Margetuximab With Retifanlimab in HER2+, PD-L1+ First-Line Unresectable/Metastatic Gastroesophageal Adenocarcinoma (GEA): MAHOGANY Cohort A

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Poster #1379P

MAHOGANY (NCT04082364)

Background

- Margetuximab is an Fc-engineered, anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody (mAb) targeting the same epitope as trastuzumab, approved in breast cancer and investigational in GEA[1-3]
  - Margetuximab showed 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)[1,3]
- Recently, the checkpoint inhibitor pembrolizumab in combination with trastuzumab and chemotherapy (CTX) has received accelerated approval in the United States for the first-line treatment of patients with advanced HER2+ GEA[4-6]
  - Initial results of the KEYNOTE-811 study presented at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting[5] showed that pembrolizumab plus trastuzumab and CTX provided a 74.4% objective response rate (ORR), with a statistically significant 22.7% improvement in ORR compared with placebo + trastuzumab and CTX
- Retifanlimab (MGA012, INCMGA00012) is an investigational humanized, hinge-stabilized, immunoglobulin G4k anti-programmed death-protein 1 (PD-1) mAb blocking binding of PD-ligand 1 (PD-L1) or PD-ligand 2 to PD-1[7]
- We previously reported that a CTX-free regimen consisting of margetuximab plus pembrolizumab (PD-1 blockade) was well tolerated and induced a favorable antitumor activity in patients with previously treated HER2+ GEA, based on data from a Phase 1/2 study (CP-MGAH22–05).[8] The efficacy results, including ORR of 44% (11/25) and DCR of 72% (18/25) reported in the HER2 immunohistochemical (IHC)3+ and PD-L1+ subgroup in this study[8] support a CTX-free cohort (Cohort A) in the MAHOGANY study conducted in patients with HER2+ GEA in the first-line setting[9]

Objectives

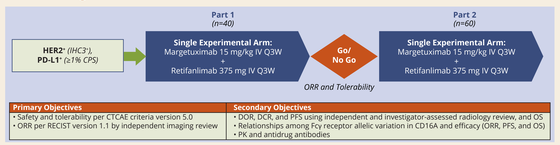
- The primary objectives for Cohort A are to evaluate the safety and tolerability of margetuximab + retifanlimab in patients with untreated locally advanced or metastatic GEA that is HER2 IHC3+ and PD-L1+ by IHC staining and to evaluate the independently reviewed ORR of margetuximab + retifanlimab in HER2 IHC3+, PD-L1+, and non-microsatellite instability-high (MSI-H) patients

Methods

Study Design

- The MAHOGANY study (NCT04082364) is a Phase 2/3 study conducted in two cohorts in treatment-naïve patients with metastatic/locally advanced HER2+ GEA[9]
- Cohort A (**Figure 1**) is a non-randomized single arm with a Simon 2-stage design evaluating efficacy/safety of margetuximab combined with retifanlimab in patients who are positive for both HER2 IHC3+ and PD-L1+ (determined by a central laboratory before enrollment)

Figure 1. MAHOGANY Cohort A: Non-Randomized, Single-Arm, Open-label Study Testing a CTX-Free Regimen



CPS, combined positive score; CTCAE, Common Terminology Criteria for Adverse Events; CTX, chemotherapy; DCR, disease control rate; DOR, duration of response; HER2+, human epidermal growth factor receptor 2 positive; IHC, immunohistochemical; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetic; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

- In Cohort A, the efficacy of the margetuximab/retifanlimab combination is evaluated in approximately 100 patients that are HER2 IHC3+, PD-L1+, and non–MSI-H (40 in Part 1 and 60 in Part 2)
- Enrollment is occurring without prior ascertainment of MSI status
  - If the MSI status is determined to be MSI-H, patients are allowed to remain on treatment but are not included in the efficacy analysis
- An interim analysis assessing efficacy and safety will be conducted on the first 40 non–MSI-H patients enrolled (Part 1), and if at least 21 (53%) responders (confirmed complete response or partial response by independent review) are observed, the study will proceed to Part 2, enrolling ~60 additional response-evaluable non–MSI-H patients

Results

Patients

- The first patient was dosed on October 15, 2019
- As of August 3, 2021 data cutoff, 43 patients were enrolled (intention-to-treat [ITT] population) and also treated (Safety population): 25 (58%) with gastric cancer and 18 (42%) with gastroesophageal junction cancer, most (84%) with metastatic disease (**Table 1**)

