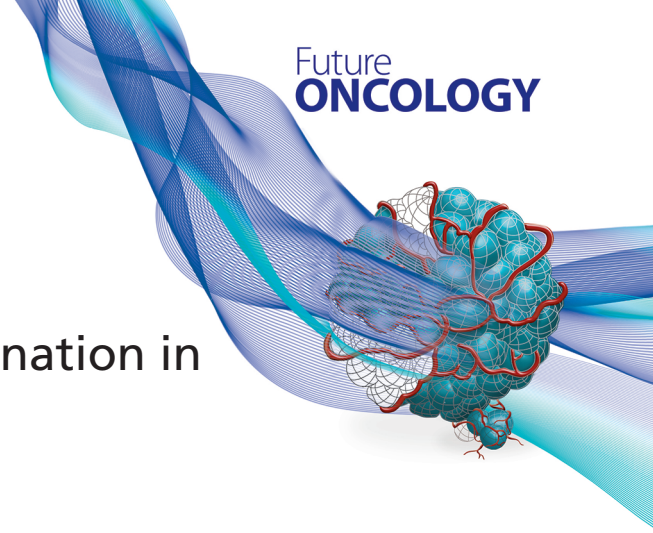
Clinical Trial Protocol

Future ONCOLOGY



MAHOGANY: margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma

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Standard-of-care, first-line therapy for patients with advanced HER2+ gastric/gastroesophageal junction adenocarcinoma is chemotherapy plus trastuzumab, a monoclonal antibody (mAb) targeting HER2. Margetuximab is an Fc-optimized mAb that binds HER2. Retifanlimab, a humanized IgG4 mAb, binds to PD-1 and blocks its interaction with PD-L1/2. Tebotelimab, an IgG4κ bispecific DART® molecule, binds PD-1 and lymphocyte activation gene 3 concomitantly, disrupting these nonredundant inhibitory pathways to further restore exhausted T-cell function. Here, we describe the design and rationale of the randomized, open-label, Phase II/III MAHOGANY trial evaluating margetuximab plus retifanlimab with/without chemotherapy and margetuximab plus tebotelimab with chemotherapy in first-line unresectable metastatic/locally advanced gastroesophageal junction adenocarcinoma. Primary end points include objective response rate, overall survival and safety/tolerability.

Clinical trial registration: NCT04082364 (ClinicalTrials.gov)

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Novel checkpoint inhibitors are being investigated for multiple types of cancer [1], including gastric and gastroesophageal junction adenocarcinoma (GEA) [2–4]. The monoclonal antibody (mAb) trastuzumab in combination with chemotherapy has been the standard-of-care first-line therapy in HER2+ metastatic GEA for a decade [5,6]. The anti-PD-1 mAbs pembrolizumab (in the USA) and nivolumab (in Japan, Taiwan and Korea) have been approved for treatment of GEA after prior chemotherapy [7–10]. Margetuximab is an anti-HER2 mAb that was engineered to potentiate innate immunity (including antibody-dependent cellular cytotoxicity), adaptive immunity (including anti-HER2-directed T-cell responsiveness) and *in vitro* upregulation of tumor cell PD-L1 expression and was designed to confer enhanced fragment crystallizable (Fc)-dependent antitumor activities across all Fc region gamma receptor (FcγR)IIIA (*CD16A*) genotypes [11–15]. Margetuximab in combination with retifanlimab (MGA012, INCMGA00012; anti-PD-1 mAb) or tebotelimab (MGD013; anti-PD-1 and anti-*LAG-3* bispecific mAb) is being studied as a novel approach for HER2+ GEA.

Background & rationale

PD-L1 positivity by combined positive score (CPS) >1 is found in approximately 60% of patients with gastric cancer [16]. Retifanlimab (MGA012) is a humanized, hinge-stabilized, immunoglobulin (Ig)G4κ mAb that recog-

nizes human PD-1, blocking the binding of PD-L1 and PD-1 ligand 2 (PD-L2) to cell surface-expressed PD-1 in a dose-dependent manner [17]. The binding properties of retifanlimab are comparable to the approved anti-PD-1 mAbs nivolumab and pembrolizumab [17].

