CLINICAL STUDY PROTOCOL: CP-MGAH22-06
PROTOCOL AMENDMENT 5

Study Title:	A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer
Study Number:	CP-MGAH22-06
Study Phase:	Phase 2/3
Product Name:	Margetuximab
Product Number:	INCMGA00012 (also known as MGA012 or retifanlimab), MGD013 (also known as tebotelimab)
IND Number:	
EudraCT Number:	
Indication:	Treatment-naïve (metastatic or locally advanced) HER2-positive gastric cancer or gastroesophageal junction cancer
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 301-251-5172
Sponsor's Medical Monitor:	Refer to study contact list

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SPONSOR SIGNATURES

Study Title: A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer

Study Number: CP-MGAH22-06

This clinical study protocol has been approved by the Sponsor:

Signed: ***See Appended Electronic Signature Page*** Date: _____

Chief Medical Officer
MacroGenics, Inc.

Signed: ***See Appended Electronic Signature Page*** Date: _____

Senior Director, Biostatistics
MacroGenics, Inc.

LIST OF ABBREVIATIONS

The list of abbreviations of specialist terms does not include general scientific abbreviations of temperature, weight, and volume.

Abbreviation	Term
5-FU	5-fluorouracil
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BOR	Best overall response
CI	Confidence Interval
CL	Total body clearance
C_{max}	Maximum concentration
CPI	Checkpoint inhibitor
CPS	Combined positive score
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CT	Computed tomography
C_{trough}	Trough concentration
DCR	Disease control rate
DoR	Duration of response
EAP	Expanded access program
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOI	End of infusion
EOTV	End of Treatment Visit
ePPND	Enhanced pre- and postnatal development
FACT-Ga	Functional Assessment of Cancer Therapy - Gastric
FcRn	Neonatal FcR
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescent in situ hybridization

Abbreviation	Term
GC	Gastric cancer
GEJ	Gastroesophageal junction
HBV	Hepatitis B virus
HCB	Hepatitis C virus
HR	Hazard ratio
HER2	Human epidermal growth factor receptor 2
ICF	Informed consent form
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
IV	Intravenous
irAE	Immune-related adverse events
LAG-3	Lymphocyte-activation gene 3
LVEF	Left ventricular ejection fraction
mAb	Monoclonal Antibody
MedDRA	Medical dictionary for regulatory activities
mFOLFOX-6	Modified fluorouracil, leucovorin, and oxaliplatin regimen 6
MHC-II	Major histocompatibility complex class II
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability-High
MUGA	Multigated acquisition ventriculography scanning
NK	Natural killer
NE	Not evaluable
NSCLC	Non-small cell lung carcinoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PEP	Primary efficacy population
PFS	Progression-free survival

Abbreviation	Term
PK	Pharmacokinetics
PPK	Population PK
PQC	Product Quality Complaint
PR	Partial response
PREP	Primary response evaluable population
PRO	Patient-reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
REP	Response Evaluable Population
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
ToGA	Trastuzumab for Gastric Cancer
TRAE	Treatment-related adverse event
US	United States
V_D	Volume of distribution at steady state
WOCBP	Women of child-bearing potential
XELOX	Capecitabine and oxaliplatin

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:**
Name of Product: Margetuximab, INCMGA00012 (also known as MGA012), MGD013	
Study Title: A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer	
Study Number: CP-MGAH22-06	
Study Phase: 2/3	
Investigator(s)/Centers: Cohort A Part 1 and Part 2 will be conducted in approximately 40-80 centers in approximately 10 countries. Cohort B Part 1 will be conducted at approximately 50-70 centers in approximately 10 countries.	
Primary Objective(s): <u>Cohort A:</u> • To evaluate the safety and tolerability of margetuximab + INCMGA00012 in patients with untreated locally advanced or metastatic gastric cancer (GC) or gastroesophageal junction (GEJ) cancer that is human epidermal growth factor 2 (HER2) immunohistochemistry (IHC) 3+ and PD-L1+ by IHC staining. • To evaluate the objective response rate (ORR) of margetuximab + INCMGA00012 for non-microsatellite instability-high (non-MSI-H) patients in the response evaluable population (REP) using Investigator-assessed radiology reviews.	
Secondary Objective(s): **<u>Cohort A:</u>** • To determine duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) using Investigator-assessed radiology review for non-MSI-H patients. • To evaluate the number of patients with anti-drug antibodies (ADA) to margetuximab or INCMGA00012, or both. Cohort B, Part 1: • To evaluate ORR and DCR of each treatment arm. • To evaluate the number of patients with ADA to margetuximab, MGD013, and INCMGA00012.	
Study Drugs: Margetuximab is an Fc-optimized mouse-human chimeric anti-HER2 monoclonal antibody (mAb). INCMGA00012 is a hinge-stabilized, humanized immunoglobulin (Ig)G4κ anti-programmed death receptor 1 (PD-1) mAb. MGD013 is a humanized Fc-bearing bispecific tetravalent (bivalent for each antigen) DART® molecule with specificity for PD-1 and LAG-3.	

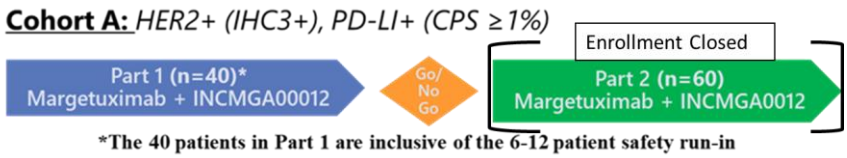
Study Design:

This is a Phase 2/3, randomized, open-label study for the treatment of patients with HER2+ GC or GEJ cancer will determine the efficacy of margetuximab combined with a checkpoint inhibitor (CPI) INCMGA00012 in patients who are positive for both HER2 and PD-L1 (Cohort A), and a margetuximab plus CPI (INCMGA00012 or MGD013) plus chemotherapy compared to trastuzumab (marketed as HERCEPTIN®) plus chemotherapy in patients who are HER2 positive, irrespective of PD-L1 status (Cohort B). Patients will be treated in 3-week (21-day) cycles. Cohort A and Cohort B will not be opened simultaneously at the same institution.

Cohort A (Single Arm):

Cohort A was closed prior to completing enrollment target.

INCMGA00012 plus margetuximab. The efficacy of INCMGA00012 plus margetuximab will be evaluated in up to approximately 100 patients that are HER2 IHC3+, PD-L1+, and non-MSI-H. Enrollment will occur without prior ascertainment of MSI status. If the MSI status is determined to be MSI-H, patients will be allowed to remain on treatment but will be removed from the efficacy analysis. It is expected that about 110 patients will need to be enrolled to have approximately 100 non-MSI-H patients. Patients will receive 375 mg of INCMGA00012 once every 3 weeks (Q3W) plus 15 mg/kg of margetuximab Q3W. In addition to regular Sponsor medical oversight, the independent data monitoring committee (IDMC) will review all accumulated safety data from all enrolled patients and provide a recommendation to the Sponsor. The first scheduled IDMC meeting will take place after the first 12 patients have completed at least 1 cycle of study treatment, or at 6 months from first enrollment, whichever comes first. Enrollment will continue during the evaluation. Reviews will continue in 6-month intervals (± 1 month). After approximately 40 patients have enrolled and are evaluable for response, data will be analyzed for ORR, as determined by central imaging review, and safety. Additional patients will be enrolled in Part 2 of the cohort if the threshold for study continuation is met. Decision rules that govern the analysis of the ORR from Part 1 and continuation of Part 2 of Cohort A are outlined in **Section 14.7.1**.



Cohort B Part 1 (Randomized, open-label):

Cohort B was closed prior to completing enrollment target.

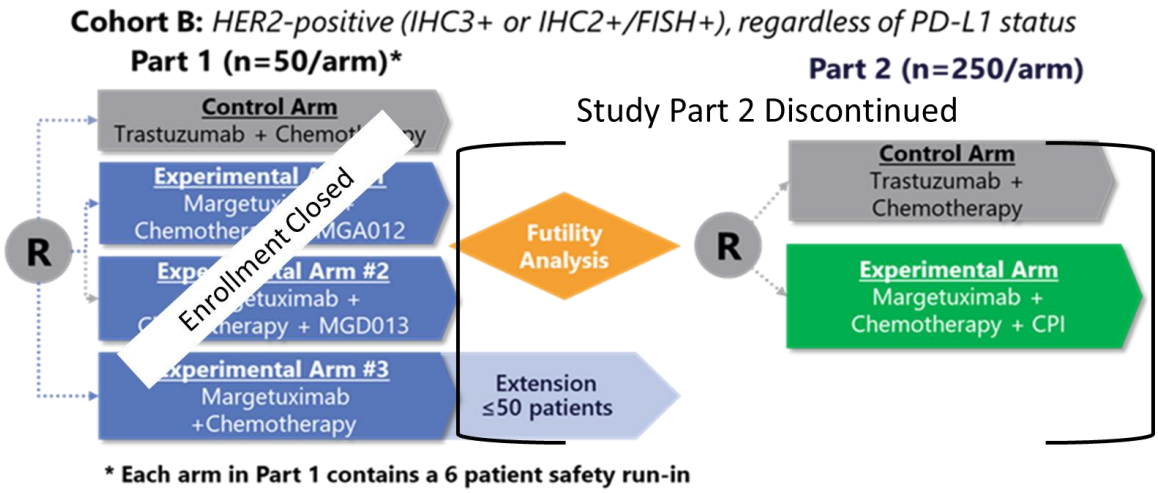
Cohort B Part 1 consists of 4 arms: 1 control arm of trastuzumab plus chemotherapy and 3 experimental arms of margetuximab-containing regimens. Experimental Arms 1 and 2 will combine margetuximab plus a CPI plus chemotherapy. The CPI for Experimental Arm 1 is INCMGA00012, and the CPI for Experimental Arm 2 is MGD013. Experimental Arm 3 will evaluate margetuximab alone in combination with chemotherapy. Chemotherapy will be capecitabine and oxaliplatin (XELOX) or modified 5-FU, leucovorin, and oxaliplatin regimen 6 (mFOLFOX-6), according to the investigator's choice based on local approval and availability. The first safety evaluation by the IDMC will take place after 20 patients in each arm have enrolled and completed at least 1 cycle of treatment, or at approximately 6 months from first enrollment, whichever comes first. Reviews will continue in 6-month intervals (± 1 month). Once the first assessment in Cohort B is completed, to the extent possible, safety and efficacy data from Cohort A and Cohort B will be reviewed at the same meeting.

Control arm: trastuzumab at an 8 mg/kg loading dose then 6 mg/kg Q3W, in combination with XELOX or mFOLFOX-6 chemotherapy.

Experimental Arm 1: 375 mg of INCMGA00012 Q3W plus 15 mg/kg of margetuximab Q3W, in combination with XELOX or mFOLFOX-6 chemotherapy.

Experimental Arm 2: 600 mg MGD013 Q3W plus 15 mg/kg of margetuximab Q3W, in combination with XELOX or mFOLFOX-6 chemotherapy.

Experimental Arm 3: margetuximab 15 mg/kg in combination with XELOX or mFOLFOX-6 chemotherapy.



IHC = immunohistochemistry; R = randomize,

Number of Patients Enrolled:

There were 48 patients enrolled in Cohort A (Parts 1 and 2). There were 34 patients randomized of which 33 patients were treated Cohort B Part 1. No patients were enrolled in Cohort B Part 2.

Patient Population/Key Entry Criteria:

The patient population to be enrolled in this study will consist of adult patients with a histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2+ GC or GEJ adenocarcinoma. Patients will have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and no clinically significant cardiovascular disease. For Cohort A, patients will be HER2+ (IHC 3+), PD-L1+ [combined positive score (CPS ≥ 1%)] by central review. Cohort B patients will be HER2+ [IHC 3+, or IHC 2+ and fluorescent in situ hybridization (FISH+)], irrespective of PD-L1 status.

Duration of Treatment and Study Duration:

Study treatment will continue until completion of therapy, persistent CR, disease progression, unacceptable toxicity, withdrawal of consent, physician recommendation to discontinue therapy, or death. Patients will be evaluated at the end of every 3 cycles (± 7 days) for the first 9 months for radiographic evidence of disease progression. Beginning with Cycle 13, assessments will occur every 4 cycles (± 7 days).

The maximum duration of protocol-specified study treatments are:

Cohort A	35 cycles of margetuximab and INCMGA00012			
Cohort B, Part 1	Arm	Chemotherapy	Anti-HER2 Therapy	Anti PD-1/PD-L1 Therapy
	Control	8 cycles XELOX or 12 cycles mFOLFOX-6	35 cycles trastuzumab	N/A
	1		35 cycles margetuximab	35 cycles INCMGA00012
	2		35 cycles margetuximab	35 cycles MGD013
	3		Until disease progression	N/A

Discontinuation of study treatment may be considered for patients who have attained persistent CR. The criteria for **persistent CR include:**

- confirmed CR and at least 8 complete cycles (approximately 6 months) of study treatments, and
- an additional 2 cycles of study treatment must be completed beyond the date of initial CR.

Patients in Cohort A only who have radiographic progression but are clinically stable may remain on study treatments until the next scheduled radiographic evaluation, upon Sponsor Medical Monitor consultation.

There is no crossover in this study to a different treatment arm or different cohort. Following discontinuation of study treatment, each patient will be followed for safety for up to 30 days, or until initiation of subsequent anticancer therapy, whichever comes first. Patients currently in survival follow-up will be discontinued from the study.

The end of study occurs after the last patient completes the safety follow-up period.

Criteria for Evaluation:

Safety Assessments:

The safety assessment will be based on the evaluation of adverse events (AE) that occur from the time of initiation of study treatment through 30 days after the last dose of study treatment or until the start of a subsequent anticancer therapy. Determination of AEs are based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients as appropriate. Progression of the underlying neoplasm resulting in hospitalization or death [e.g., patient hospitalized for, or death from, PD only, without any other serious adverse events (SAE)] will be documented as an antitumor activity outcome and not as an SAE.

Tumor Assessments:

Tumor assessments will be obtained using computed tomography (CT) or magnetic resonance imaging (MRI) scans and evaluated using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) guideline. Assessments will be performed every 3 cycles (± 7 days) for the first 9 months, beginning at Cycle 13 every 4 cycles (± 7 days) until treatment discontinuation. Measurement or assessment of individual lesions is not required. Overall response per assessment should be recorded per RECIST v1.1.

Pharmacokinetic Assessments:

Serum concentrations of margetuximab, INCMGA00012, and MGD013 will be monitored using validated assay methods.

Immunogenicity Assessments:

The generation of ADA for margetuximab, INCMGA00012, and MGD013 will be monitored using validated bioanalytical methods.

Pharmacodynamics/Biomarker Assessments

Biomarker assessments related to entry criteria will be performed prospectively prior to enrollment. Other biomarker assessments not related to entry criteria will be prospectively collected and retrospectively analyzed.

Cohort A

- MSI status performed by a central laboratory
- PD-L1 and HER2 expression by IHC will be conducted with Food and Drug Administration (FDA)-approved assays by a central laboratory for eligibility.