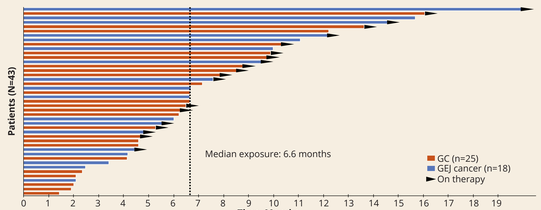
Table 1. Baseline Patients' Characteristics

	ITT population (N=43)
Age, years	
Mean (±SD)	64 (±11.5)
Median (range)	65 (24-82)
Gender, n (%)	
Male	39 (90.7)
Female	4 (9.3)
Race, n (%)	
White	20 (46.5)
Asian	19 (44.2)
Black or African American	2 (4.7)
Other/not reported	2 (4.7)
ECOG performance status, n (%)	
0	17 (39.5)
1	26 (60.5)
Primary tumor site, n (%)	
GC	25 (58.1)
GEJ cancer	18 (41.9)
Extent of the disease at study entry, n (%)	
Metastatic	36 (83.7)
Locally advanced	7 (16.3)
Prior anticancer systemic treatment, n (%)	
Adjuvant therapy	9 (20.9)
Neoadjuvant therapy	6 (14.0)
Neoadjuvant/adjuvant radiotherapy	9 (20.9)
Prior surgeries with therapeutic intent, n (%)	
Total gastrectomy	6 (14.0)
Partial gastrectomy	7 (16.3)
Other	14 (32.6)

ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJ, gastroesophageal junction; ITT, intention-to-treat; SD, standard deviation.

- All 43 patients were treated with margetuximab/retifanlimab combination therapy, receiving a median of 9 cycles
  - The median duration of treatment was 6.6 months (**Figure 2**)
- Of the 43 treated patients, 20 (46.5%) are continuing to receive margetuximab/retifanlimab combination therapy (**Figure 2**), and 23 (53.5%) discontinued the study treatment
  - The reasons for discontinuation were progressive disease (n=18 [41.9%]), adverse events (AE) (n=3 [7.0%]), and physician decision (n=2 [4.7%])
- The median duration of follow-up was 7.6 months among all 43 patients

Figure 2. Duration of Treatment by Primary Tumor Site in the ITT Population (N=43)



GC, gastric cancer; GEJ, gastroesophageal junction; ITT, intention-to-treat.

Safety

- In the safety population (N=43), the most common treatment-related AEs (TRAE) were fatigue (21%), infusion-related reaction (19%), rash (19%), diarrhea (16%), and pruritus (16%)
- 9 Grade 3 TRAEs were reported in 8 patients and no Grade 4 TRAEs
- Eight serious TRAEs were reported in 7 patients
- Infusion-related reaction considered as AEs of special interest occurred in 6 patients
- Three patients discontinued margetuximab/retifanlimab combination therapy because of immune-related AEs: with Grade 3 renal dysfunction, Grade 3 hepatitis, Grade 1 diabetic ketoacidosis (1 each)
  - Additional immune-related AEs, which did not lead to treatment discontinuation, were Grade 1-2 hypothyroidism (n=3) and Grade 1-2 pneumonitis (n=2)
- No AE led to death

Table 2. Safety Summary

	Safety population (N=43)	
	Treatment emergent, n (%)	Treatment related, n (%)
Any AE	42 (97.7)	35 (81.4)
Any grade 3-4 AE	18 (41.9)	8 (18.6)
Any SAE	14 (32.6)	7 (16.3)
Any AE resulting in death	0	0
AEs leading to margetuximab discontinuation	3 (7.0)	3 (7.0)
AEs leading to retifanlimab discontinuation	3 (7.0)	3 (7.0)
AEs leading to margetuximab interruption	12 (27.9)	10 (23.3)
AEs leading to retifanlimab interruption	8 (18.6)	5 (11.6)

AE, adverse event; SAE, serious adverse event.