PD-1 and LAG-3 – two checkpoint molecules expressed by T lymphocytes ($CD4^+$ and $CD8^+$) – act as negative regulators of T-cell function upon interaction with their respective ligands [18]. PD-1 and LAG-3 expression on tumor-infiltrating lymphocytes or chronically viral-infected T cells have been associated with immune dysfunction, characterized as 'T-cell exhaustion' [19]. An analysis of 34 gastric cancer specimens revealed LAG-3-positive immune infiltrates in 88% of the specimens [20]. Tebotelimab (MGD013) is a hinge-stabilized IgG4 molecule designed to bind concomitantly to PD-1 and LAG-3 and to inhibit their interaction with PD-L1 or PD-L2 and major histocompatibility complex class II [18]. Thus, by inhibiting PD-1 and LAG-3 interaction with their respective ligands, tebotelimab can potentially reverse T-cell inhibitory effects mediated by PD-1 and LAG-3, leading to restoration of exhausted T-cell function and, hence, enhanced antitumor immunity. Although the binding properties of tebotelimab are comparable with nivolumab and relatlimab (BMS-986016), the ability of tebotelimab to restore T-cell activation was greater than that achieved by the combination of nivolumab and relatlimab, suggesting that tebotelimab may offer additional clinical benefit beyond that observed with the antibody combination [18]. Safety, tolerability and preliminary efficacy of tebotelimab are being explored in the ongoing Phase I CP-MGD013-01 study (NCT03219268) [21]. Furthermore, it is hypothesized that dual blockade targeting of PD-1 and LAG-3 will increase effectiveness of margetuximab by enhancing innate and adaptive immune responses against HER2-overexpressing tumor cells (Figure 1) [7,12–14,22,23].

In vitro studies revealed that margetuximab, when incubated with human peripheral blood mononuclear cells and HER2+ gastric tumor cells, enhances PD-1/PD-L1 axis expression and LAG-3 on natural killer (NK) and NK T cells [24]. Moreover, blockade of PD-1 by retifanlimab enhances margetuximab-dependent induction of NK cell activation, proliferation and cytolytic potential [25]. In mice bearing HER2+ tumors (CT26-HER2 tumors), the antitumor activity mediated by a poxvirus-based HER2 vaccine (MVA-BN-HER2: poxvirus vaccine with an engineered HER2 tumor-associated antigen vector) was accompanied by upregulation of PD-L1 expression in the tumor microenvironment [26]. The antitumor activity mediated by the HER2 vaccine was enhanced when combined with PD-1 blockade but resulted in increased LAG-3 expression in tumor-infiltrating $CD8^+$ T cells, possibly as a compensatory mechanism. Addition of anti-LAG-3 and anti-PD-L1 mAbs to MVA-BN-HER2 led to complete tumor regression of CT26-HER2 tumors in 100% of the treated mice, compared with 10% of the mice treated with MVA-BN-HER2 alone, 30% of those treated with the anti-PD-L1 mAb alone and 45% of those treated with MVA-BN-HER2 in combination with the anti-PD-L1 mAb [26].

Safety and clinical activity of the combination of margetuximab plus the anti-PD-1 mAb pembrolizumab were evaluated in CP-MGAH22-05 (NCT02689284), an ongoing, global, multicenter, Phase Ib/II study in pretreated HER2+ gastroesophageal adenocarcinoma [22]. The combination was well tolerated and provided extended median overall survival (OS) to 12.5 months compared with historical data (GATSBY, 7.9 months; TyTAN, 11.0 months; and T-ACT, 10.2 months) [22]. Therefore, on the basis of efficacy results in the double-positive population (HER2 immunohistochemistry [IHC] 3^+ and PD-L1+ by IHC CPS >1) from CP-MGAH22-05 [22], the combination of retifanlimab and margetuximab in double-positive first-line patients is being assessed relative to the combination of trastuzumab plus chemotherapy. Patients in Cohort A (margetuximab 15 mg/kg every 3 weeks [Q3W] in combination with retifanlimab 375 mg Q3W) will be required to be HER2 IHC 3^+ and PD-L1+ since this was identified as the population with the highest disease control rate (DCR) in the CP-MGAH22-05 study. Study designs that enrich specific populations to achieve maximal benefit are increasingly more common [27]. In preliminary clinical data, the combination of margetuximab with tebotelimab or retifanlimab has not shown any adverse events beyond those seen with the single agents [11,24,28]. While the individual agents can have cardiac toxicities, there were no cardiac toxicities observed with the combinations.

