Background

- Trastuzumab, a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2), plus chemotherapy (CT), is the standard of care for adjuvant first-line therapy for patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) cancer (Table 1).

- Margetuximab is an investigational fi-engineered anti-HER2 mAb targeting the same epitope as trastuzumab (Table 1).

- Five amino acid substitutions in the immunoglobulin (Ig) G1 Fc domain of margetuximab

- MGD013 is a humanized, Fc-bearing bispecific tetravalent DART


- Pending chronic toxicity study (if regimen with

- Figure 2

- Binds and activates immune cells

- Protein that concomitantly

- 8.4 ×

- ↓

- 3,5

- Binds PD-1 with high affinity (>4× greater than nivolumab and >6× greater than pembrolizumab)

- We hypothesize that dual blockade targeting of PD-1 and LAG3 will increase effectiveness

- Bispecific, tetravalent PD-1 × LAG3 co-engages both molecules (PD-1 and LAG3) for blockade

- Same specificity and affinity

- Five amino acid substitutions in the immunoglobulin (Ig) G1 Fc domain of margetuximab

Study Design

- The MARGETUXIMAB (NCCTT43052) described here is a phase 2, randomized, open-label study investigating the efficacy, safety, and tolerability of margetuximab + checkpoint inhibitor–containing arm (MGA012 or MGD013) ± CTX in treatment-naive patients with metastatic/locally advanced HER2+ GC or GEJ (Figure 2).

- Key study objectives are summarized in Table 2.

- The study will be conducted in 2 cohorts (Figure 2):

- Cohort A: select the dosing efficiency of margetuximab combined with MGA012 in patients who are positive for both HER2 immunohistochemistry (IHC) 3+ and programmed death-ligand 1 (PD-L1) (IHC 3+ or 2+).

- Cohort B: select the best margetuximab ± investigator-choice chemotherapy (trastuzumab, CTX, and checkpoint inhibitor–containing arm (MGA012 or MGD013)) for further evaluation in a phase 3 study involving a larger number of patients.

- In Cohort A, Part 1, 200 patients will be randomized 1:1:1 between 3 arms, stratified by PD-L1 status

- In Cohort B, Part 2, ~500 patients will be randomized 1:1 between 2 arms, stratified by PD-L1 status

Key Inclusion Criteria

- Adult patients with histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2+ GC or GEJ (or oesophagogastric junction—per protocol, GC is defined as any tumor that invades the histological transition from columnar epithelium (gastric) to squamous epithelium (esophageal))

- Eastern Cooperative Oncology Group performance status of 0 or 1

- For Cohort A, patients will be HER2 (IHC 3+) or PD-L1+ (combined positive score ≥1%)

- For Cohort B, patients will be HER2 (IHC 3+), or PD-L1+ (≥50%) or MSI-H.

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

## Table 1. Monoclonal Antibodies in MAGEHANE Phase 2/3 Study of First-line 4G or GC

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Therapeutic Category</th>
<th>Target</th>
<th>FcγRIIB (CD32B)</th>
<th>FcγRIIIA (CD16A)</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margetuximab</td>
<td>HER2</td>
<td>HER2</td>
<td>Activating</td>
<td>Activating</td>
<td>Antibody-dependent cellular cytotoxicity (ADCC)</td>
</tr>
<tr>
<td>MGD013</td>
<td>HER2</td>
<td>HER2</td>
<td>Activating</td>
<td>Activating</td>
<td>Antibody-dependent cellular cytotoxicity (ADCC)</td>
</tr>
<tr>
<td>MGA012</td>
<td>PD1</td>
<td>PD1</td>
<td>Activating</td>
<td>Non-activating</td>
<td>Antibody-dependent cellular cytotoxicity (ADCC)</td>
</tr>
</tbody>
</table>

## Table 2. Key study Objectives

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Primary objectives</td>
<td>Primary objectives</td>
<td>Primary objectives</td>
</tr>
<tr>
<td>ORR of margetuximab as assessed by CTCAE v5.0</td>
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</tr>
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<td>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–containing arm (MGA012 or MGD013)-containing arms</td>
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</tbody>
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## References

- Nordic Group of Medical Oncology; Swiss Group for Clinical Cancer Research (SAKK); and Swiss Group for Clinical Cancer Research (SAKK).

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Prepared on behalf of the study sponsor by presenting author Emily Collins, MD, and reference reviewers, PhD, of The Oncology Group Clinical Development. The presented study results have not been published previously.