Cohort B

- Determination of MSI status by a central laboratory
- LAG-3 expression based on FFPE tumor tissue

- Determination of PD-L1 and HER2 expression will be conducted with FDA-approved assay for central confirmation.

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, respectively. Patients enrolled in Cohort B will be analyzed according to the actual treatment received rather than the treatment group they were assigned. This population will also be used to summarize baseline data for Cohort A.

PK Evaluable Population: All patients who received at least one dose of study drug, date and time of dose administration and relative PK sample collection are known and have sufficient concentration data to derive at least one PK parameter.

ADA Evaluable Population: All patients who received at least one dose of study treatment, date and time of dose administration and relative PK sample collection are known and have sufficient concentration data to derive at least one PK parameter.

ITT Population: All patients who are assigned to treatment in Cohort A and all patients who are randomized into Cohort B of the study for each of the respective cohorts. Patients will be analyzed according to the treatment assigned. This population will be used to summarize baseline data and evaluate PFS.

Response Evaluable Population (REP): All patients who received at least one dose of study drug and had baseline radiographic tumor assessment. This population will be used for response related efficacy analyses for Cohort A and Cohort B, respectively, and will be analyzed according to the actual treatment received.

Statistical Methods:

A separate statistical analysis plan (SAP) and statistical programming plan will further describe the details regarding statistical methods and will govern the analysis.

Sample Size:

The planned sample sizes are described below. The study enrollment was closed. There are 48 patients treated in Cohort A. There were 34 patients randomized of which 33 patients were treated in Cohort B Part 1. Cohort B Part 2 has never started.

Cohort A: The sample size of approximately 100 non-MSI-H patients is based on a Simon two-stage design to provide approximately 83% power to test ORR of at a 2-sided alpha level of 0.05. The first stage (Part 1) will enroll and treat response evaluable 40 non-MSI-H patients. If at least 21 (53%) responders [complete response (CR) or partial response (PR)] are observed, the study will move to the second stage (Part 2) with enrollment of approximately 60 additional response evaluable non-MSI-H patients. Other efficacy data such as DoR and PFS will be considered as well in enrollment decision-making. If the study continues to enroll an additional 60 patients, the null hypothesis H_0: ORR = would be rejected at 1-sided alpha level of 0.025 (or equivalently, 2-sided 0.05) if the observed ORR from all 100 response evaluable non-MSI-H patients is ≥ . The totality of the data will be assessed to determine not only statistical significance but a clinically meaningful effect. The total number of patients to be enrolled in Cohort A is expected to be approximately 110 in order to obtain approximately 100 non-MSI-H patients.

Cohort B: The sample size for Cohort B is determined based on a Phase 2/3 design. The sample size will consist of patients that are HER2+ by central confirmation. Entry criteria for HER2 may be based on a local test, however, enrollment will continue until the sample size is accrued based on central confirmation. The total planned sample size for Cohort B is approximately 750, consisting of two parts:

Cohort B Part 1, approximately 200 patients will be randomized in a 1:1:1:1 ratio to 1 of 4 arms (one control arm and three margetuximab-containing arms). The randomization will be stratified by two stratification factors: chemotherapy regimen (XELOX vs mFOLFOX-6) and results of local HER2 testing (IHC 2+/FISH+ vs IHC 3+). Selection of which margetuximab and CPI-containing arm to move to the Phase 3 part of the study (Cohort B Part 2) for further testing will be primarily based on ORR but may also take into consideration PFS and safety.

During the interim analysis, up to 50 additional patients will be added to Experimental Arm 3.

Cohort B Part 2, approximately 500 additional patients will be randomized in a 1:1 ratio between the control arm and the selected margetuximab arm. The randomization will be stratified by two stratification factors: chemotherapy regimen (XELOX vs. mFOLFOX-6) and results of local HER2 testing (IHC 2+/FISH+ vs IHC 3+).

By applying the closed testing procedure and the inverse normal p-value combining method to test OS, respectively, at the end of the Cohort B Part 2 part of the study, the sample size of approximately 650 planned enrollment [Cohort B Part 1: control arm (50 patients) and 2 margetuximab and CPI-containing arms (100 patients)] and 500 patients from Cohort B Part 2] will provide approximately 80% power to detect OS hazard ratio (HR) = (median OS increase from months for control arm to months for either selected margetuximab and CPI-containing arm) at 1-sided 0.025 (or equivalently, 2-sided 0.05) alpha level.

Safety:

AEs will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Only treatment-emergent AEs will be summarized in tables. Events prior to treatment (e.g., due to study-related procedure) will be listed in an appendix to the final study report.

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by laboratory panel (e.g., hematology, blood chemistry, and urinalysis) and will be displayed by visit for each laboratory parameter.

Efficacy:

Primary Efficacy Endpoint and Analyses for Cohort A

The primary efficacy endpoint for Cohort A is ORR per RECIST v1.1, defined as the proportion of non-MSI-H patients in the Response Evaluable Population who achieve the best overall response (BOR) of CR or PR (called responders) per RECIST v1.1. The 2-sided 95% exact binomial confidence interval (CI) of ORR will be calculated.

For RECIST v1.1, the BOR will be categorized as CR, PR, stable disease (SD), PD, or not evaluable (NE). To be qualified as BOR, CR, and PR require confirmation at least 4 weeks after initial observation response. SD requires to be observed at least once after 6 weeks. BOR will be evaluated from the start of study treatment.

The analysis of ORR will be based on investigator review determined response data.

Secondary Efficacy Endpoints and Analyses for Cohort A

The secondary efficacy endpoints for non-MSI-H patients in Cohort A are:

- PFS, defined as the time from start of study treatment to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first.
- DoR, defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first.
- DCR, defined as the percentage of the REP who experienced response of CR, PR, or SD for at least 3 months from start of study treatment.

Efficacy Endpoints and Analyses for Cohort B Part I

The efficacy endpoints for Cohort B Part I are ORR and DCR based on the response evaluable population. The analysis methods are same as those for Cohort A.

2 BACKGROUND INFORMATION

Gastric cancer (GC) is the fifth most common malignancy, with half of all diagnoses occurring in Eastern Asia. It is the third leading cause of cancer death worldwide, with the highest estimated mortality rates occurring in Eastern Asia (http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). In the United States (US) in 2018, it is estimated that about 26,240 people will be diagnosed with GC and 10,800 individuals will die from this disease (**51**, **57**). Human epidermal growth factor receptor 2 (HER2) positivity has been observed in 7% to 35% of GC tumors (**4**). The introduction of targeted treatments for GC has improved overall survival (OS) rates for specific populations.

2.1 Anti-HER2 Therapy in Gastric Cancer

In the Trastuzumab for Gastric Cancer (ToGA) trial (**4**), trastuzumab, a monoclonal antibody (mAb) against HER2, in combination with chemotherapy increased median OS by approximately 2.7 months and is now used for the first-line treatment of HER2+ advanced GC or gastroesophageal junction (GEJ) cancer. This trial established HER2 as a validated target in patients with GC or GEJ cancer and demonstrated that patients with overexpression of HER2 benefit from receiving trastuzumab in addition to standard (frontline) fluoropyrimidine/cisplatin chemotherapy. Median OS and progression-free survival (PFS) in the chemotherapy plus trastuzumab-treated patients were 13.8 months and 6.7 months, respectively, compared to 11.1 months and 5.5 months, respectively, in patients treated with chemotherapy alone. An exploratory analysis conducted in patients whose tumors had high HER2 expression [as defined by HER2 3+ or 2+ by immunohistochemistry (IHC)] combined with amplification by in-situ hybridization (ISH), demonstrated a median OS of 16 months for patients treated with chemotherapy plus trastuzumab vs 11.8 months for patients treated with chemotherapy alone. These results have formed the basis for using trastuzumab as standard of care for frontline treatment of HER2+ GC or GEJ cancer patients (**28**).

The US Food and Drug Administration (FDA) granted trastuzumab approval for use in patients with advanced GC with positive ISH results or an IHC score 3+ (**21**). The European Medicines Agency (EMA) limited the approval to patients with GC with HER2 overexpression as defined by HER2 IHC score 2+, confirmed by a positive ISH result, or by HER2 IHC 3+ (**15**). Following publication of the results of the ToGA trial, trastuzumab in combination with fluoropyrimidine/cisplatin/ became a standard first-line treatment for patients with HER2+ advanced GC. Due to its more favorable toxicity profile, fluoropyrimidine in combination with oxaliplatin has become a preferred first-line treatment option for the management of advanced gastroesophageal cancers. Two Phase 2 studies have explored the combination of trastuzumab with capecitabine and oxaliplatin (XELOX) in patients with HER2+ advanced GC. Both studies demonstrated objective response rates (ORRs) of 67% and tolerability of this combination therapy (**23**, **48**).

A recent meta-analysis of studies comparing chemotherapy to trastuzumab plus chemotherapy in advanced HER2+ GC, reported that trastuzumab plus chemotherapy provides only 20% improvement of OS and 30% improvement in PFS over chemotherapy alone (**64**).

2.2 Anti–PD-1 Therapy in Gastric Cancer

Programmed death receptor 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1), are expressed in up to 70% of GC or GEJ cancers (**8**, **50**, **63**). PD-L1 expression has been associated with a poor prognosis (**13**, **46**), although occasional studies have found a reverse correlation (**35**). By overexpressing PD-L1 directly or inducing PD-1 expression on immune cells, cancer cells exploit the PD-1/PD-L1 pathway to promote an immunosuppressive environment and allow immune escape and tumor growth. The antitumor activity of various anti–PD-1 antibodies, including both nivolumab and pembrolizumab, has been investigated in various studies in patients with GC or GEJ cancer.

In KEYNOTE-012, a Phase 1b study of pembrolizumab in 39 patients with recurrent or metastatic PD-L1+ (≥ 1% tumor cell cutoff; 22C3 assay) GC or GEJ cancer, the ORR by central review was 22% and the median OS was 11.4 months overall. Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 13% of patients. In KEYNOTE-059 Cohort 1, 259 patients received pembrolizumab monotherapy as third-line or later treatment (**18**). The ORR in this cohort was 12%, with a trend for higher ORR in PD-L1+ vs PD-L1 negative tumors (16% vs 6%, respectively). Median OS was 5.5 months. PD-L1 status was based on a combined positive score (CPS) of ≥ 1% PD-L1+ tumor or immune cells via the 22C3 assay. Grade ≥ 3 TRAEs occurred in 18% of patients. Results from this cohort led to the accelerated approval of pembrolizumab by the FDA as third-line treatment for patients with advanced PD-L1+ GC or GEJ cancer.

In KEYNOTE-061, 592 patients received pembrolizumab monotherapy as second-line treatment (**50**). Median OS was 9.1 months (95% confidence interval [CI] 6.2–10.7) with pembrolizumab and 8.3 months (7.6–9.0) with paclitaxel (hazard ratio [HR] 0.82, 95% CI 0.66–1.03; one-sided p = 0.0421). Median PFS was 1.5 months (95% CI 1.4–2.0) with pembrolizumab and 4.1 months (3.1–4.2) with paclitaxel (HR 1.27, 95% CI 1.03–1.57). In the total population, Grade 3–5 TRAEs occurred in 42 (14%) of the 294 patients treated with pembrolizumab and 96 (35%) of the 276 patients treated with paclitaxel.

Nivolumab was approved for the treatment of unresectable advanced or recurrent GC that has progressed after chemotherapy, based on the Phase 3 study ATTRACTION-2 (ONO-4538-12), in which nivolumab significantly reduced patients' risk of death by 37% (HR 0.63; 95% CI 0.51–0.78, P < 0.0001) when compared to placebo (**33**). Furthermore, nivolumab demonstrated a greater OS rate at 12 months vs placebo: 26.2% (95% CI 20.7–32.0) and 10.9% (95% CI 6.2–17.0), respectively. TRAEs of any grade and Grade 3 or 4 occurred in 42.7% vs 26.7% and 10.3% vs 4.3% of nivolumab-treated and placebo-treated patients, respectively. Grade 3 or 4 TRAEs reported in more than 2 patients were diarrhea, fatigue, decreased appetite, pyrexia, increased aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in the nivolumab group. Fatigue and decreased appetite were reported in the placebo group. Nivolumab and placebo-treated patients had similar rates of TRAEs leading to discontinuation, 2.7% and 2.5%, respectively.

A summary PD-L1 status in recent studies is provided in **Table 1**.

Table 1 PD-L1 Status in Trials of Available Anti–PD-1/PD-L1 Monotherapy Data in GC or GEJ Cancer

Study ID	ATTRACTION-2		KEYNOTE-059			KEYNOTE-061			
PD-L1 status	NR		PD-L1			CPS < 1		CPS ≥ 1	
	plb	Nivo	+	-	Total	Pembro	Ptx	Pembro	Ptx
ORR	0	11.2	15.5	6.4	11.6	NR	NR	15.8	13.6
mPFS	NR	NR	NR	NR	2.0	NR	NR	1.5	4.1
mOS	4.14	5.26	5.8	4.9	5.6	4.8	8.2	9.1	8.3

CPS = combined positive score, Nivo = nivolumab, NR = not reported, PD-L1 = programmed death ligand 1, Pembro = pembrolizumab, plb = placebo, Ptx = Paclitaxel

2.3 Anti-LAG-3 Therapy in Gastric Cancer

In addition to PD-1, another immune checkpoint molecule of growing interest is lymphocyte-activation gene 3 (LAG-3), a membrane protein that belongs to the immunoglobulin (Ig) superfamily and binds to major histocompatibility complex class II (MHC-II). LAG-3 engagement enhances regulatory T-cell activity and negatively regulates T-cell proliferation and differentiation (**3**). LAG-3 has been shown to be expressed on dysfunctional, “exhausted” T cells and is a marker for regulatory T cells, suggesting an immune suppressive role (**52**). Blockade of PD-1 and LAG-3 in animal tumor models generated enhanced antitumor immunity via distinct, nonredundant signaling pathways that fostered the accumulation of functionally competent CD8+ T cells in mice (**26**, **62**). In GC, several intrinsic factors, including LAG-3 and PD-1 have been recognized as negative regulatory proteins that block the expansion and suppress the effector function of antigen-specific CD8+ T cells (**56**). An IHC analysis conducted by the Sponsor of tumor specimens from 34 GC patients revealed the majority (30/34) contained lymphocyte infiltrates with detectable LAG-3 expression (**Table 2**). Because PD-1 and LAG-3 expression on both CD4+ and CD8+ T cells are upregulated in GC, dual targeting PD-1 and LAG-3 may be an effective way to enhance the treatment of GC (**38**, **56**).