MAHOGANY study design & treatment

The MAHOGANY trial (NCT04082364) described here is a randomized, open-label, Phase II/III study investigating the efficacy, safety and tolerability of margetuximab plus the checkpoint inhibitor retifanlimab (anti-PD-1) with or without chemotherapy and margetuximab plus the checkpoint inhibitor tebotelimab (bispecific anti-PD-1 and anti-LAG-3 DART® molecule) with chemotherapy in treatment-naïve patients with unresectable metastatic or locally advanced HER2+ GEA (Figure 2) [29]. The study will be conducted in two cohorts. Cohort A (single-arm design) will determine the efficacy/safety of margetuximab 15 mg/kg Q3W in combination with retifanlimab

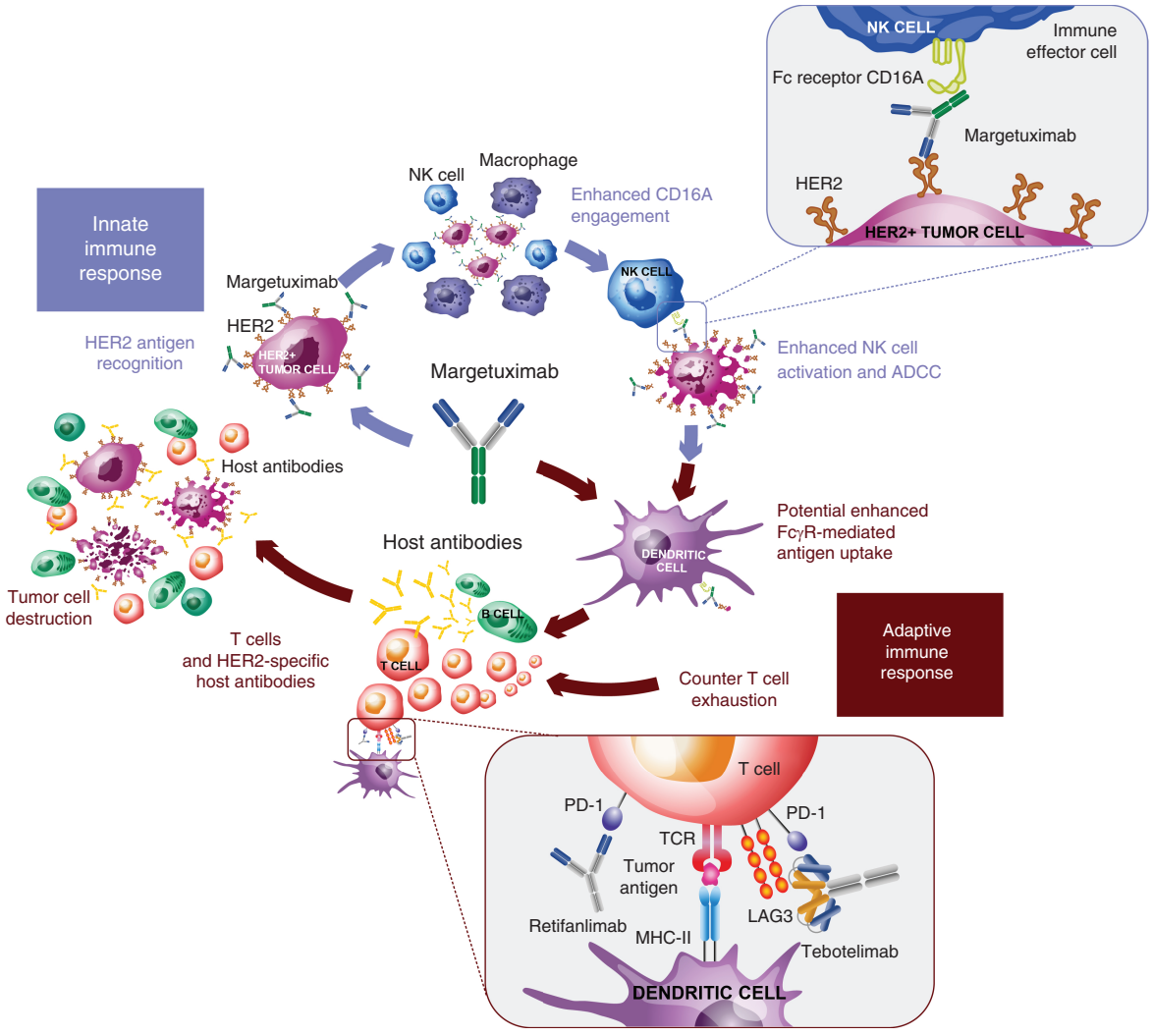

Figure 1. Proposed synergistic mechanism of action of margetuximab and checkpoint inhibitors (retifanlimab and tebotelimab).
ADCC: Antibody-dependent cellular cytotoxicity; CD: Cluster of differentiation; NK: Natural killer.

375 mg Q3W in patients who are both HER2 IHC 3^+ and PD-L1+ and are non–microsatellite instability-high (determined by a central laboratory before enrollment). Cohort B (randomized, open-label design), in which patients who are HER2+ (IHC 3^+ or IHC 2^+ and fluorescence *in situ* hybridization $[FISH]^+$) are enrolled, irrespective of PD-L1 status, consists of two parts. In Cohort B/Part 1, patients will be randomized 1:1:1:1 to four arms:

- Control arm, trastuzumab 6 mg/kg Q3W (8-mg/kg loading dose) plus chemotherapy;
- Experimental arm 1, retifanlimab (375 mg Q3W) plus margetuximab (15 mg/kg Q3W) and chemotherapy;
- Experimental arm 2, tebotelimab (600 mg Q3W) plus margetuximab (15 mg/kg Q3W) and chemotherapy;
- Experimental arm 3, margetuximab (15 mg/kg Q3W) plus chemotherapy.

In Cohort B/Part 2, patients will be randomized 1:1 to two arms:

- Control arm, trastuzumab 6 mg/kg Q3W (8-mg/kg loading dose) plus chemotherapy;
- Experimental arm: one of the two checkpoint inhibitors from Cohort B/Part 1 (retifanlimab [375 mg Q3W] or tebotelimab [600 mg Q3W]) plus margetuximab and chemotherapy.

