC)
    - In Cohort B, Part 2, ~500 patients will be randomized 1:1 between 2 arms, stratified by CTX regimen (XELOX vs mFOLFOX-6) and tumor location (GEJ vs GC):
      - In the experimental arm either MDA012 or MDG013 (selected in Cohort B, Part 1) will be evaluated in combination with margetuximab and CTX
    - The CTX regimen for Cohort B will be either XELOX or mFOLFOX-6, according to the Investigator's choice (based on local approval and availability)

Table 2. Key Study Objectives

	Primary Objectives	Secondary Objectives
Cohort A, Part 1 and Part 2	▪ Safety and tolerability of margetuximab + MGA012 as assessed by CTCAE v5.0 ▪ ORR of margetuximab + MGA012 per RECIST v1.1	▪ DoR, DCR, and PFS using independent and investigator-assessed radiology review, and OS ▪ Relationships among Fcγ receptor allelic variation in CD16A and efficacy (ORR, PFS, and OS) ▪ PK of margetuximab and MGA012 ▪ Antidrug antibodies to margetuximab, MGA012, or both
Cohort B, Part 1	▪ Select best margetuximab, CTX, and checkpoint inhibitor–containing combination regimen (MGA012 or MGD013) for further evaluation in Cohort B, Part 2	▪ PFS, DoR, and DCR of each treatment arm ▪ ORR, DoR, DCR, PFS, and OS in the double-positive (HER2 IHC 3+ and PD-L1+) and non-MSI-H population in the margetuximab + CTX arm ▪ Relationships among Fcγ receptor allelic variation in CD16A and efficacy (ORR, PFS, and OS) ▪ PK of margetuximab, MGD013, or MGA012 ▪ Antidrug antibodies to margetuximab, MGD013, or MGA012
Cohort B, Part 2	▪ OS of patients treated with margetuximab, CTX, and checkpoint inhibitor–containing arm (MGA012 or MGD013) compared with OS of patients treated with trastuzumab + CTX (control arm)	▪ PFS, OS, DoR, ORR, and DCR of each treatment arm ▪ ORR, PFS, DoR, DCR, and OS in the double-positive (HER2 IHC 3+ and PD-L1+) and non-MSI-H population in the margetuximab + checkpoint inhibitor (MGA012 or MGD013)–containing arm ▪ Relationships among Fcγ receptor allelic variation in CD16A and clinical response ▪ PK of margetuximab and MGD013 or MGA012 ▪ Antidrug antibodies to margetuximab, MGD013, or MGA012 ▪ Relationships among PD-L1 expression, HER2 expression, MSI status, and clinical response ▪ Quality of life, as assessed using the FACT-Ga, associated with the margetuximab–containing arm vs the trastuzumab–containing control arm

DCR, disease control rate; DoR, duration of response; CTCAE, Common Terminology Criteria for Adverse Events; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 2. MAHOGANY Study Schema: a Randomized, Open-label Phase 2/3 Study



[a]Up to ~50 additional non-randomized patients will continue to be enrolled into the margetuximab + CTX arm only; [b]Pending chronic toxicity study (if regimen with MGD013 is selected).
Investigator's choice chemotherapy: mFOLFOX-6 consists of oxaliplatin 85 mg/m² IV over 2 hours on day 1; leucovorin 400 mg/m² IV over 2 hours on day 1; 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day for 2 days (total 2400 mg/m² IV over 46–48 hours) continuous infusion (repeat Q2W for 6 months). XELOX consists of oxaliplatin 130 mg/m² IV over 2 hours on day 1; capecitabine 1000 mg/m² PO twice daily on days 1–14 (repeat Q3W for 6 months).
Checkpoint inhibitors: MGA012 375 mg Q3W; MGD013.
Anti-HER2 mAbs: margetuximab 15 mg/kg Q3W; trastuzumab 8-mg/kg loading dose, then 6 mg/kg Q3W.
BLA, biologics licence application; CPS, combined positive score; IV, intravenous; OS, overall survival; PO, by mouth; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomize.

Key Inclusion Criteria

- Adult patients with histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2+ GC or GEJ adenocarcinoma
  - Per protocol, GEJ cancer is defined as any tumor that invades the histological transition from columnar epithelium (gastric) to squamous epithelium (esophagus)
- Eastern Cooperative Oncology Group performance status of 0 or 1
- For Cohort A, patients will be HER2+ (IHC 3+), PD-L1+ (combined positive score ≥1%), and non-MSI-H by central review
- For Cohort B, patients will be HER2+ (IHC 3+, or IHC 2+ and FISH+), irrespective of PD-L1 status

Key Exclusion Criteria

- Patients with a known additional malignancy that is progressing or has required treatment within the past 5 years
- Clinically significant cardiovascular disease or gastrointestinal disorder

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