Table 2 LAG-3+ Tumor Infiltrating Lymphocyte Profile Across Gastric Adenocarcinoma

Any detectable LAG-3$^+$ TIL	Moderate or above LAG-3$^+$ TIL	Heavy LAG-3$^+$ TIL
30/34 (88.2%)	19/34 (55.9%)	15/34 (44.1%)

LAG-3–positive tumor infiltrating lymphocyte prevalence rate determined by IHC analyses across 34 independent GC patient specimens. IHC was performed with anti–LAG-3 antibody EPR4392 (Abcam) using the Ventana Discovery Ultra Platform and the following scoring criteria applied within the area of highest observed density LAG-3 expressing lymphocytes by 40x magnification: negative scoring < 1 LAG-3$^+$ lymphocyte; light: 1-5 LAG-3$^+$ lymphocytes; moderate: 6-15 LAG-3$^+$ lymphocytes; and heavy: > 15 LAG-3$^+$ lymphocytes.

2.4 Rationale for Study Treatments

2.4.1 Margetuximab

Increased clinical activity of the anti-HER2 mAb trastuzumab has been seen in patients with HER2+ breast cancer (**20**, **42**) or HER2+ GC (**59**) who were homozygous for CD16A-158V, compared with CD16-A 158F allele carriers (F/F and V/F). The homozygous V/V genotype is present in approximately 15% of Caucasian, African American, and Asian populations, and the lower affinity F/F and intermediate affinity F/V carriers comprise the remainder of the population. Since most patients carry the lower affinity allele of CD16A, the engineered Fc domain of margetuximab is expected to confer benefit to the whole patient population and not disproportionately to the higher affinity CD16A V/V homozygotes.

Margetuximab is an Fc-optimized mouse-human chimeric mAb that binds to the human HER2/neu antigen. Margetuximab was derived from the murine precursor to the humanized therapeutic antibody, trastuzumab, 4D5. Margetuximab is produced as a full-length glycosylated IgG1 κ immunoglobulin using a Chinese hamster ovary cell line. Margetuximab maintains the same direct anti-proliferative activity as trastuzumab but, in contrast to trastuzumab, margetuximab binds with increased affinity to both allotypes of the activating Fc receptor, CD16A, and decreased affinity to the inhibitory Fc receptor, CD32B, due to specific mutations introduced into its Fc region.

Consistent with its enhanced binding to CD16A, margetuximab exhibits enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) activity in vitro against HER2-expressing tumor cell lines and enhanced antitumor activity against HER2+ xenografts in mice transgenic for human CD16A-158F.

In studies with N87 (HER2 3+ GC) target cells and natural killer (NK) effector cells obtained from donors with differing CD16A-158 genotypes, margetuximab was 7- to 84-fold more potent in mediating ADCC than trastuzumab (**37**). A greater fold difference in potency was evident with NK cells that expressed the more common, lower affinity FF and VF genotypes than those that expressed the less common, high affinity VV genotype.

When peripheral blood mononuclear cells (PBMCs) and HER2 3+ N87 cells are incubated with margetuximab, NK ($CD56^+CD3^-$) cells and NKT ($CD56^+CD3^+$) cells are induced to express markers of activation (CD137), cytolytic capability (granzyme B, perforin) and proliferation (Ki67) to levels that are greater than those induced by trastuzumab. By contrast, an Fc null variant of margetuximab was generally ineffective, indicating that the induced changes in NK and NKT cells were Fc-dependent (**37**). Thus, margetuximab with an engineered Fc domain induces NK and NKT responses more effectively than trastuzumab with a wild type Fc domain. These differential effector cell responses occurring in the presence of HER2-expressing target cells are consistent with the higher ADCC potency of margetuximab compared to trastuzumab.

Enhanced ADCC activity may result in increased tumor antigen presentation and an improved adaptive immune response. Analysis of blood samples collected from patients in the Phase 1 study (CP-MGAH22-01) demonstrated that single-agent margetuximab treatment of HER2+ cancer patients, who had received multiple prior treatments, was associated with enhanced HER2-specific T-cell and antibody responses together with increased T-cell receptor CR clonality, which is indicative of a more focused T-cell repertoire. The high frequency of HER2-specific immunity observed in the margetuximab-treated patients (> 95%) is consistent with the enhanced Fc region of margetuximab contributing to linkage of innate and adaptive immune responses.

2.4.2 Margetuximab in Combination with Checkpoint Inhibitors

Combination with Anti–PD-1

Enhanced ADCC activity mediated by margetuximab toward HER2-overexpressing tumor cells may facilitate cross-talk between innate and adaptive immune responses. The Sponsor hypothesizes that induction of ADCC against HER2+ tumor cells and facilitation of adaptive immunity by margetuximab may be further potentiated in combination with immune CPIs. Trastuzumab-mediated upregulation of PD-L1 through engagement of immune effector cells has been reported as a potential mechanism of trastuzumab resistance (**12**). Emerging evidence suggests that anti–PD-1 antibodies could potentiate the antitumor activity of anti-HER2 antibodies (**55**, **60**).

Study CP-MGAH22-05 evaluates simultaneous targeting of HER2 with margetuximab and PD-1 with pembrolizumab as therapy for relapsed or refractory HER2+ GC. As of 10 July 2019, 95 patients received the combination of margetuximab and pembrolizumab. TRAEs irrespective of grade were reported in 63.2% (60/95) of patients, and 20.0% (19/95) had a TRAE grade ≥3. The most common TRAEs occurring in ≥10% of patients were pruritus (n=16; 16.8%), diarrhea (n=14; 14.7%), infusion-related reaction (IRR; n=13; 13.7%), and fatigue (n=13; 13.7%). Serious grade 3 TRAEs were: autoimmune hepatitis (n=2), pneumonitis (n=1), hyponatremia (n=1), diabetic ketoacidosis (n=1), hypotension (n=1), IRR (n=1), and dehydration (n=1) and grade 2 dizziness (n=1). TRAEs of special interest were hyperthyroidism (n=3), adrenal insufficiency (n=3), autoimmune hepatitis (n=2), pneumonitis (n=2), left ventricular ejection fraction dysfunction (n=2), diabetes mellitus (n=1), hyperglycemia (n=1), and hypothyroidism (n=1). There were no grade 5 TRAEs reported.

HER2 eligibility in CP-MGAH22-05 was based on archival tissue. Published data show loss of HER2 expression after trastuzumab therapy (44, 49). As an exploratory endpoint, HER2 expression post-trastuzumab was evaluated by measuring ERBB2 amplification on cell-free tumor DNA; data showed retention of HER2 expression in approximately 60% of patients. GC had higher PD-L1 expression than GEJ cancer (43% vs 9%, respectively). This coincided with more responses in IHC 3+ GC than GEJ patients. Response to treatment is displayed in **Table 3**. In the HER2 3+ and PD-L1+ GC population (n=25), responses were observed in 11 (44.0%) patients.

Table 3 Efficacy Results in Gastric Cancer Population by Biomarker Expression

	N	ORR (cCR+cPR), n (%) [95% CI]	DCR (cCR+cPR+SD), n (%) [95% CI]
Response evaluable population [a, b]	92	17[c] (18.48) [11.15–27.93]	49 (53.26) [42.56–63.74]
HER2 IHC3+	71	17 (23.94) [14.61–35.54]	44 (61.97) [49.67–73.24]
HER2 IHC2+	21	0	5 (23.81) [8.22–47.17]
PD-L1+	33	11 (33.33) [17.96–51.83]	22 (66.67) [48.17–82.04]
PD-L1–	43	3 (6.98) [1.46–19.06]	19 (44.19) [29.08–60.12]
HER2 IHC3+ & PD-L1+ [c]	25	11 (44.00) [24.40–65.07]	18 (72.00) [50.61–87.93]
HER2 IHC2+ & PD-L1–	9	0	0
HER2 IHC3+ & PD-L1–	34	3 (8.82) [1.86–23.68]	19 (55.88) [37.89–72.81]
HER2 IHC2+ & PD-L1+	8	0	4 (50·00) [15·70–84·30]
***ERBB2*^{amp}+ (by ctDNA)**	48	15 (31.25) [18.66–46.25]	31 (64.58) [49.46–77.84]
***ERBB2*^{amp}– (by ctDNA)**	34	2 (5.88) [0.72–19.68]	13 (38.24) [22.17–56.44]

a. Confirmed responses only are included in this table; there were 3 additional unconfirmed responses.
b. Patients who received at least one dose of margetuximab at the 15 mg/kg IV q3w dose and had baseline measurable disease.
c. One cCR was observed in double-positive (HER2 IHC3+ & PD-L1+) subgroup.

BL=baseline; cCR=confirmed complete response; cPR=confirmed partial response; DCR=disease control rate; ctDNA=circulating tumor DNA; ERBB2amp=ERBB2 amplifications; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; ORR=objective response rate; PD-L1=programmed death-ligand 1; SD=stable disease.

Based on efficacy results in the double-positive population from CP-MGAH22-05, combined INCMGA00012 (also known as retifanlimab) and margetuximab in double-positive first-line patients may be comparable to standard treatment with trastuzumab and chemotherapy. Patients in Cohort A (chemotherapy-free regimen) will be required to be HER2 ICH 3+, since

this was identified as the population with the highest disease control rate (DCR) in Study CP-MGAH22-05.

Recent data from a study of trastuzumab plus pembrolizumab plus XELOX chemotherapy in the first-line setting was published (32). All of the 24 evaluable patients had tumor regression (ranging from -22% to -100%). The Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) ORR was 83% (95% CI 63%-95%) (17 PR, 3 CRs), and median PFS 11.4 (95% CI 6-15) months. A Phase 3 clinical trial to evaluate pembrolizumab vs placebo in combination with trastuzumab and chemotherapy has been initiated.

INCMGA00012 is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1. INCMGA00012 contains a hinge-stabilized human IgG4 Fc domain to limit effector function, while retaining neonatal FcR (FcRn) binding to extend circulating half-life. INCMGA00012 binds to PD-1 expressing cells in a dose-dependent manner. Consistent with its specific binding properties and designed mechanism of action, INCMGA00012 blocks the binding of the ligands PD-L1 and programmed death ligand 2 (PD-L2) to cell surface-expressed PD-1 in a dose-dependent manner. These properties of INCMGA00012 are comparable to those observed with replicas of the approved anti–PD-1 mAbs, nivolumab and pembrolizumab (**Table 4**). INCMGA00012 also blocks the PD-1/PD-L1 inhibitory axis (measured with a luciferase reporter assay system) in a dose-dependent manner that is comparable to those observed with the nivolumab and pembrolizumab replicas (**Table 4**).

Table 4 Comparison of In Vitro Potencies of INCMGA00012 and Nivolumab and Pembrolizumab Replicas

Property	EC_{50} (or IC_{50}) Values (µg/mL) [1] Mean ± SEM		
	INCMGA00012	Nivolumab Replica	Pembrolizumab Replica
Binding to PD-1-expressing NS0/PDCD1 cells	0.138 ± 0.046	0.158 ± 0.058	0.140 ± 0.048
Inhibition of sPD-L1 binding to PD-1 expressing NS0/PDCD1 cells	0.010 ± 0.001	0.016 ± 0.005	0.014 ± 0.001
Inhibition of sPD-L2 binding to PD-1 expressing NS0/PDCD1 cells	0.021 ± 0.001	0.028 ± 0.004	0.028 ± 0.003
Inhibition of PD-1/PD-L1 Signaling in luciferase reporter assay	0.090 ± 0.008	0.171 ± 0.017	0.103 ± 0.016

EC_{50} = effective concentration at 50% of maximal activity; IC_{50} = effective concentration at 50% inhibition of activity.

In vitro studies revealed that margetuximab, incubated with human PBMCs and HER2+ gastric tumor cells, enhances PD-1/PD-L1 axis expression and LAG-3 on NK and NKT cells (**Figure 1**). Moreover, blockade of PD-1 by INCMGA00012 enhances margetuximab-dependent induction of NK cell activation, proliferation, and cytolytic potential.

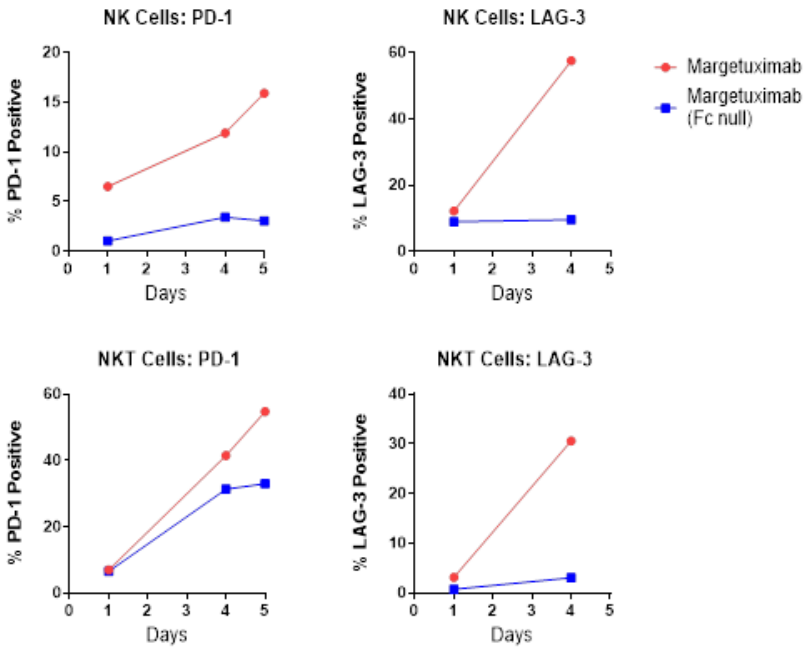
The safety, tolerability, and preliminary efficacy of INCMGA00012 has been explored in a Phase 1 study, CP-MGA012-01 as described in **Section 2.6.1**.

Combination with Anti–PD-1 and Anti–LAG-3

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. The antitumor activity mediated by the HER2 vaccine was enhanced when combined with PD-1 blockade. Additional administration of anti–LAG-3 and anti–PD-L1 mAbs led to complete regression of CT26-HER2 tumors (16). In other models, LAG-3 expression was upregulated with anti–PD-L1 therapy, possibly as a compensatory measure (1, 29, 62).

When PBMCs and HER2 IHC 3+ N87 cells are incubated with margetuximab, NK cells and NKT cells are induced to express elevated levels of PD-1 and LAG-3 (**Figure 1**). By contrast, an Fc null variant of margetuximab was much less effective, indicating that PD-1 and LAG-3 induction is Fc-dependent. Blockade of PD-1 and LAG-3 by MGD013 may enhance the Fc-dependent, effector cell-mediated activities of margetuximab, such as ADCC.

Figure 1 **Margetuximab-Dependent Induction of PD-1 and LAG-3 on NK NKT Cells**



Human PBMC and N87 (HER2 3+ GC) cells were incubated (E:T ratio 15:1) with margetuximab or an Fc null variant of margetuximab at 50-100 ng/mL for the indicated number of days and percentages of NK cells ($CD56^+CD3^+$) or NKT cells ($CD56^+CD3^+$) that were positive for PD-1 or LAG-3 were determined.