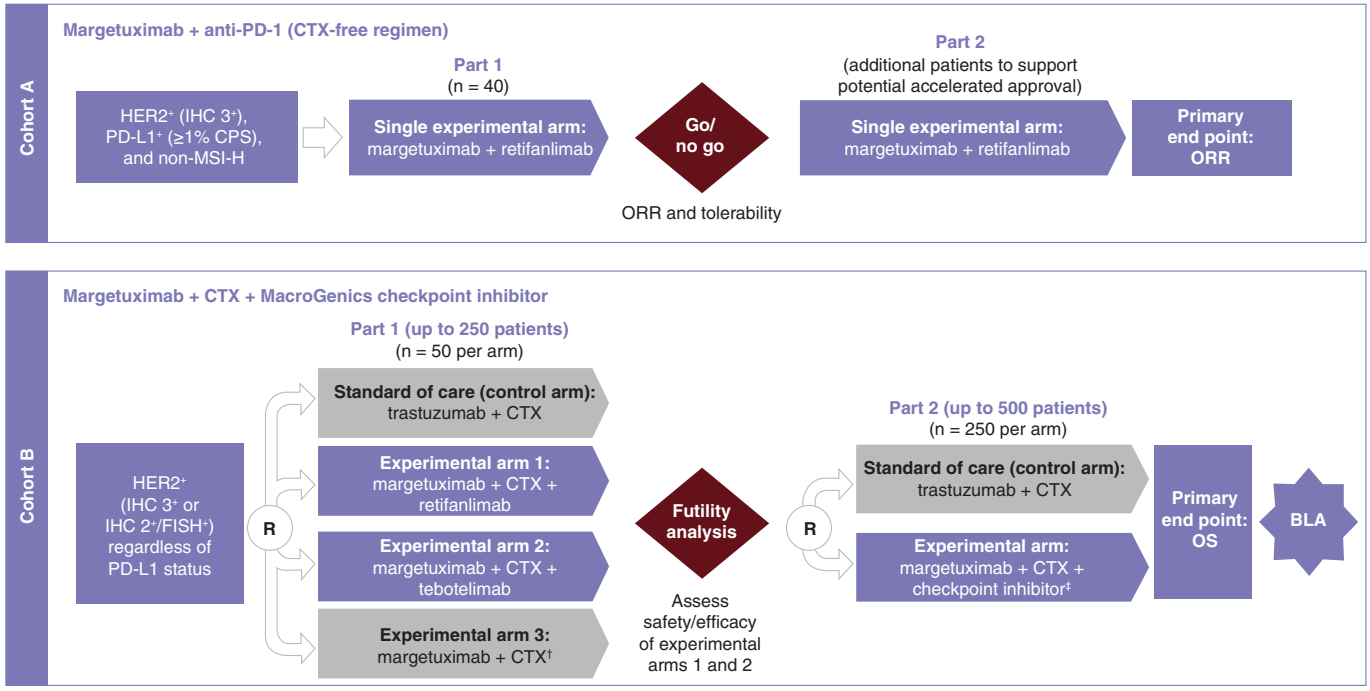

Figure 2. MAHOGANY study schema: a randomized, open-label, Phase II/III study.
†Up to approximately 50 additional nonrandomized patients will continue to be enrolled into the margetuximab + CTX arm only.
‡Pending chronic toxicity study (if regimen with tebotelimab is selected).
BLA: Biologics license application; CPS: Combined positive score; CTX: Chemotherapy; FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemistry; MSI-H: Microsatellite instability-high; ORR: Objective response rate; OS: Overall survival; R: Randomization.

The checkpoint inhibitor for the experimental arm will be determined based on the interim analysis from Cohort B/Part 1 data. In Cohort B, randomization will be stratified by chemotherapy regimen (XELOX [capecitabine and oxaliplatin] vs modified FOLFOX-6 [oxaliplatin, 5-fluorouracil and leucovorin]) and results of local HER2 testing (IHC 2^+/FISH+ vs IHC 3+). A central randomization scheme using permuted blocks will be prepared for Cohort B randomization. The choice of chemotherapy will be at the investigator's discretion. To minimize bias, chemotherapy will be selected and documented prior to patient randomization. Formalin-fixed, paraffin-embedded tumor tissue for analysis of PD-L1 and microsatellite instability-high status will be prospectively collected during the study and retrospectively analyzed by a central laboratory.

The study population comprises patients with previously untreated, unresectable metastatic or locally advanced HER2+ (IHC 3^+ or IHC2^+ and FISH+) GEA. Prior systemic treatment in the perioperative setting is allowed. However, patients must have had a disease-free interval of at least 6 months from the end of chemotherapy with or without surgery. Patients receiving perioperative anti-HER2 therapy require repeat testing of HER2 status for eligibility. No prior immunotherapy is allowed.