Table 3. AEs[a] Reported in ≥15% of Patients

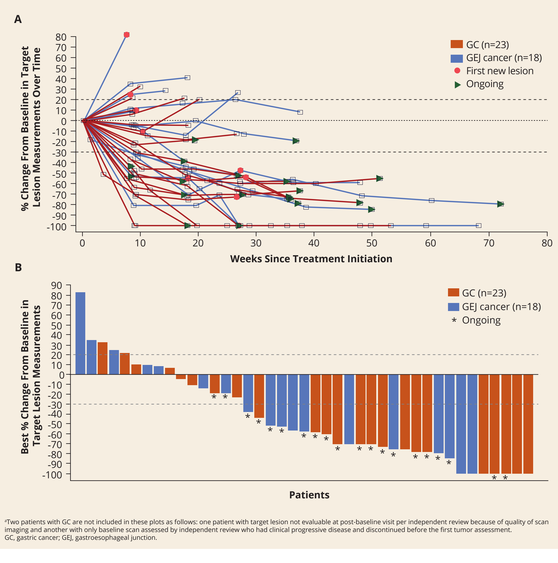
	Safety population (N=43)			
	Treatment emergent, n (%)		Treatment related, n (%)	
	Any grade, n (%)	Grade 3-4, n (%)	Any grade, n (%)	Grade 3-4, n (%)
Any AE	42 (97.7)	18 (41.9)	35 (81.4)	8 (18.6)
Diarrhea	15 (34.9)	2 (4.7)	7 (16.3)	1 (2.3)
Nausea	14 (32.6)	2 (4.7)	4 (9.3)	0
Anemia	13 (30.2)	4 (9.3)	2 (4.7)	0
Decreased appetite	11 (25.6)	2 (4.7)	0	0
Fatigue	11 (25.6)	1 (2.3)	9 (20.9)	0
Abdominal pain	10 (23.3)	2 (4.7)	3 (7.0)[b]	0
Pruritus	10 (23.3)	0	7 (16.3)	0
Vomiting	9 (20.9)	1 (2.3)	1 (2.3)	1 (2.3)
Infusion-related reaction	8 (18.6)	0	8 (18.6)	0
Rash	8 (18.6)	0	8 (18.6)	0
Dyspnea	8 (18.6)	0	2 (4.7)	0
Peripheral edema	8 (18.6)	0	1 (2.3)	0

[a]Patients are counted only once by preferred term.
[b]In 1 patient, abdominal pain was a symptom of an infusion-related reaction.
AE, adverse event.

Efficacy

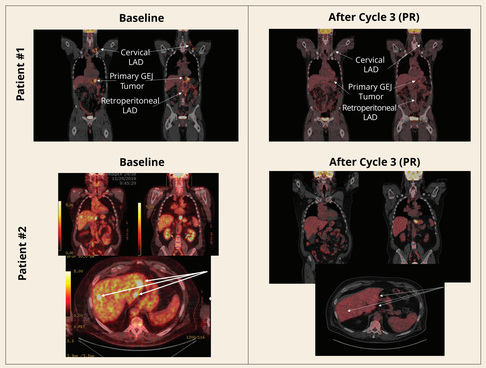
- Tumor shrinkage was seen in 32/41 (78.0%) patients with at least 1 post-baseline target lesion measurement (**Figure 3** and **Figure 4**)
- The best overall response by independent assessment for the first 40 response-evaluable non–MSI-H patients was 52.5% as shown in **Table 4**
- Progression-free survival by independent assessment and overall survival are shown in **Figure 5** and **Figure 6**

Figure 3. Change in Tumor Size Over Time (A) and Best Change in Tumor Size (B) by Independent Assessment (n=41)[a]



[a]Two patients with GC are not included in these plots as follows: one patient with target lesion not evaluable at post-baseline visit per independent review because of quality of scan imaging and another with only baseline scan assessed by independent review who had clinical progressive disease and discontinued before the first tumor assessment.
GC, gastric cancer; GEJ, gastroesophageal junction.

Figure 4. Radiographic Scans of Two Patients Who Achieved PRs After Treatment With Margetuximab + Retifanlimab



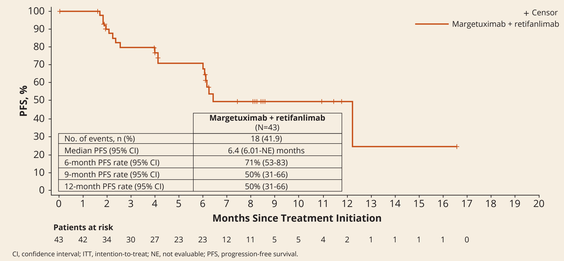
GEJ, gastroesophageal junction; LAD, lymphadenopathy; PR, partial response.

Table 4. Best Overall Response by Independent Assessment

	First 40 response-evaluable patients (N=40)
Best overall response,n (%)	
CR[a]	4 (10.0)
PR[a]	17 (42.5)
SD	9 (22.5)
PD	8 (20.0)
NE	2 (5.0)[b]
Objective response (CR + PR), n (%) [95% CI]	21 (52.5) [36.1-68.5]
Disease control (CR + PR + SD ≥3 months), n (%) [95% CI]	29 (72.5) [56.1-85.4]
Median duration of response,[c] (min, max) [95% CI], months	10.3 (2.10-14.52) [4.57-NE]

Data cutoff July 19, 2021.
[a]CR and PR includes only confirmed responses.
[b]Two patients with GC are NE: one patient with target lesion not evaluable at post-baseline visit per independent review because of quality of scan imaging and another with only baseline scan assessed by independent review who had clinical PD and discontinued before the first tumor assessment.
[c]Calculated only for patients with objective response of CR or PR (21 responders).
CR, complete response; CI, confidence interval; max, maximum; min, minimum; PR, partial response; NE, not evaluable; PD, progressive disease; SD, stable disease.