In an initial efficacy study of the combination of nivolumab and the LAG-3 inhibitor BMS-986016 was evaluated in 55 heavily pretreated patients with melanoma. Patients had either relapsed while receiving anti–PD-1/PD-L1 directed therapy or had disease progression while receiving an anti–PD-1/PD-L1 directed therapy. In the 41 patients with radiographically evaluable efficacy, 15 patients experienced a reduction in tumor burden. The ORR was 13% (confirmed and unconfirmed) and DCR was 54%, with benefit observed in some patients refractory to prior anti–PD-1. The safety profile of the combined treatment is similar to nivolumab monotherapy (**2**).

MGD013 (also known as tebotelimab) is a humanized Fc-bearing bispecific tetravalent (bivalent for each antigen) DART® protein engineered as a hinge-stabilized IgG4 molecule and is designed to concomitantly bind PD-1 and LAG-3. MGD013 is derived from the humanized murine proprietary mAb clones, MG13.78 (anti–PD-1) and MG14.99 (anti–LAG-3), which were generated using standard hybridoma technology from mice immunized with a His-tagged, human PD-1 extracellular domain molecular and human LAG-3 extracellular domain molecule. MGD013 contains a hinge-stabilized IgG4 molecule to limit effector function, while retaining FcRn binding to extend circulating half-life. MGD013 is produced in Chinese hamster ovary cells. The molecular weight of the molecule is approximately 166.7 kDa. MGD013 is cross-reactive with both human and cynomolgus monkey PD-1 and LAG-3 proteins.

MGD013 is designed to bind concomitantly to PD-1 and LAG-3, 2 checkpoint molecules expressed by T (CD4+ and CD8+) lymphocytes, and to inhibit their interaction with their respective ligands, PD-L1 or PD-L2 and MHC-II. Upon interaction with their respective ligands, PD-1 and LAG-3 act as negative regulators of T-cell function. PD-1 and LAG-3 expression on tumor infiltrating lymphocytes (TILs) or chronically viral-infected T cells have been correlated with immune dysfunction, also known as “T cell exhaustion.” Thus, by inhibiting PD-1 and LAG-3 interaction with their ligands, MGD013 can potentially reverse T cell inhibitory effects mediated by PD-1 and LAG-3, leading to restoration of the function of exhausted T cell and enhanced antitumor immunity.

Consistent with its specific binding properties, MGD013 blocked the binding of PD-L1 and PD-L2 to cell surface–expressed PD-1 and blocked the binding of LAG-3 to cell surface–expressed MHC-II. MGD013 directly blocked the PD-1/PD-L1 inhibitory axis, as measured by a co-culture reporter assay system, in which disruption of PD-1/PD-L1 interactions between the 2 cell lines resulted in enhanced TCR-mediated NFAT-driven luciferase signaling by the PD-1 expressing cell line. MGD013 also demonstrated the ability to enhance interferon-gamma (IFN-γ) secretion by human PBMCs stimulated with staphylococcal enterotoxin B (SEB) or memory T cells stimulated with tetanus toxoid (TTd) beyond that observed with an equimolar combination of replicas for nivolumab (anti–PD-1) and BMS-986016 (anti–LAG-3). The nivolumab and BMS-986016 replicas were constructed as $IgG_4κ$ molecules by MacroGenics based on published sequences.

Thus, MGD013 is functionally active in interfering with the PD-1 – PD-L1/PD-L2 and LAG-3/MHC-II inhibitory signaling pathways. Although the binding properties of MGD013 were comparable to those of the replicas of nivolumab and BMS-986016, the functional properties of MGD013 were greater than those achieved by the combination of the nivolumab

and BMS-986016 replicas, suggesting that MGD013 may offer additional effects beyond those observed with the combination of antibodies.

Safety, tolerability, and preliminary efficacy of MGD013 has been explored in a Phase 1 study, CP-MGD013-01, as described in **Section 2.7.1**.

We hypothesize 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.

2.4.3 Chemotherapy Backbone Treatment

Based on the ToGA study, trastuzumab has been approved for use in combination with fluoropyrimidine plus cisplatin for the treatment of HER2+ advanced GC (**4**). Combination therapy of trastuzumab and XELOX showed comparable efficacy and tolerability to the ToGA regimen of 5-fluorouracil (5-FU) and cisplatin (FP) or capecitabine and cisplatin (XP) in multicenter Phase 2 study (**48**). Modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX-6) and XELOX are commonly used regimen for first-line HER2 positive GC and GEJ cancer patients worldwide (**39**, **61**). The previous studies showed similar efficacy and safety profile in trastuzumab combination with mFOLFOX-6 or XELOX regimen (**48**, **54**).

2.5 Margetuximab Background Information

2.5.1 Margetuximab Clinical Experience

Margetuximab has been, or is currently being, evaluated in 4 clinical studies. As of 23 February 2019, 763 patients have been enrolled in trials investigating margetuximab.

Overall, most adverse effects noted in patients participating in clinical investigations of margetuximab (single-agent and combination studies combined, excluding the EAP [n=758]) have been mild (Grade 1) to moderate (Grade 2) in severity. Cumulatively, in the single-agent studies, the most frequently reported AEs, regardless of causality, include nausea (24.2%), fatigue (23.1%), vomiting (19.8%), infusion-related reaction (18.7%), diarrhea (17.6%), and anemia (17.6%). The most frequently reported AEs in the ongoing randomized portion of the study CP-MGAH22-04 in patients treated with margetuximab plus chemotherapy include fatigue (39.8%), nausea (31.8%), neutropenia (28.4%), diarrhea (24.2%), and anemia (18.6%). Adverse events occurring with a ≥5% higher incidence among patients treated with margetuximab plus chemotherapy compared with those treated with trastuzumab plus chemotherapy include neutropenia (28.4% vs 19.5%), vomiting (19.7% vs 14.3%), asthenia (17.05% vs 11.7%), and infusion related reaction (12.9% vs 3.8%). Infusion-related reactions (including the terms infusion related reaction and cytokine release syndrome [CRS]) have occurred in 76 of 492 (15.4%) patients administered margetuximab in MacroGenics-sponsored clinical studies.

The combination of margetuximab with immune CPI pembrolizumab is being evaluated in ongoing Study CP-MGAH22-05, where safety data are available through 10 July 2019. TRAEs irrespective of grade were reported in 63.2% (60/95) of patients, and 20.0% (19/95)

had a TRAE grade ≥3. The most common TRAEs occurring in ≥10% of patients were pruritus (n=16; 16.8%), diarrhea (n=14; 14.7%), infusion-related reaction (IRR; n=13; 13.7%), and fatigue (n=13; 13.7%). Serious grade 3 TRAEs were: autoimmune hepatitis (n=2), pneumonitis (n=1), hyponatremia (n=1), diabetic ketoacidosis (n=1), hypotension (n=1), IRR (n=1), and dehydration (n=1) and grade 2 dizziness (n=1). TRAEs of special interest were hyperthyroidism (n=3), adrenal insufficiency (n=3), autoimmune hepatitis (n=2), pneumonitis (n=2), left ventricular ejection fraction dysfunction (n=2), diabetes mellitus (n=1), hyperglycemia (n=1), and hypothyroidism (n=1). There were no grade 5 TRAEs reported.

Margetuximab has demonstrated an acceptable safety profile as monotherapy and in combination with chemotherapeutic agents or an anti–PD-1 antibody (pembrolizumab). Refer to the currently effective version of the **Margetuximab Investigator's Brochure** for details on its safety profile.

2.5.2 Margetuximab Clinical Pharmacokinetics

Steady-state exposure estimates are shown in **Table 5** for margetuximab when dosed at 6.0 mg/kg weekly for 3 of every 4 weeks (Q4W) (n = 19), 15.0 mg/kg every 3 weeks (Q3W) (n = 6), and 18.0 mg/kg Q3W (n = 6) in Study CP-MGAH22-01. At steady state, these doses and regimens are estimated to have very similar exposure. Serum trough concentrations (C_{trough}) for all 3 doses are nearly identical, are at or above those reported for trastuzumab in patients with breast cancer (**22**), and are above that required for inhibition of HER2 signaling as demonstrated for trastuzumab in published reports (**11**). Similarly, area under the concentration-time curve (AUC) values are also very similar, with the 15.0 mg/kg slightly lower than either 6.0 mg/kg or 18.0 mg/kg. Maximum concentration (C_{max}) differs among the 3 doses, as would be expected with higher maximal concentrations seen in the 15.0 mg/kg and 18.0 mg/kg doses compared with 6 mg/kg.

Table 5 Margetuximab Pharmacokinetics at Steady State: 6 mg/kg, 15 mg/kg, and 18 mg/kg – CP-MGAH22-01

Parameter (unit)		Margetuximab Dose and Schedule		
		6 mg/kg QW [a] N = 19	15 mg/kg Q3W [b] N = 6	18 mg/kg Q3W [b] N = 6
Ctrough (µg/mL)	Mean	73.0	69.9	86.1
	(SD)	(38.2)	(42.9)	(47.9)
	Median	66.9	61	77.6
	(95% CI)	(20.5 - 169)	(15.8 - 180)	(20.8 - 207)
Cmax (µg/mL)	Mean	217	360	429
	(SD)	(58.1)	(93.9)	(103)
	Median	211	345	417
	(SD)	(125 - 355)	(222 - 590)	(263 - 660)
AUC (µg/mL*h)	Mean	84700	72200	87500
	(SD)	(30000)	(27200)	(30300)
	Median	80500	66800	82200
	(95% CI)	(40700 - 15800)	(35300 - 139000)	(43600 - 160000)

a. Dosed once weekly (QW) for 3 weeks in 4-week (28-day) cycles
b. Dosed once every 3 weeks (Q3W) in 3-week (21-day) cycles.
SD = standard deviation

Clinical pharmacokinetics (PK) of margetuximab was also investigated by tumor type. Median total body clearance (CL), volume of distribution at steady state (V_D), and $t_{1/2}$ values and associated percentile intervals suggested that the PK of margetuximab was similar in patients with gastric, breast, and other tumor types (**Table 6**).

Table 6 Summary of Disposition Parameters for Patients Administered 6 to 18 mg/kg Margetuximab Doses

Tumor Type	Median BW (kg)	Statistic	CL (mL/h/kg)	V_D (mL/kg)	$t_{1.2}$ (h)
Gastric	67.3	Median	0.18	94.5	387.1
		Q05-Q95	0.13-0.26	59.0-144.2	262.7-481.6
		Q10-Q90	0.14-0.24	75.0-128.8	264.2-467.0
Breast	59.9	Median	0.15	77.4	389.4
		Q05-Q95	0.12-0.31	58.8-127.7	173.5-629.4
		Q10-Q90	0.12-0.25	61.2-120.3	303.2-537.7
Other	63.0	Median	0.17	88.1	348.1
		Q05-Q95	0.13-0.35	62.6-110.3	211.6-546.6
		Q10-Q90	0.14-0.33	66.9-108.4	239.5-478.1

Source: Population PK Report for CP-MGAH22-01
Abbreviations: BW = body weight; CL = total body clearance; Qx = x percentile of the distribution; $t_{1/2}$ = terminal elimination half-life; V_D = volume of distribution at steady state
NOTE: Median BWs are estimations

2.5.3 Margetuximab Nonclinical Experience

Margetuximab was well tolerated in male and female cynomolgus monkeys when administered by intravenous (IV) infusion at a single dose of 50 mg/kg and at 6-weekly doses of 0, 15, 50, or 150 mg/kg and supports a no-observed-adverse-effect level of 150 mg/kg.

Thirteen weeks of margetuximab dosing (0, 15, 50, and 100 mg/kg) was well tolerated with the exception of 1 moribund animal (100 mg/kg). Findings suggested decreased red cell production and/or hemolysis; however, a clear mechanism could not be determined and similar findings were not observed for any other animals receiving margetuximab. There have been no cardiac-related toxicities, including no margetuximab-related changes in serum concentrations of troponin I, electrocardiogram (ECG) assessments, or gross or microscopic findings in heart tissue.

No carcinogenicity, mutagenicity, or fertility studies have been conducted for margetuximab. In an enhanced pre- and postnatal development (ePPND) toxicology study, pregnant cynomolgus monkeys received 0, 50, or 100 mg/kg margetuximab by IV infusion starting on gestational day (GD) 20, Q3W until infant delivery. Consistent with other biologics in this pharmacological class, treatment with margetuximab during pregnancy resulted in oligohydramnios beginning on GD 75 in maternal animals administered 50 mg/kg (44% incidence) or 100 mg/kg (82% incidence). The majority of infants had decreased kidney weights and microscopic findings of immature nephrons that frequently correlated with increased concentrations of serum urea nitrogen and creatinine. One female infant (mother received 100 mg/kg) was sacrificed in moribund condition on maturation phase Day 63, which was attributed to margetuximab-related kidney degeneration.

Please refer to the currently effective version of the **Margetuximab Investigator's Brochure** for additional details.

2.6 INCMGA00012 Background Information

2.6.1 INCMGA00012 Clinical Experience

Retifanlimab (INCMGA00012) is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. Retifanlimab contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. Retifanlimab is designed to target PD-1–expressing cells, including T cells, and sustain or restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

In vitro studies with retifanlimab have demonstrated high affinity binding to both recombinant human and cynomolgus monkey PD-1 as well as to PD-1 expressed on the cell surface. Consistent with its intended mechanism of action and functional properties, retifanlimab has been shown to inhibit the binding of PD-L1 and PD-L2 to PD-1, to disrupt the PD-1–PD-L1 inhibitory axis, and to enhance IFN-γ secretion in SEB-stimulated human PBMCs with activity comparable to pembrolizumab and nivolumab replicas (generated by MacroGenics, Inc. based on the published sequences of these antibodies). Retifanlimab does not induce ADCC or CDC, mitogenic activity, hemolysis, or cytokine release.

Retifanlimab is currently under development as a therapeutic candidate for the treatment of multiple solid tumors, both as a monotherapy and in combination with other agents.

As of 23 Sep 2021, 818 unique participants have been exposed to retifanlimab as monotherapy (660 participants), in combination with epacadostat (97 participants), in combination with pemigatinib (19 participants), in combination with parsaclisib (22 participants), in combination with INCB001158 (6 participants), in combination with INCB081776 (3 participants), or in combination with INCAGN02385 and INCAGN02390 (11 participants). Additionally, 427 participants have been exposed to retifanlimab or placebo in blinded studies (INCMGA 0012-303 [57 participants] and INCMGA 0012-304 [370 participants]). Retifanlimab was administered as a monotherapy in 6 ongoing clinical trials at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, 10 mg/kg Q4W, 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W. The most frequently reported TEAEs were asthenia (17.3%), fatigue (16.1%), and diarrhea (15.9%). The most frequently reported serious TEAEs were urinary tract infection (2.1%), pneumonia (1.8%), and abdominal pain (1.5%). None of the serious TEAEs with a fatal outcome occurred in more than 1 participant. Fatal TEAEs that were considered related to retifanlimab by the investigator were lymphangiosis carcinomatosa, concomitant disease progression, tumor hyperprogression, and nephritis. Immune-related AEs occurred in 181 participants, including in 130 participants (28.3%) receiving 500 mg Q4W retifanlimab monotherapy. The most frequent irAE was hypothyroidism (9.2%). The most frequent nonendocrine irAE was skin reactions (7.1%). Most irAEs were Grade 1 or 2 in severity. The most frequent Grade 3 or higher irAEs were acute kidney injury and pneumonitis (0.9% each). Infusion-related reactions were infrequent (7.0%). All infusion-related reactions were Grade 1 or 2 in severity with the exception of 2 Grade 3 events in 2 participants (0.3%). The overall safety profile of retifanlimab is as expected for a PD-L1 inhibitor.