Primary objectives

The primary objectives in Cohort A are safety/tolerability and efficacy of margetuximab in combination with retifanlimab. The primary objective in Cohort B/Part 1 is the selection of the best checkpoint inhibitor (retifanlimab or tebotelimab), based on safety and efficacy, to use in combination with margetuximab and chemotherapy for further evaluation in Cohort B/Part 2. The primary objective in Cohort B/Part 2 is OS in patients treated with margetuximab plus chemotherapy and either retifanlimab or tebotelimab, compared with OS in patients treated with trastuzumab plus chemotherapy (control arm).

Key inclusion criteria

- Adult patients with histologically or cytologically confirmed diagnosis of previously untreated, unresectable metastatic or locally advanced HER2+ gastric, gastroesophageal junction, or esophageal adenocarcinoma;

- Prior systemic perioperative treatment is allowed; however, patients must have had a disease-free interval of at least 6 months from the end of chemotherapy or surgery;
- Patients receiving perioperative anti-HER2 therapy require testing of HER2 status for eligibility;
- For Cohort A, patients will be HER2+ (IHC 3^+) and PD-L1+ (CPS of ≥ 1) by central review;
- For Cohort B, patients will be HER2+ (IHC 3^+ or IHC 2^+ and FISH+) by local review, irrespective of PD-L1 status;
- Availability of formalin-fixed, paraffin-embedded tumor specimen, unstained slides, or contemporaneous biopsy for tumor target testing;
- Eastern Cooperative Oncology Group Performance Status of 0 or 1;
- Life expectancy of ≥ 6 months;
- At least one radiographically measurable target lesion;
- Acceptable laboratory parameters and adequate organ function.