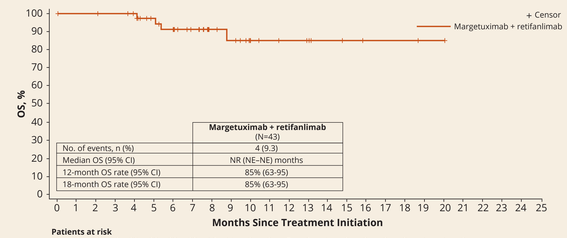
Figure 5. PFS by Independent Assessment in the ITT Population (N=43)



	Margetuximab + retifanlimab (N=43)
No. of events, n (%)	18 (41.9)
Median PFS (95% CI)	6.4 (6.01-NE) months
6-month PFS rate (95% CI)	71% (53-83)
9-month PFS rate (95% CI)	50% (31-66)
12-month PFS rate (95% CI)	50% (31-66)

CI, confidence interval; ITT, intention-to-treat; NE, not evaluable; PFS, progression-free survival.

Figure 6. OS in the ITT Population (N=43)



	Margetuximab + retifanlimab (N=43)
No. of events, n (%)	4 (9.3)
Median OS (95% CI)	NR (NE–NE) months
12-month OS rate (95% CI)	85% (63-95)
18-month OS rate (95% CI)	85% (63-95)

CI, confidence interval; ITT, intention-to-treat; NE, not evaluable; NR, not reached; OS, overall survival.

Conclusions

1. In MAHOGANY study, the majority of patients (32/41; 78%) had tumor shrinkage at first scan. Number of confirmed responders (21/40, 53%; median duration of response [DOR] of 10.3 months) by independent review exceeded prespecified futility boundary for trial. Antitumor activity was comparable to historical data from experimental arm of ToGA study (trastuzumab + CTX; n=294; ORR of 47%; median DOR of 6.9 months)[10] and initial data from control arm (placebo + trastuzumab + CTX) of KEYNOTE-811 study (ORR of 52%; median DOR of 9.5 months).[5]
2. Safety findings on 43 patients treated with margetuximab + retifanlimab suggest combination was well tolerated, with durable antitumor activity.
   a. Treatment-emergent AEs of Grade ≥3 occurred in 41.9% (18/43) of patients; 7.0% (3/43) of patients discontinued study treatment due to AEs (immune-related renal dysfunction, immune-related hepatitis, and diabetic ketoacidosis); no AEs led to death.
   b. MAHOGANY safety data compare favorably to ToGA experimental arm in which overall Grade 3-4 AEs were 68% (vs. 19% for MAHOGANY), and treatment-related mortality was 3% (vs. none for MAHOGANY).[10]
   c. Initial results from KEYNOTE-811 presented at 2021 ASCO Annual Meeting[5] indicated that AEs of Grade 3-5 occurred in 57.1% of patients in experimental arm (pembrolizumab + trastuzumab + CTX) and in 57.4% of patients in control arm, AEs leading to death occurred in 3.2% vs 4.6%, and AEs leading to discontinuation of any study drug occurred in 24.4% vs 25.9% of patients, respectively. Despite limitations of cross-study comparisons, there may be clinically relevant safety differences with regimens containing CTX (e.g., AEs of Grade ≥3, AEs leading to death or treatment discontinuation).
3. Findings from Cohort A Part 1 suggest this CTX-free combination may be a potential option for first-line HER2+ patients. Therefore, enrollment is anticipated to continue to Cohort A Part 2.

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Acknowledgments

This study is sponsored by MacroGenics, Inc. Professional medical writing support was provided by Nikola Vojtov, PhD, Emily Cullinan, PhD, CMPP, and Francesca Balordi, PhD, of The Lockwood Group (Stamford, CT, USA), in accordance with Good Publication Practice (GPP3) guidelines, funded by MacroGenics, Inc.

Disclosures

D. Catenacci has received personal fees from Archer, Astellas Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Five Prime, Foundation Medicine, Guardant Health, Genentech/Roche, Gritstone Oncology, Lilly, Merck, Natera, Pieris Pharmaceuticals, QED Therapeutics, Seattle Genetics, Taiho Pharmaceutical, Tempus Labs, and Zymeworks.

Presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2021 | September 16-21, 2021

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