Retifanlimab has shown clinical activity as monotherapy against a variety of solid tumors, including lung, urothelial, renal, Merkel cell, anal squamous, cervical, and endometrial carcinomas, as well as melanoma (**6**, **7**, **24**, **25**, **40**, **47**). This activity is representative of the PD-(L)1 inhibitor class.

2.6.2 INCMGA00012 Nonclinical Experience

In a single-dose PK study, administration of INCMGA00012 by IV infusion was well-tolerated in cynomolgus monkeys at a dose level of 10 mg/kg. There were no changes in circulating immune cell subsets and no evidence of cytokine release. Binding profiles of INCMGA00012 to PD-1 on CD4+ and CD8+ T cells were similar to those exhibited by pembrolizumab but more durable than those exhibited by the nivolumab replica.

In repeat-dose GLP toxicology studies, INCMGA00012 was administered at dose levels of 0 - 150 mg/kg to cynomolgus monkeys. All the infusions were well tolerated. There were no preterm deaths nor treatment-related toxicities. The only findings related to INCMGA00012 were modest decreases in lymphocytes after the first infusion and microscopic changes at the IV administration site consistent with effects of repeated injections.

Please refer to the currently effective version of the **INCMGA00012 Investigator's Brochure** for additional details.

2.7 MGD013 Background Information

2.7.1 MGD013 Clinical Experience

The first-in-human Phase 1 Study CP-MGD013-01 is ongoing in patients with unresectable or metastatic neoplasms. This trial characterizes safety, tolerability, PK, pharmacodynamic, immunogenicity, and preliminary antitumor activity of MGD013 given by IV infusion on a Q2W schedule.

Dose Escalation

As of a data-cutoff date of 01 October 2019, 49 patients with diverse solid tumor types have been treated in Dose Escalation with MGD013 at flat doses ranging from 1 mg to 1200 mg given Q2W. Patients were treated at escalating dose levels as follows: 1 patient at 1 mg, 1 patient at 3 mg, 4 patients at 10 mg, 5 patients at 30 mg, 4 patients at 120 mg, 10 patients at 400 mg, 8 patients at 800 mg, and 7 patients at 1200 mg. Patients who were not safety evaluable were replaced at various dose levels, and additional patients were enrolled in the 400 mg and 800 mg cohorts to gain additional clinical experience. Separately, escalating doses of MGD013 (120 mg, 400 mg, and 600 mg) have been evaluated specifically in patients with advanced hepatocellular carcinoma (n=9).

Forty-eight of 49 (98.0%) patients treated with MGD013 monotherapy in Dose Escalation experienced at least one AE, irrespective of attribution. Common AEs, reported in > 15% of patients, include fatigue (n=13 [26.5%]); nausea, vomiting, and abdominal pain (n=11 [22.5%] each); constipation, pyrexia, and pruritus (n = 10 [20.4%] each); diarrhea (n=9 [18.4%]); and chills (n=8 [16.3%]).

TRAEs have been reported in 39 of 49 patients (79.6%) treated in Dose Escalation. Common TRAEs include fatigue (n=9 [18.4%]); nausea (n=8 [16.3%]); pruritus (n=7 [14.3%]); IRR and rash (n=6 [12.2%] each); and diarrhea, vomiting, pyrexia, and chills (n=5 [10.2%] each). Other potential irAEs observed less commonly include hypothyroidism (n=4 [8.2%]); arthralgia, AST increased, and lipase increased (n=3 [6.1%] each); immune-mediated hepatitis, hyponatremia, and myalgia (n=2 [4.1%] each); and hyperthyroidism, adrenal insufficiency, colitis, stomatitis, ALT increased, and transaminases increased (n=1 [2.0%] each).

The majority of TRAEs observed in Dose Escalation have been mild-to-moderate in severity (i.e., Grade 1 or Grade 2). Eleven of 49 patients (22.4%) treated in Dose Escalation have had at least one Grade 3 TRAE. These events include IRR and lipase increased (n=2, each) and anemia, adrenal insufficiency, diarrhea, colitis, vomiting, fatigue, immune-mediated hepatitis, amylase increased, transaminases increased, hypophosphatemia, arthritis, myalgia, rash, and pruritus (n=1, each). Additionally, 1 other patient treated in the limited HCC dose escalation at 120 mg experienced Grade 4 elevations of amylase and lipase with no clinical or radiographic signs or symptoms of pancreatitis. No patients have experienced a Grade 5 TRAE.

SAEs were limited to 10 of 49 patients (20.4%) treated with MGD013 in Dose Escalation. Five patients (10.2%) had a treatment-related SAE, including immune-mediated hepatitis

(n = 2, 400 mg and 1200 mg); colitis (n = 1, 800 mg); adrenal insufficiency (n = 1, 400 mg); hypophosphatemia (n = 1, 400 mg), and anemia (n=1, 400 mg). SAEs assessed not to be related to MGD013 include abdominal pain, pyrexia, lung infection, urinary tract infection, small intestinal obstruction, dyspnea, inappropriate antidiuretic hormone secretion, and pulmonary hemorrhage. These events were related to the respective patients' underlying malignancies or comorbid conditions.

The dose of 600 mg Q2W was chosen to carry forward in the Cohort Expansion Phase. This decision was based on the totality of clinical, PK, and receptor occupancy data. Within Dose Escalation, MGD013 demonstrated antitumor activity with acceptable tolerability. The MTD was not defined or exceeded, and 1200 mg represents the maximum dose level to be administered in Study CP-MGD013-01. Three patients (TNBC, mesothelioma, and GC) experienced confirmed partial responses (PRs), while 18 other patients with various tumor types had stable disease as a best response.

Cohort Expansion

As of 01 October 2019, 150 patients with advanced cancer have been treated with MGD013 600 mg Q2W. One hundred thirty-two of the 150 patients (88.0%) experienced at least one AE, irrespective of attribution. Common AEs, reported in > 10% of patients, include fatigue (n=36 [24.0%]); anemia, nausea, and decreased appetite (n=20 [13.3%] each); dyspnea (n=18 [12.0%]), vomiting, and AST increased (n=16 [10.7%] each); and abdominal pain, constipation, and pyrexia (n=15 [10.0%] each).

TRAEs have been observed in 94 of 150 patients (62.7%) treated with MGD013 monotherapy in Cohort Expansion. The only TRAE occurring in > 10% of patients is fatigue (n=27 [18.0%]). Potential irAEs and other notable TRAEs observed less commonly include rash (n=13 [8.7%]); IRR and AST increased (n=10 [6.7%] each); hyperthyroidism and lipase increased (n=9 [6.0%] each); ALT increased (n=8 [5.3%]); amylase increased, arthralgia, and hypothyroidism (n=7 [4.7%] each); headache (n=5 [3.3%]); hyponatremia, myalgia, confusional state, and hyperbilirubinemia (n=3 [2.0%] each); and pancytopenia, CRS, immune-mediated hepatitis, and pneumonitis (n=1 [0.7%] each). The majority of TRAEs have been mild to moderate in severity (i.e., Grade 1 or Grade 2), and 31 of the 150 patients (20.7%) have had at least one Grade ≥ 3 TRAE.

SAEs have been limited to 47 of 150 patients (31.3%) treated with MGD013 monotherapy in Cohort Expansion. Fifteen patients (10.0%) experienced a treatment-related SAE, including the following events: diarrhea and IRR (n=2, each) and anemia, pancytopenia, hyperthyroidism, small intestinal hemorrhage, pyrexia, immune-mediated hepatitis, CRS, headache, confusional state, immune-mediated pneumonitis, and hypotension (n=1, each).

Overall, the cumulative safety data continue to support an acceptable safety profile for the treatment of patients with unresectable or metastatic neoplasms. The safety observations observed are consistent with the mechanism of action of MGD013, and irAEs have been manageable with proactive surveillance to identify early symptoms, prompt and aggressive management with systemic immune-modulating agents, and adherence to protocol guidelines on treatment interruption or discontinuation. The safety profile has not clearly demonstrated

synergistic toxicity between the blockade of the anti-PD-1 and anti-LAG-3 arms and is largely consistent with the safety demonstrated with established anti-PD-L1 monoclonal antibodies.

Although it is premature for definitive conclusions regarding the efficacy of MGD013 in the multiple tumor types being evaluated, early signs of antitumor activity have been observed in Cohort Expansion. Objective responses have been reported in epithelial ovarian cancer (n=2), NSCLC (n=3), TNBC (n=1), and DLBCL (n=2), and a substantial proportion of response evaluable patients (46.9%) have experienced stable disease as a best response.

HER2+ Combination Cohort

Within CP-MGD013-01, a separate cohort of patients with HER2+ solid tumors is being treated with margetuximab (anti-HER2 mAb) 15 mg/kg in combination with escalating doses of MGD013 (300 mg and 600 mg) on a Q3W schedule. As of 10 January 2020, 10 patients have been treated with this combination, including 3 at the first dose level (MGD013 300 mg) and 7 patients at the top dose level (MGD013 600 mg).

The MGD013 plus margetuximab combination has been well tolerated among patients treated to date. Both dose levels were cleared in a 3+3 dose escalation scheme with no observed DLTs, and additional patients are currently being treated at the top dose level. No treatment-related SAEs have occurred, and the solitary Grade ≥ 3 TRAE occurred in one patient at the 300 mg dose level who experienced Grade 3 AST elevation which occurred in the setting of liver metastasis, and the transaminitis recovered to baseline with oral corticosteroid treatment. Although the data are immature, initial tumor assessments of the response-evaluable population (n=6) have demonstrated early signs of antitumor activity. Two breast cancer patients have had partial responses (PRs), one confirmed. One of these patients, with extensive chest wall involvement, experienced dramatic disease regression 2 weeks after a single administration of the combination, with a confirmed PR demonstrated at subsequent disease assessments. Other patients have had stable disease (n=2) and progressive disease (n=2) as best response.

2.7.2 MGD013 Nonclinical Experience

MGD013-related changes were limited to transient decline with subsequent rebound in circulating immune cell populations between 23 and 71 hours post end of infusion (EOI) at 150 mg/kg. Clinical signs of emesis or vomitus and watery and/or green feces in males at ≥ 40 mg/kg and watery and/or green feces in females at 100 mg/kg that occurred sporadically during the dosing phase. Microscopic observations of increased frequencies of minimal mononuclear cell infiltrates in several organs in males at ≥ 10 mg/kg and females at ≥ 40 mg/kg at the end of the dosing phase. The observations showed a trend towards reversibility at the end of the 10-week recovery period.

Single- and multiple-dose studies with selected toxicological endpoints were conducted in cynomolgus monkeys. MGD013 was administered at 0 to 150 mg/kg by a 1-hour IV infusion. All the infusions were well tolerated. There were no preterm deaths. Infusion of MGD013 did not induce an increase in serum concentrations of IFN-γ, IL-2, IL-4, IL-5, or TNF-α. Transient

increases in IL-6 levels were observed. MGD013 occupancy is detectable in circulating T cells that express PD-1.

Please refer to the currently effective version of the **MGD013 Investigator's Brochure** for additional details.

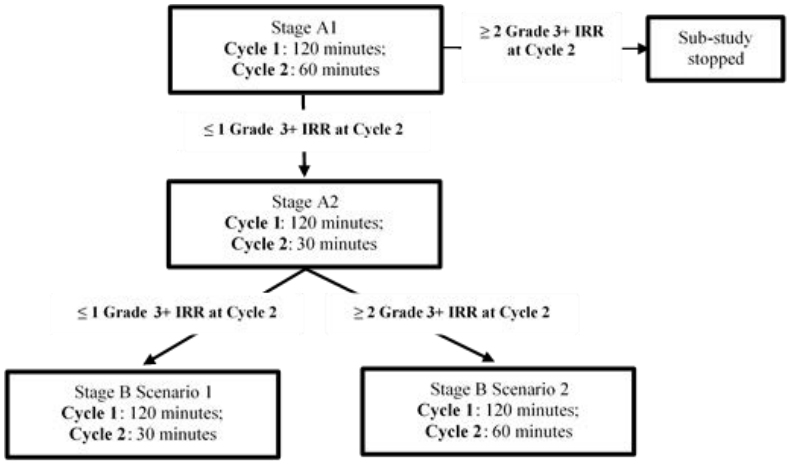
2.8 Dose Selection

2.8.1 Margetuximab Dose Selection

The margetuximab dose and schedule selected, 15.0 mg/kg, infused over 120 minutes Q3W, is based on the observed safety and efficacy profile of margetuximab at all doses tested to date and the predictable PK characteristics. A dose of 15 mg/kg is the recommended Phase 3 dose in the ongoing breast cancer study (CP-MGAH22-04) and the recommended dose for an ongoing study in combination with pembrolizumab (CP-MGAH22-05).

The feasibility of a reduced infusion duration of margetuximab at Cycle 2 and thereafter was explored in a sub-study of CP-MGAH22-04. Patients were enrolled into the study in 3 stages, as depicted in **Figure 2**. Margetuximab was administered at a dose of 15 mg/kg after receiving an Investigator's choice of chemotherapy. Patients, initially dosed with a Cycle 2 60-minute infusion, were eligible for further reduction in infusion duration to 30 minutes at the end of Stage A2.

Figure 2 **CP-MGAH22-04 Sub-study Schema**



No patients experienced ≥ Grade 3 infusion-related reactions (IRRs) in Stages A1 and A2. The Stage B Cycle 2 target infusion duration was confirmed at 30 minutes. As of the 17-Jun-2019 cutoff date, 88 subjects enrolled to the CP-MGAH22-04 Infusion Substudy, and 79 received accelerated infusions at or after Cycle 2. Of 88 enrolled, 37 subjects remained on the study, 14 died, 13 had SAEs, and 3 discontinued due to adverse events (AEs). Of 88 enrolled, 18 had a first-cycle IRR, none of which were ≥ Grade 3. One patient had an IRR in Cycle 2. This nonrandomized cohort study remains ongoing. Summary information on cumulative exposure is displayed in **Table 7**.

Table 7 CP-MGAH22-04 Infusion Sub-study Cumulative Exposure (Safety Population)

Number (%) of Patients with an Observation	Total (N=88)
Enrolled Study Stage A1	8 (9.1)
Enrolled Study Stage A2	9 (10.2)
Enrolled Study Stage B	71 (80.7)[a]
Subject Exposure	
Stage A1	
Cycle 1 (120 minutes)	8 (9.1)
Cycle 2 (60 minutes)	7 (8.0)
Stage A2	
Cycle 1 (120 minutes)	9 (10.2)
Cycle 2 (30 minutes)	8 (9.1)
Stage B	
Cycle 1 (120 minutes)	69 (78.4) [a]
Cycle 2 (30 minutes)	68 (77.3)

Data cutoff: 17-Jun-2019

a Although 71 patients enrolled in Stage B, 2 did not complete Cycle 1 due to IRR, but did complete Cycle 2. Three patients did not complete Cycle 2, including 1 due to non-radiologic disease progression, 1 due to patient decision, and 1 due to septic shock.