Key exclusion criteria

- Patients with a known additional malignancy that is progressing or has required treatment within the past 5 years;
- History of allogeneic stem cell or tissue/solid organ transplantation;
- Central nervous system metastases;
- Clinically significant cardiovascular disease, gastrointestinal disorder, or pulmonary compromise.

Planned sample size

Cohort A will enroll approximately 100 patients. Cohort B will enroll approximately 750 patients in total (part 1, n = 250; part 2, n = 500). After 200 patients are randomized in part 1, up to 50 patients will be allocated to the margetuximab plus chemotherapy arm as an overflow arm during the interim analysis to select an experimental arm containing either retifanlimab or tebotelimab for part 2.

Planned study period

The study started in September 2019, and recruitment is ongoing. Study treatment may continue until persistent complete response (CR), progressive disease (PD), unacceptable toxicity, withdrawal of consent, physician recommendation to discontinue therapy, or death.

Patients will be evaluated at the end of every three cycles (±7 days) for the first 9 months for radiographic evidence of PD; beginning with cycle 13, assessments will occur every four cycles (±7 days). The maximum treatment duration allowed is approximately 6 months for chemotherapy (eight cycles for XELOX and 12 cycles for modified FOLFOX-6) and ~2 years for checkpoint inhibitors (35 cycles for retifanlimab or tebotelimab). Margetuximab or trastuzumab can be administered until confirmed CR or unequivocal PD. Discontinuation of study treatment may be considered for patients who attain a persistent CR. There is no crossover to a different treatment arm or different cohort. After study treatment discontinuation (and regardless of whether another nonstudy anticancer therapy is initiated), patients will have follow-up for survival approximately every 3 months until loss to follow-up, withdrawal of consent, or death, for up to 3 years or until the end of study. The end of study is reached when the number of deaths required for the final OS analysis is attained for cohort B.

Analysis populations

- Safety population: all patients who received at least one dose of study drug. The safety population will be used to summarize safety data for cohort A and cohort B of the study. This population will also be used to summarize baseline data for cohort A;
- Intention-to-treat population: all patients who are assigned to treatment in cohort A and are randomized into cohort B of the study. This population will be used to summarize baseline data and evaluate progression-free survival (PFS) and OS;
- Primary efficacy population: all patients in the intention-to-treat population who have centrally confirmed HER2+ (IHC 3^+ or IHC 2^+ and FISH+) GEA. This population will be used for OS evaluation at the end of cohort B/part 2;
- Response-evaluable population: All patients who received at least one dose of study drug and had a baseline radiographic tumor assessment. This population will be used for response-related efficacy analyses in cohort A and cohort B;

- Primary response-evaluable population: All patients in the response-evaluable population who have centrally confirmed HER2+ (IHC 3^+ or IHC 2^+ and FISH+) GEA. This population will be used for response-related efficacy analyses in cohort B/part 1 for selection of the margetuximab and checkpoint inhibitor-containing arm for further evaluation in cohort B/part 2.

Table 1. Primary and secondary study end points by cohort.