Abbreviations IRR: infusion related reaction; N: number of patients in dataset.

The 30-minute infusion resulted in comparable PK to the 120-minute infusion in the randomized study. Based on median C_{trough}, margetuximab is at steady-state by the end of Cycle 3 or in Cycle 4. Median C_{trough} remains consistently above the putative threshold target concentration (30 mcg/mL) for margetuximab efficacy. Chemotherapy coadministration with margetuximab has no clinically meaningful effects on margetuximab PK (C_{trough} and C_{max}). Exposure was comparable across Stages A1, A2, and B.

Two of 80 evaluable subjects (2.5%) developed anti-drug antibodies (ADA) on or after margetuximab therapy. No subjects developed neutralizing antibodies. ADA induction by margetuximab is modest. Accelerated 30-minute margetuximab infusions demonstrated acceptable safety and tolerability. There were no Grade 3 or higher IRRs in this Infusion Substudy. Starting from Cycle 2, IRRs during 30-minute infusions had similar incidence and character when compared to 120-minute infusions. Reduction of infusion duration to 30 minutes for Cycle 2 and beyond does not adversely affect margetuximab safety or increase IRR risk or severity.

Margetuximab can be safely administrated, alone or with chemotherapy, as a 120-minute infusion for Cycle 1 then 30-minute infusion for Cycle 2 and beyond.

2.8.2 INCMGA00012 Dose Selection

Retifanlimab will be administered at 375 mg Q3W. The selection of this dose regimen was based on modeling of clinical PK data from 219 participants enrolled in the first in human monotherapy study, INCMGA 0012-101 (NCT03059823). Participants were treated with both

body weight–based and flat doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, 10 mg/kg Q4W, 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W.

Pharmacokinetic data from Study INCMGA 0012-101 suggested that retifanlimab exposure increased in a dose-dependent manner with doses ranging from 1 to 10 mg/kg (including flat doses of 375 to 750 mg). Full and sustained PD-1 receptor occupancy was observed with all doses studied on both PD-1 expressing CD4+ and CD8+ cells. The PK of retifanlimab following IV administration was well characterized by a 2-compartment linear disposition model with time-dependent elimination. A population PK model estimated typical retifanlimab CL as 0.0127 L/h with a steady-state t½ of 18.4 days. Similar PK profiles were observed for the 3 mg/kg Q2W and 500 mg Q4W doses.

Simulations demonstrated that the median steady-state trough concentration of retifanlimab 500 mg Q4W and 375 mg Q3W was approximately 21.1 µg/mL, which is the median trough concentration for pembrolizumab 2 mg/kg Q3W (**17**). The 500 mg Q4W and 375 mg Q3W regimens also resulted in steady-state exposure that was similar to the 3 mg/kg Q2W regimen (Ctrough). In addition, full PD-1 receptor occupancy was observed on PD-1 expressing CD4+ and CD8+ cells with effects on circulating cytokines that are typical for a PD-1 inhibitor in all dose regimens of Study INCMGA 0012-101. Therefore, the 500 mg Q4W dose regimen was selected for further development in monotherapy treatments, and the 375 mg Q3W dose regimen was selected to facilitate the development of combination regimens, such as chemotherapy treatments, with a shorter cycle length. No meaningful exposure-response relationships have been demonstrated for either safety or efficacy.

Pharmacokinetic data were obtained from 15 participants who received retifanlimab 375 mg Q3W in the cohort-expansion portion of Study INCMGA 0012-101. Following the first dose of the 375 mg Q3W regimen, retifanlimab had mean t½ (12.9 days) and CL (0.366 L/day) values comparable to those of the 500 mg Q4W and 750 mg Q4W doses. Furthermore, Ctrough at steady state following a 375 mg Q3W infusion was 43.0 ± 15.0 mg/L with the accumulation ratio at approximately 1.5, making this a comparable dose to 500 mg Q4W (Ctrough at steady state 58.7 ± 26.8 mg/L with the accumulation ratio at approximately 1.3).

For more information, refer to the retifanlimab IB

2.8.3 MGD013 Dose Selection

Within Dose Escalation, MGD013 demonstrated antitumor activity with acceptable tolerability up to a dose of 1200 mg without exceeding the MTD. Based on receptor occupancy data and other clinical data, a dose of 600 mg was selected for further study in monotherapy. MGD013 in combination with margetuximab was evaluated in a HER2+ solid tumor cohort in Study CP-MGD013-01. The safety and tolerability of the combination of MGD013 and margetuximab Q3W was confirmed and a dose of 600 mg of MGD013 will be used for combination treatment.

2.8.4 Chemotherapy

Preferred chemotherapeutic treatments for first-line metastatic GC are a fluoropyrimidine (infusional 5-FU or oral 5-FU prodrug) in combination with cisplatin or oxaliplatin (**41**, **43**, **53**). Modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX-6) and XELOX are commonly used regimen for first-line HER2 positive GC and GEJ cancer patients worldwide (**39**, **61**). The previous studies showed similar efficacy and safety profile in trastuzumab combination with mFOLFOX-6 or XELOX regimen (**48**, **54**). **Table 9**, in Section 6.1, describes the protocol-specific chemotherapy dose and schedule combinations with the standard dose of trastuzumab.

2.9 Risk and Benefit Assessment

2.9.1 Risk Assessment

Study Risks

Infusion-related reaction (IRR) is a known identified risk for margetuximab. As of 10 Jan 2022, the IRR incidence rate for the combination of INCMGA00012/margetuximab with or without chemotherapy (across Cohorts A and B), the combination of MGD013/margetuximab+chemotherapy, and margetuximab+chemotherapy was: 12/56 subjects (21.4%), 2/5 subjects (40.0%) and 3/8 subjects (37.5%), respectively. All IRRs were either Grade 1 or 2 except for one Grade 3 event reported with margetuximab+chemotherapy.

The combination of margetuximab and INCMGA00012 or MGD013 can potentially increase the risk of cardiac toxicities. Decreased left ventricular ejection fraction (LVEF) is an important potential risk for margetuximab. As of 10 Jan 2022, the incidence rate of decreased LVEF for the combination of INCMGA00012/margetuximab with or without chemotherapy (across Cohorts A and B), the combination of MGD013/margetuximab+chemotherapy, and margetuximab+chemotherapy was: 3/56 subjects (5.3%), 0/5 subjects (0.0%) and 1/8 subjects (12.5%), respectively. One Grade 2 cardiac failure event (1/56 subjects; 1.8%) was reported with the combination of INCMGA00012/margetuximab therapy (across Cohorts A and B). The cardiac failure event occurred in Cohort A. No cardiac failure events have been reported with the combination of MGD013/margetuximab+chemotherapy or margetuximab+chemotherapy.

Immune-related adverse events (irAEs) are important identified risks for INCMGA00012 and MGD013. Thus far, the incidence rate of irAEs in the combination of margetuximab and INCMGA00012 or MGD013 is comparable with other anti-PD-1 targeted therapies.

The combination of margetuximab and INCMGA00012 or MGD013 did not show any synergistic toxicity between investigational drugs in both combination and is largely consistent with the safety profile of each monotherapy.

SARS-cov-2 (COVID-19) infection

Investigators must ensure that their institution can provide the protocol-specified safety and efficacy assessments during the pandemic period. All procedures should continue as per protocol and study manuals. Prospective protocol waivers remain unacceptable and that patients should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations. Enrollment and continuing participation in the study should follow any national or local guidance related to COVID-19.

Telemedicine visits may be considered, in alignment with national and local guidance, to monitor adverse events and any other medical issues as necessary.

The risk of treatment delays associated with the COVID-19 pandemic is not increased by participation in the clinical trial. If patients are unable to receive study treatments at the enrolling site, continuing participation at another open site should be considered in consultation with the MacroGenics and in accordance with local and national guidance.

Remote monitoring of clinical data using electronic medical records will follow all local and regional guidelines regarding the access to and protection of patient's identifiable medical information.

As with any infection, confirmed cases of COVID-19 infection or suspected infection should be reported as AEs or SAEs (if seriousness criteria are met) within 24 hours. All medications/treatment administered for these respective events and corresponding unscheduled visits must be entered in EDC.

2.9.2 Potential Benefits

The investigation of margetuximab in combination with INCMGA00012 or MGD013 may potentially yield a novel therapeutic option with an acceptable benefit-risk profile. The simultaneous targeting of HER2 and PD-1 (by margetuximab plus INCMGA00012) or HER2 and PD-1 plus LAG3 (by margetuximab plus MGD013) provides an opportunity to focus the immune system and potentially enhance the antitumor response compared to treatment with either molecule alone. The rationale for this is supported by the complementary biology of HER2, PD-1 and LAG3 in mediating tumor evasion and the ability of margetuximab and INCMGA00012 or MGD013 to coordinately leverage both innate and adaptive immune responses by virtue of their respective functional properties. The Phase 1/2 evaluation of margetuximab in combination with anti-PD-1 therapy has demonstrated efficacy and tolerable safety in gastric cancer patients that benchmarks favorably to historical experience with standard of care.

Additionally, Cohort A, may provide a chemotherapy-free treatment option with a potentially favorable safety profile. In Cohort B, all patients will receive an anti-HER2 agent in combination with chemotherapy. Based on recently published clinical data (**31**), there is synergy of anti-tumor effect with combination of an anti- HER2 agent (trastuzumab) + anti-PD-1 agent (pembrolizumab) + chemotherapy. Further, as seen in emerging preliminary data regarding the margetuximab + MGD013 combination therapy in study CP-MGD013-01

margetuximab +MGD013 + chemotherapy could potentially bring similar efficacy to PD-L1 negative patients to PD-L1 positive patients.

2.9.3 Overall Assessment

The patients expected to enroll in the study have metastatic or locally advanced, unresectable, treatment-naïve, HER2-positive gastric or gastroesophageal junction cancer. The administration of study drugs in patients with advanced cancer in the CP-MGAH22-06 could potentially prevent disease progression, which may result in longer survival.

In reference to safety concerns for COVID-19, there is currently no evidence of increased risk for COVID-19 infection or its exacerbation during treatment with margetuximab, INCMGA00012 or MGD013, or a combination of either INCMGA00012 or MGD013 with margetuximab.

In conclusion, the currently available data for margetuximab in combination with INCMGA00012 or MGD013 indicate that there is an acceptable benefit-risk profile which supports the conduct of the CP-MGAH22-06 trial. MacroGenics' medical team will continue to review and monitor patient data and ensure patient safety at all times.

3 STUDY PURPOSE AND OBJECTIVES

3.1 Primary Objective

Cohort A:

- To evaluate the safety and tolerability of margetuximab + INCMGA00012 in patients with untreated locally advanced or metastatic GC or gastroesophageal junction (GEJ) cancer that is HER2 IHC 3+ and PD-L1+ by IHC staining.
- To evaluate the ORR of margetuximab plus INCMGA00012 for non-MSI-H patients in the response evaluable population (REP) using Investigator-assessed radiology reviews.

3.2 Secondary Objectives

Cohort A:

- To determine DoR, DCR, PFS, using Investigator-assessed radiology review and for non-MSI-H patients.
- To evaluate the number of patients with ADA to margetuximab or INCMGA00012, or both.

Cohort B, Part 1:

- To evaluate ORR and DCR of each treatment arm.
- To evaluate the number of patients with ADA to margetuximab, MGD013, or INCMGA00012.

4 OVERALL STUDY DESIGN AND PLAN

This is a Phase 2/3, randomized, open-label study for treatment of patients with HER2+ GC or GEJ cancer. The study will be conducted in 2 cohorts. Cohort A will determine efficacy of margetuximab combined with CPI INCMGA00012 in patients who are positive for both HER2 IHC 3+ and PD-L1+ and are non-MSI-H (as determined by a central laboratory). Cohort B will determine the efficacy of a margetuximab plus CPI (INCMGA00012 or MGD013) plus chemotherapy compared to trastuzumab plus chemotherapy in patients who are HER2+ [IHC 3+, or IHC 2+ and fluorescent in situ hybridization (FISH)+], irrespective of PD-L1 status. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue for analysis of PD-L1 and MSI status will be prospectively collected during the study and retrospectively analyzed by a central laboratory. Patients will be treated Q3W.

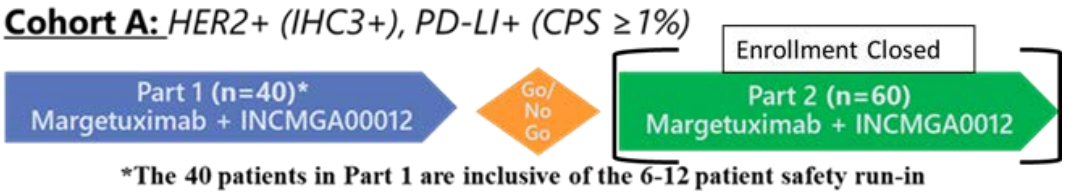
The study population consists of patients with previously untreated locally advanced, unresectable or metastatic, HER2+ (IHC 3+, or IHC2+ and FISH+) GC or GEJ cancer. Prior systemic treatment in the perioperative setting is allowed. However, the patient must have had a disease-free interval of at least 6 months from complete surgical resection or from the initiation of adjuvant chemotherapy, whichever is later. Patients receiving perioperative anti-HER2 therapy require repeat testing of HER2 status for eligibility. No perioperative immunotherapy is allowed.

Cohort A (Single Arm)

Cohort A was closed prior to completing enrollment target. There were 48 patients enrolled in Cohort A.

The efficacy of INCMGA00012 plus margetuximab will be evaluated in approximately 100 patients that are HER2 IHC3+, PD-L1+, and non-MSI-H (**Figure 3**). Enrollment will occur without prior ascertainment of MSI status. If the MSI status is determined to be MSI-H, patients will be allowed to remain on treatment but will be removed from the efficacy analysis. It is expected that about 110 patients will need to be enrolled to have 100 non-MSI-H patients.