Cohort	Primary end points	Secondary end points
Cohort A/parts 1 and 2	• Safety and tolerability of margetuximab plus retifanlimab as assessed by NCI CTCAE v5.0 • Independently reviewed ORR of margetuximab plus retifanlimab per RECIST v1.1	• DoR, DCR and PFS using independent and investigator-assessed radiology review and OS for non-MSI-H patients • Relationships among FcγR allelic variation in *CD16A* and efficacy (ORR, PFS and OS) for non-MSI-H patients • PK of margetuximab and retifanlimab • Antidrug antibodies to margetuximab, retifanlimab or both
Cohort B/part 1	• Safety and tolerability • Investigator-assessed ORR per RECIST v1.1	• 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 plus CTX arm • Relationships among FcγR allelic variation in *CD16A* and efficacy (ORR, PFS and OS) • PK of margetuximab, tebotelimab or retifanlimab • Antidrug antibodies to margetuximab, tebotelimab or retifanlimab • Relationships among PD-L1 expression, HER2 expression, MSI status and clinical response
Cohort B/part 2	• OS in patients treated with margetuximab, CTX and checkpoint inhibitor-containing arm (retifanlimab or tebotelimab) compared with OS in patients treated with trastuzumab plus CTX (control arm)	• PFS, OS, DoR, ORR and DCR of each treatment arm • OS in the intention-to-treat and non-primary efficacy populations • ORR, PFS, DoR, DCR and OS in the double-positive (HER2 IHC 3^+ and PD-L1+) and non-MSI-H population in the margetuximab plus checkpoint inhibitor-containing arm (retifanlimab or tebotelimab) • Relationships among FcγR allelic variation in *CD16A* and clinical response • PK of margetuximab, tebotelimab or retifanlimab • Antidrug antibodies to margetuximab, tebotelimab, or retifanlimab • 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 versus the trastuzumab-containing control arm

CD: Cluster of differentiation; CTX: Chemotherapy; DCR: Disease control rate; DoR: Duration of response; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; IHC: Immunohistochemistry; MSI: Microsatellite instability; MSI-H: Microsatellite instability-high; NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetics; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, version 1.1.

End points

End points are summarized in Table 1. The primary efficacy end point for cohort A is independently reviewed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). The best overall response will be categorized as CR, partial response (PR), stable disease (SD), PD or not evaluable. The primary efficacy end point for cohort B/part 1 is investigator-assessed ORR per RECIST v1.1. The primary efficacy end point for cohort B/part 2 is OS. Secondary efficacy end points for cohort A are PFS, OS, duration of response (DoR) and DCR. Secondary efficacy end points for cohort B for the margetuximab plus chemotherapy arm include ORR, DCR, DoR, PFS and OS. The secondary efficacy end points for other arms include PFS, ORR, DCR and DoR, based on investigator assessments, estimated from patients enrolled in both parts of cohort B. Safety end points and analyses will summarize treatment-emergent adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analyses

The two-sided 95% exact binomial CI of ORR and DCR will be calculated, and Kaplan–Meier methodology will be applied to estimate DoR, PFS and OS curves, their median times, PFS rates at 6, 9 and 12 months, and OS rates at 12, 18 and 24 months, respectively, for each treatment arm. The Brookmeyer and Crowley method will be used to construct 95% CIs for median time of each time-to-event end point. The 95% CIs for PFS and OS rates at each time point of interest will be calculated by normal approximation after log(-log) transformation.

The sample size of approximately 100 patients in Cohort A is based on a Simon two-stage design to provide approximately 83% power to test an ORR of 47 versus 62% at a two-sided alpha level of 0.05. The sample size of approximately 750 patients in Cohort B is based on a Phase II/III design to provide approximately 80% power to detect an OS hazard ratio of 0.757 at a two-sided alpha level of 0.05.

Conclusion

In patients with GEA, simultaneous targeting of HER2 and PD-1 (margetuximab plus retifanlimab) or HER2 and PD-1 plus LAG-3 (margetuximab plus tebotelimab) provides an opportunity to enhance the antitumor response compared to treatment with either agent alone. The rationale for this is supported by the complementary biology of HER2, PD-1 and LAG-3 in mediating tumor evasion and the ability of margetuximab and retifanlimab or tebotelimab to enhance both innate and adaptive immune responses. Based on recently published clinical data, a potential synergic antitumor effect was observed with the combination of an anti-HER2 agent (trastuzumab) plus an anti-PD-1 agent (pembrolizumab) and chemotherapy [30]. Furthermore, as seen in emerging preliminary data regarding margetuximab plus tebotelimab combination therapy in study CP-MGD013-01 (NCT03219268) [24], margetuximab plus tebotelimab and chemotherapy could potentially provide similar efficacy to patients with PD-L1- tumors as those with PD-L1+ tumors. The Phase I/II chemotherapy-free evaluation of margetuximab in combination with anti-PD-1 therapy has demonstrated clinically meaningful efficacy and tolerable safety in patients with HER2+ GEA that benchmarks favorably versus historical standard-of-care experience [22]. In conclusion, the currently available data for margetuximab in combination with retifanlimab or tebotelimab indicate that there is potential synergic antitumor activity with good tolerability, supporting the conduct of the MAHOGANY trial in patients with GEA.