Figure 3 Study Design for Cohort A: Margetuximab + INCMGA00012 (Chemotherapy-free Regimen)



Patients will receive 375 mg of INCMGA00012 Q3W plus 15 mg/kg of margetuximab Q3W. In additions to regular Sponsor medical oversight, the independent data monitoring committee (IDMC) will review all accumulated safety data from all enrolled patients and provide a recommendation to the Sponsor. The first scheduled IDMC meeting will take place after the

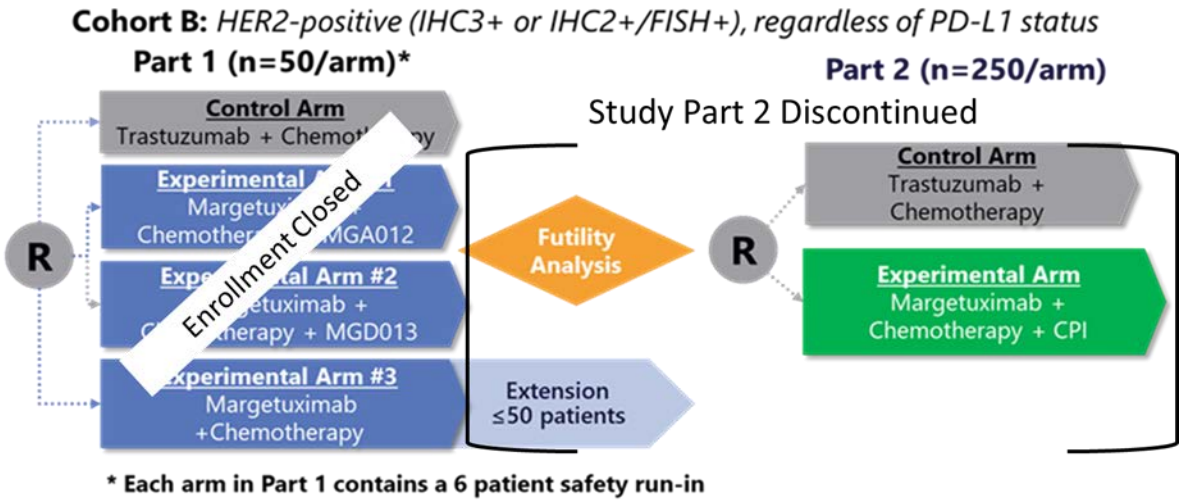
first 12 patients have completed at least 1 cycle of study treatment, or at 6 months from first enrollment, whichever comes first. Enrollment will continue during the evaluation. Reviews will continue in 6-month intervals (± 1 month). After approximately 40 patients have enrolled and are evaluable for response, data will be analyzed for ORR, as determined by independent imaging review, and safety. Additional patients will be enrolled in Part 2 of the cohort if the threshold for study continuation is met. Decision rules that govern the analysis of the ORR from Part 1 and continuation of Part 2 of Cohort A are outlined in **Section 14.7.1**.

Cohort B (Randomized, Open-label)

Cohort B was closed prior to completing enrollment target. There were 34 patients randomized of which 33 were treated in Cohort B, Part 1. No patients were enrolled in Cohort B, Part 2.

Cohort B Part 1 consists of 4 arms: 1 control arm of trastuzumab plus chemotherapy and 3 experimental arms of margetuximab-containing regimens. Experimental Arms 1 and 2 will combine margetuximab plus a CPI plus chemotherapy. The CPI for Experimental Arm 1 is INCMGA00012, and the CPI for Experimental Arm 2 is MGD013. Experimental Arm 3 will evaluate margetuximab alone in combination with chemotherapy. Entry criteria for HER2 may be based on a local test, however, enrollment will continue until the sample size is accrued based on central confirmation. Chemotherapy will be XELOX or mFOLFOX-6, according to the Investigator's choice based local approval and availability. The study schema is displayed in **Figure 4**.

Figure 4 **Study Design for Cohort B: Margetuximab plus Chemotherapy plus Checkpoint Inhibitor (INCMGA00012 or MGD013)**



IHC = immunohistochemistry; R = randomize

The first safety evaluation by the IDMC will take place after 20 patients in each arm have enrolled and completed at least 1 cycle of treatment, or at approximately 6 months from first enrollment, whichever comes first. The IDMC may meet at any time if evolving safety data

warrant a safety review. Reviews will continue in 6-month intervals (± 1 month). Once the first assessment in Cohort B is completed, to the extent possible, safety and efficacy data from Cohort A and Cohort B will be reviewed at the same meeting. However, frequency of IDMC meetings may be adjusted in accordance with the consensus of the IDMC and reflected in the IDMC Charter.

Chemotherapy treatment will be capped at approximately 6 months (8 cycles of XELOX and 12 cycles of mFOLFOX-6). INCMGA00012, MGD013, and trastuzumab will be capped at 35 cycles (approximately 2 years).

- Control arm: trastuzumab at an 8 mg/kg loading dose then 6 mg/kg Q3W, in combination with XELOX or mFOLFOX-6 chemotherapy
- Experimental Arm 1: 375 mg of INCMGA00012 Q3W plus 15 mg/kg of margetuximab Q3W, in combination with XELOX or mFOLFOX-6 chemotherapy.
- Experimental Arm 2: 600 mg of MGD013 Q3W plus 15 mg/kg of margetuximab Q3W, in combination with XELOX or mFOLFOX-6 chemotherapy.
- Experimental Arm 3: margetuximab 15 mg/kg in combination with XELOX or mFOLFOX-6 chemotherapy.

4.1 Guidelines for Dose Modification

4.1.1 General Guidelines

No dose modification will be allowed for margetuximab, INCMGA00012, MGD013, or trastuzumab, with the exception of reduction of infusion rate during re-challenge for patients experiencing an infusion reaction (see **Section 7.1**) for any of the antibodies or decreased cardiac function (see **Section 4.1.3**) for margetuximab. If a patient experiences an irAE, the Investigator should follow the management guidelines outlined in **Section 7.2**. For patients in whom the toxicity is assessed as related to chemotherapy, other components of study treatment (i.e., margetuximab, INCMGA00012, or MGD013) may be continued upon consultation with the Sponsor's Medical Monitor.

Please refer to the respective Investigator's Brochures for information on special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, and undesirable effects associated with margetuximab, INCMGA00012, or MGD013.

4.1.2 Modifications for SARS-CoV-2 Infection

The following guidelines apply to patients actively on study treatment with confirmed (positive by regulatory authority approved/authorized test) or presumed (test pending/clinical suspicion) COVID-19/SARS-CoV-2 infection:

- For patients with confirmed or presumed SARS-CoV-2 infection, study drug should be delayed for at least 14 days from the start of symptoms. Consideration for study treatment continuation will be made on a case-by-case basis with the Medical Monitor and the Principal Investigator.
- Prior to restarting study drug, patients should be afebrile for at least 72 hours and SARS-CoV-2–related symptoms should have recovered to ≤ Grade 1 or baseline for a minimum of 72 hours.
- The Sponsor should be informed when resuming study drug.

The Sponsor must be informed within 24 hours of awareness of a participant with confirmed or presumed COVID-19/ SARS-CoV-2 infection. Suspected COVID 19/SARS-CoV-2 cases should be tested per local practice/institutional guidelines with an approved/authorized test.

At the discretion of the investigator, non-live COVID-19 vaccines may be administered per local practice. Patients may have study drug held to allow for COVID-19 vaccination.

4.1.3 Margetuximab

No reductions in the dose of margetuximab are allowed. The rate of margetuximab infusion or dose schedule may be modified for IRRs or decreased cardiac function, respectively, that are determined to be associated with margetuximab based on the following parameters:

- Infusion-related reactions: Follow the guidelines described in **Section 7.1**
- Decreased cardiac function: Withhold margetuximab for at least 4 weeks if either of the following criteria are met:

  ≥ 16 % absolute decrease in left ventricular ejection fraction (LVEF) from pre-treatment value, or

  LVEF below institutional normal limits (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pre-treatment values.

LVEF will be monitored at regular intervals during the study. If a decrease in cardiac function is suspected, LVEF should be determined using the same method as used prior to treatment.

Margetuximab may be resumed if, within 8 weeks, the LVEF returns to within normal limits and the decrease from baseline is ≤ 15%. Margetuximab should be permanently discontinued if a decline in LVEF persists for > 8 weeks or if dosing is interrupted for more than 3 occasions due to cardiomyopathy.

4.1.4 INCMGA00012 and MGD013

No reductions in the dose of INCMGA00012 or MGD013 are allowed. Dose interruption or discontinuation should be used for the management of drug-related toxicity. The management

of IRR is specified in **Section 7.1.2**. The dose interruption and overall management of irAEs is specified in **Section 7.2**.

For other Grade 3 and higher drug-related AEs, that are not designated as IRR or irAE, study treatments will be withheld until resolution to ≤ Grade 1, or baseline. Patients with AEs leading to dose interruption that does not resolve to ≤ Grade 1 within 12 weeks, despite optimal medical management, should be discontinued from the study.

Dose interruption is allowed for patients with intolerable or persistent Grade 2 drug-related AEs. Permanently discontinue study drug for persistent Grade 2 AE for which treatment with study drug has been held, and that does not recover to Grade 0 - 1 within 12 weeks of the last dose.

Patients who experience Grade 4 drug-related events should be permanently discontinued from the study with the following exceptions:

- Grade 4 lymphopenia
- isolated laboratory abnormalities lasting less than 72 hours and not otherwise associated with clinical complications

4.1.5 Trastuzumab (HERCEPTIN®)

Patients may continue trastuzumab (marketed as HERCEPTIN®) therapy during periods of reversible, chemotherapy-induced toxicity. Additional monitoring for resolution of chemotherapy-related toxicity may be warranted.

The trastuzumab package insert should be consulted for any modifications or adjustments to the dosing schedule or rate of infusion. Trastuzumab dosing will be modified for infusion reactions and cardiomyopathy.

- Infusion-related reactions: Follow the guidelines described in **Section 7.1**
- Decreased cardiac function: Withhold trastuzumab for at least 4 weeks if either of the following criteria are met:
  - ≥ 16 % absolute decrease in LVEF from the pre-treatment value, or
  - LVEF below institutional normal limits (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pretreatment values

LVEF will be monitored at regular intervals during the study. If a decrease in cardiac function is suspected, LVEF should be determined using the same method as used prior to treatment.

Trastuzumab may be resumed if, within 8 weeks, the LVEF returns to within normal limits and the percentage point decrease from baseline is ≤ 15%. Trastuzumab should be

permanently discontinued if a decline in LVEF persists for > 8 weeks or if dosing is interrupted for more than 3 occasions due to cardiomyopathy.

4.1.6 Chemotherapy

General guidance for dose modification for toxicity due to chemotherapy agents are provided in **Table 8**. However, this guidance is not intended to replace local requirements or standard practice of medicine.

One or more chemotherapy agents can be interrupted for chemotherapy-related toxicity. A change to a different chemotherapy regimen is not allowed. Continued treatment with other assigned study drugs may continue. Chemotherapy treatment should be reinstituted once toxicity has improved or resolved. If continued treatment is not tolerable with interruption or dose modification, chemotherapy may be discontinued. The patient may continue the other components of the chemotherapy regimen. Patients who require cessation of chemotherapy because of chemotherapy-related toxicity should continue on the other study treatments. If all components of chemotherapy regimen were held for 2 or more consecutive cycles due to toxicity, prior to completing 8 cycles or XELOX or 12 cycles of mFOLFOX-6, restart of chemotherapy is not allowed.

Table 8 Dose Modification Recommendations for Chemotherapy

Agent	Toxicity	Grade [a]	Action	Subsequent Dosing
5-FU	Palmar-plantar erythrodysesthesia	2-3	Interrupt	Resume at a 25% dose reduction dose when resolved to ≤ Grade 1
	Mucositis	3-4		
	Myelosuppression	4		
	Other severe toxicity	3-4		
	Diarrhea	2		Resume at 100% dose
		2 (recurrent)		Resume at a 25% dose reduction dose when resolved to ≤ Grade 1
		3-4		
Capecitabine [b]	Second appearance any AE	2	Interrupt	50-75% dose reduction when resolved to ≤ Grade 1
	Third appearance any AE			50% dose reduction when resolved to ≤ Grade 1
	Fourth appearance any AE		Discontinue	Drug withdrawn
	First appearance any AE	3	Interrupt	50-75% dose reduction when resolved to ≤ Grade 1
	Second appearance any AE			50% dose reduction when resolved to ≤ Grade 1
	Third appearance any AE		Discontinue	Drug withdrawn
	First appearance any AE	4	Discontinue	Drug withdrawn
Oxaliplatin	Neuropathy	2 (persistent)	Interrupt	Reduce to 65 mg/m^2 (mFOLFOX-6) or 100 mg/m^2 (XELOX)
		3 (persistent)	Interrupt	Consider discontinuation
		4	Discontinue	Drug withdrawn
	Neutropenia	4	Interrupt	Delay the next dose until neutrophils ≥ 1.5 × 10^9/L
	Febrile neutropenia	3-4		
	Thrombocytopenia	3-4	Interrupt	Delay the next dose until neutrophils ≥ 75 × 10^9/L
	Gastrointestinal AE	3-4	Interrupt	Reduce dose to 65 mg/m^2 and dose reduce 5-FU to 300 mg/m^2 IV bolus and 1800 mg/m^2 as a 46-hour infusion (m-FOLFOX-6). or 100 mg/m2 (XELOX)
	Hypersensitivity Reaction	Any	Discontinue	Drug withdrawn
	Posterior reversible encephalopathy syndrome			
	Confirmed interstitial lung disease or pulmonary fibrosis			
	Rhabdomyolysis			

a. NCI CTCAE v5.0

b. Recommendations for dose reductions reflect local availability of dosage forms of capecitabine.

4.2 Study Duration

Study treatment will continue until completion of protocol-specified therapy, persistent CR, disease progression, unacceptable toxicity, withdrawal of consent, physician recommendation to discontinue therapy, or death.

The maximum duration of protocol-specified study treatments are:

Cohort A	35 cycles of margetuximab and INCMGA00012			
Cohort B, Part 1	Arm	Chemotherapy	Anti-HER2 Therapy	Anti PD-1/PD-L1 Therapy
	Control	8 cycles XELOX or 12 cycles mFOLFOX-6	35 cycles trastuzumab	N/A
	1		35 cycles margetuximab	35 cycles INCMGA00012
	2		35 cycles margetuximab	35 cycles MGD013
	3		Until disease progression	N/A

Discontinuation of study treatment may be considered for patients have attained persistent CR. The criteria for persistent CR include:

- confirmed CR and at least 8 cycles of XELOX or 12 cycles of mFOLFOX-6 (approximately 6 months) of study treatments, and
- an additional 2 cycles of study treatment must be completed beyond the date of initial CR.

Patients in Cohort A only who have radiographic progression but are clinically stable may remain on study treatments until the next scheduled radiographic evaluation, upon Sponsor Medical Monitor consultation.

There is no crossover in this study to a different treatment arm or different cohort. Following discontinuation of study treatment, each patient will be followed for safety for up to 30 days, or until initiation of subsequent anticancer therapy, whichever is earlier. Patients currently in survival follow-up will be discontinued from the study, as having completed protocol-specified follow-up.

4.2.1 Definition of End of Study

The end of study occurs after the last patient completes the safety follow-up period.

4.3 Appropriateness of Measurements

4.3.1 MSI Status

Microsatellites are short, tandem repeated DNA sequences 1–6 base pairs in length. Microsatellite markers can be used to detect a form of genomic instability called microsatellite instability (MSI). MSI is a change in length of a microsatellite allele due to insertion or

deletion of repeat units during DNA replication and failure of the DNA mismatch repair system to correct these errors.