Author contributions

All authors provided critical inputs on the study design. M Rosales drafted the manuscript. All authors critically reviewed or revised the manuscript for important intellectual content. All authors reviewed the final version and agree with the content and approved of the decision to submit.

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Ethical conduct of research

The authors state that they obtained appropriate institutional review board approval and followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent was obtained from the participants involved.

Executive summary

Margetuximab

- Investigational fragment crystallizable (Fc)-engineered anti-HER2 monoclonal antibody targeting the same epitope as trastuzumab.
- Five amino acid substitutions in the immunoglobulin (Ig) G1 Fc domain of margetuximab lead to higher affinity, versus trastuzumab, for both 158V (high-binding) and 158F (low-binding) alleles of the activating Fc region gamma receptor (FcγR)IIIA (CD16A) and diminished binding to inhibitory FcγRIIB (CD32B).

Retifanlimab

- Humanized, hinge-stabilized, IgG4κ anti-PD-1 monoclonal antibody that blocks binding of PD-L1/PD-L2 to PD-1.

Tebotelimab

- Humanized, Fc-bearing bispecific DART® molecule that is functionally active in interfering with the PD-1–PD-L1/PD-L2 and *LAG-3*/*MHC-II* inhibitory signaling pathways.

MAHOGANY study rationale

- Dual blockade targeting of PD-1 and LAG-3 may increase effectiveness of margetuximab by enhancing innate and adaptive immune responses against HER2-overexpressing tumor cells.
- Retifanlimab blocks the PD-1/PD-L1 inhibitory axis in a dose-dependent manner, comparable with that observed with nivolumab and pembrolizumab.
- Tebotelimab can potentially reverse T-cell inhibitory effects mediated by PD-1 and LAG-3 by inhibiting interactions with PD-L1/PD-L2 or MHC-II molecules, leading to restoration of exhausted T-cell function and enhanced antitumor immunity.
- In the Phase Ib/II CP-MGAH22-05 trial (NCT02689284), margetuximab in combination with the anti-PD-1 pembrolizumab was well tolerated and provided extended median overall survival versus historical data.

MAHOGANY study design

- MAHOGANY (NCT04082364) is a randomized, open-label, Phase II/III study investigating the efficacy and safety/tolerability of margetuximab plus the checkpoint inhibitor retifanlimab with/without chemotherapy (XELOX or modified FOLFOX-6) and margetuximab plus the checkpoint inhibitor tebotelimab with chemotherapy in treatment-naive patients with unresectable metastatic/locally advanced HER2+ gastric/gastroesophageal junction/esophageal adenocarcinoma. Cohort A will evaluate margetuximab 15 mg/kg every 3 weeks (Q3W) plus retifanlimab 375 mg Q3W in patients who are both HER2 immunohistochemistry 3^+ and PD-L1+ and are non-microsatellite instability-high. Cohort B will assess margetuximab 15 mg/kg Q3W plus retifanlimab 375 mg Q3W or tebotelimab 600 mg Q3W plus chemotherapy versus trastuzumab 6 mg/kg Q3W (8-mg/kg loading dose) plus chemotherapy in patients who are HER2+, irrespective of PD-L1 status.

MAHOGANY primary study objectives/end points

- Cohort A: safety/tolerability and efficacy of margetuximab in combination with retifanlimab, according to independently reviewed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Cohort B/Part 1: selection of the best checkpoint inhibitor (retifanlimab or tebotelimab), based on safety and efficacy (according to investigator-assessed ORR per RECIST v1.1), to use in combination with margetuximab and chemotherapy for further evaluation in Cohort B/Part 2.
- Cohort B/Part 2: OS in patients treated with margetuximab plus chemotherapy plus retifanlimab or tebotelimab, compared with OS in patients treated with trastuzumab plus chemotherapy.

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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