Previous clinical trials have demonstrated the utility of MSI status as a predictive marker for response to PD-1 blockade in Stage 4 cancer including GC. Pembrolizumab monotherapy has been approved for MSI-H solid tumors. Pembrolizumab as a single agent has been studied as third-line treatment in patients with gastric cancer (KEYNOTE-059). Study results indicated a lower response rate for non-MSI-H patients of 9.0%, compared to a response rate of 57% in MSI-H patients (**18**, **36**). The higher efficacy of anti-PD1 monotherapy in MSI-H patients could confound the assessment of contribution of treatment components in this combination study. Patients with unknown MSI status are not excluded from the study; however, if the patient has MSI-H status, they will be excluded from the analyses as described in Section 14 of the protocol. For Cohort B, the correlation of MSI status with efficacy will be assessed in a sensitivity analysis. Previous studies have demonstrated that approximately 8% of patients with Stage 4 GC are MSI-H (**34**, **45**). In the TCGA database, including 92.5% of patients with early stage disease (Stage 1-3), 21.7% of patients we found to be MSI-H (**10**).

Based on previous reports (**19**, **58**) there is only a small overlap of gastric patients with HER2 amplification and MSI-H expression based on The Cancer Genome Atlas (**10**). Huang et al reported that of 59 HER2 positive tumors, 3 (5.1%) were MSI high in resectable (Stage II-III) GC (**30**). In the CP-MGAH22-05 study, MSI-H was detected in 1 of the 88 (1.1%) patients tested for MSI status. Therefore, based on these reports and the data from the CP-MGAH22-05 trial, it is anticipated that only a small number of patients (e.g., approximately 5% or less) with HER2+ and MSI-H GC would be enrolled into the trial.

MSI status will be determined with comparison of allelic profiles of microsatellite markers between tumor DNA and normal DNA at the central laboratory. Genomic DNA is extracted from tumor specimen and whole blood (normal DNA) and flowed by polymerase chain reaction-based-assay using 5 mononucleotide repeat microsatellite markers (BAT-25, BAT-26, MONO-27, NR-21, and NR-24). Greater or equal to 2 abnormal allelic shifts of the mononucleotide repeat markers out of 5 markers will be considered as MSI-H.

4.3.2 HER2 IHC Testing

As margetuximab is an anti-HER2 directed therapy, all patients must meet the inclusion criteria for HER2 positivity. HER2 testing for study for Cohort A will be conducted at a College of American Pathologists (CAP)/Clinical Laboratory Improvement Amendments (CLIA) certified central laboratory using an FDA-approved assay. In Cohort B, HER2 testing may be conducted at an appropriately qualified local laboratory using HercepTest™ and HER2 FISH pharmaDx™ assays. A confirmatory standardized HER2 test will be performed at a central laboratory contracted by the Sponsor, using an FDA-approved assay.

4.3.3 PD-L1 IHC Testing

Anti–PD-1 agents have demonstrated improved efficacy in GC patients with tumors that express PD-L1 as determined by IHC (**18**, **50**). The present study will define PD-L1 expression based on IHC staining using the FDA approved 22C3 pharmDx assay.

PD-L1 testing will be performed for all patients. For Cohort A, testing will be used to identify eligible patients with tumors that are positive for both HER2 (HER2+) and PD-L1 (PD-L1+) expression. For patients in Cohort B, PD-L1 expression will be determined retrospectively to enable pre-specified subset analyses of clinical efficacy.

The prevalence of PD-L1 positivity in patients with metastatic GC, using the 22C3 Pharm Dx and CPS ≥ 1% cutoff has been reported as approximately 70% (**50**).

4.3.4 Fcγ Receptor

Margetuximab is an Fc-engineered anti-HER2 mAb designed with increased affinity for activating Fc-receptors and reduced affinity for inhibitory Fc-receptors compared to trastuzumab. Distinct high- (V) and low- (F) affinity alleles have been described for the activating Fc-receptor, CD16A. Margetuximab binds with increased affinity to either the V or F allele of CD16A. Notably, in patients with HER2+ GC, trastuzumab efficacy appears to be reduced in patients harboring one or more F alleles (CD16A V/F and F/F) (**59**). The homozygous V/V genotype is present in approximately 15% each of Caucasian, African American, and Asian populations, and the lower affinity F/F and intermediate affinity F/V carriers comprise the remainder of the population. Since most patients carry the lower affinity allele of CD16A, the engineered Fc domain of margetuximab is expected to confer benefit to the whole patient population and not disproportionately to the higher affinity CD16A V/V homozygotes.

4.3.5 Clinical Laboratory Evaluations

Routine laboratory evaluations including hematology, chemistry, special chemistry, coagulation, and urinalysis will be performed.

Local safety laboratory assessments will be used to make treatment-related decisions.

4.3.6 Pharmacokinetic Assessments

Serum concentrations of margetuximab, INCMGA00012, and MGD013 will be analyzed using validated assay methods that will be carried out in the Sponsor's designated central laboratory to characterize the immunogenicity of margetuximab, INCMGA00012, and MGD013. Analysis of PK data will be carried out using industry standard software. Descriptive PK summaries will be provided.

4.3.7 Immunogenicity

Blood samples will be collected and assayed to determine the presence of ADA to margetuximab, INCMGA00012, and MGD013 during the study. A central laboratory, chosen by the Sponsor, will perform the assay.

5 SELECTION AND WITHDRAWAL OF PATIENTS

The patient population to be enrolled in this study will consist of adult patients with histologically or cytologically confirmed, previously untreated, locally advanced unresectable or metastatic HER2+ GC/GEJ cancer. To be eligible for study participation, patients must meet all the inclusion criteria. Patients will be excluded from the study if they meet any exclusion criteria. No exceptions to these criteria will be granted by the Sponsor.

5.1 Inclusion Criteria

1. Patient must provide signed informed consent prior to initiation of any study-related tests or procedures that are not part of standard of care.
2. Age ≥ 18 years old.
3. Histologically confirmed diagnosis of previously untreated locally advanced unresectable or metastatic HER2+ GC or GEJ adenocarcinoma (see the histology table in (**Appendix 4**). GEJ cancer is defined as any tumor that invades the GEJ.
    a. Prior systemic perioperative treatment is allowed. The patient must have a disease-free interval of at least 6 months from complete surgical resection or initiation of adjuvant chemotherapy, whichever is later.
    b. Patients receiving perioperative anti-HER2 therapy require repeat testing of HER2 status for eligibility.
    c. Cohort A: HER2+ (by IHC 3+) and PD-L1–positive (by IHC with 22C3 CPS ≥ 1%), per central review.
    d. Cohort B: HER2+ (by IHC 3+ or IHC 2+ in combination with FISH+) by local review. HER2 local test must be conducted at a CAP or equivalent accreditation organization using HercepTest™ and HER2 FISH pharmaDx™ assays. PD-L1 status is not required for enrollment.
4. Patients enrolled on the study will be required to have an identified formalin-fixed, paraffin-embedded (FFPE) tumor specimen for HER2, PD-L1, LAG-3 and MSI testing. The specimen may be a formalin-fixed paraffin-embedded (FFPE) tumor specimen block, or a minimum of 10 unstained slides, with adequate tumor cells for analysis, or contemporaneous biopsy.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, verified within 3 days of Day 1.
6. Life expectancy ≥ 6 months.
7. Has adequate organ function as determined by the site Investigator.

8. At least one radiographically measurable lesion (target lesion) as defined in RECIST v1.1 and documented by computed tomography (CT) or magnetic resonance imaging (MRI).
9. Acceptable laboratory parameters as follows:
    a. Platelet count $\geq 100 \times 10^3/\mu L$ without transfusion within 28 days prior to the initiation of study treatment.
    b. Absolute neutrophil count $\geq 1.5 \times 10^3/\mu L$ in the absence of any growth factor support within 28 days prior to the initiation of study treatment.
    c. ALT/AST $\leq 3.0 \times$ ULN; for patients with hepatic metastases, ALT and AST $\leq 5 \times$ ULN.
    d. Total bilirubin $\leq 1.5 \times$ ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
    e. Creatinine < 2 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.
10. Women patients of child-bearing potential (WOCBP), defined as not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and between menarche and 1-year post menopause, must have a negative serum pregnancy test performed within 72 hours prior to the initiation of study drug administration. Female patients must agree to abstain from egg donation during the course of the study.
11. WOCBP and male patients with partners of WOCBP must agree to use highly effective methods of contraception according to **Section 8.1.3** from the time of consent through 7 months after discontinuation of study drug administration. Male patients must agree to abstain from sperm donation during the course of the study.
12. WOCBP is not pregnant or breastfeeding or male patient is not expecting to father children within the projected duration of the study, starting with screening visit through 7 months after the last dose of study drug.

5.2 Exclusion Criteria

1. Has a known additional malignancy that is progressing or has required treatment within the past 5 years. Patients who have been successfully treated for, and are disease free, non-melanomatous skin cancer, localized prostate cancer (Gleason Score < 6), or carcinoma in situ are eligible for participation in the study.
2. Patients with known MSI-H status.
3. Has poorly controlled diarrhea, despite optimal medical intervention.

4. Clinically significant accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs.
5. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient, in the opinion of the treating Investigator.
    a. Known chronic hepatitis B virus (HBV) infection (as evidenced by detectable HBV surface antigen and HBV DNA ≥ 500 IU/ml).
        - The patient with resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) is eligible.
    b. Co-infection with hepatitis B (as evidenced by detectable HBV surface antigen and HBV DNA ≥ 500 IU/ml) and C (as evidenced by detectable hepatitis C virus [HCV] RNA); OR, hepatitis D infection in patients with hepatitis B.
        - The patient with a history resolved hepatitis B and detectable HCV antibody is eligible.
    c. Has a known history of human immunodeficiency virus 1 or 2 antibodies or has a diagnosis of immune-deficiency.
    d. Has had an allogeneic stem cell or tissue/solid organ transplant.
    e. Patients with central nervous system metastases.
    f. Patients with a history of psoriatic arthritis.
    g. Patients with any history of known or suspected autoimmune disease with the specific exceptions of vitiligo, resolved childhood atopic dermatitis, psoriasis not requiring systemic treatment within the past 2 years and patients with a history of autoimmune disease who are now clinically stable with replacement therapy and by laboratory testing.
    h. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study treatment. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than 1 week prior to the initiation of study treatment.
    i. Known hypersensitivity to recombinant proteins, or any excipient contained in the trastuzumab, margetuximab, INCMGA00012, or MGD013 drug formulation (**Section 6.4**) or contraindications to the specified chemotherapy regimens.

j. Any serious underlying medical or psychiatric condition (e.g., known complete DPD deficiency) that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site.

k. History of uncontrolled seizures within 6 months registration.

l. Active or history of alcohol or other substance abuse within 1 year prior to registration.

6. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study treatment. Inactivated annual influenza vaccination is allowed.
7. Has received an investigational agent within 4 weeks prior to the initiation of study treatment. Prior neoadjuvant or adjuvant treatment with immunotherapy is excluded.
8. Major surgical procedure, including gastrectomy, or trauma within the 4 weeks prior to the initiation of study treatment.
9. Treatment with systemic corticosteroids (≥ 10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to the initiation of study treatment.
10. Clinically significant cardiovascular disease including but not limited to:
    a. Myocardial infarction or unstable angina within the 6 months prior to the initiation of study treatment.
    b. Stroke or transient ischemic attack within 6 months prior to the initiation of study treatment.
    c. Clinically significant cardiac arrhythmias.
    d. Uncontrolled hypertension: systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥ 100 mmHg.
    e. Congestive heart failure (New York Heart Association class III-IV).
    f. Pericarditis or clinically significant pericardial effusion.
    g. Myocarditis.
    h. QTcF > 480 milliseconds as the average of 3 repeat examinations.
    i. LVEF < 50%, or below the institutional lower limit of normal.
11. Clinically significant gastrointestinal disorders including:
    a. Any history of gastrointestinal perforation unless the affected area has been deemed by the Investigator to no longer be a risk for perforation.
    b. Clinically significant gastrointestinal bleeding in the opinion of the Investigator.

c. History of acute pancreatitis within 4 weeks prior to the initiation of study drug.

d. Diverticulitis that is clinically significant in the opinion of the Investigator based on the extent or severity of known disease and/or the occurrence of clinically significant disease flares within 4 weeks prior to the initiation of study drug administration.

12. A history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
13. Severe dyspnea at rest due to complications of advanced malignancy or requiring supplemental oxygen therapy.
14. Clinically significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation.
15. The female patient who is pregnant or breastfeeding, or expecting to conceive, AND the male patient who is expecting to father children within the projected duration of the trial, starting with the screening visit through 7 months after the last dose of trial treatment.
16. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
17. Employees of MacroGenics, Inc. and Zai Lab or its corporate business partners, including Incyte Corporation, unless approved by institutional review board (IRB) and principal Investigator.
18. Prisoners or other individuals who are involuntarily detained.
19. Any investigative site personnel directly affiliated with this study.

5.3 Rules for Study Treatment Discontinuation

Patients who tolerate study treatment may continue to receive treatment with the study drug(s) as specified in the protocol until any one of the following conditions are met:

- Persistent CR (see **Section 4.2**)
- Completion of protocol defined therapy (**Section 4.2**)
- PD according to RECIST v1.1.
    - Patients with clinical deterioration should be evaluated carefully either due to clinical progression or due to AEs. If study treatment discontinuation is due to clinical progression without radiographical or clinical evidence, clear documentation is required.

  - Patients in Cohort A only who have radiographic progression but are clinically stable may remain on study treatments until the next radiographic evaluation upon Sponsor Medical Monitor consultation.

- Discontinuation of treatment due to an AE
- Withdrawal of patient consent: Patients who withdraw consent are withdrawn from all further assessment and follow-up. Study documentation should reflect the patient's decision to decline any further study contacts.
- Patient decision: Patients may decide to discontinue study treatment without withdrawing consent for the study. Patients may remain in the study after treatment discontinuation for safety assessment.
- Protocol violation or non-compliance: If the Investigator recognizes compliance issues of patients, such as repeated administration of prohibited concomitant medications, Sponsor's Medical Monitor consultation is recommended prior to treatment discontinuation.
- Pregnancy
- Lost to follow-up (LTFU)
  - A patient may be determined to be LTFU after there have been at least 3 documented contact attempts. If this fails, a letter should be sent via traceable mail to the patient. Only after these attempts have failed can a patient be determined to be LTFU.
- The Sponsor, Investigator, or Regulatory Agency terminates the study

5.4 Guidelines for Discontinuation of Patient from Study

Patients who are no longer on treatment but are still followed on the study for survival can be terminated from the study for the following reasons:

- Completion of protocol-defined follow-up period (**Section 4.2**)
- LTFU
- Withdrawal of consent
- The Sponsor, Investigator, or regulatory agency terminates the study
- Death
- End of study

6 STUDY TREATMENTS

6.1 Description of Treatments

An overview of study treatments to be administered during this study is presented in **Table 9**. The order of administration of combination therapy is displayed in **Figure 5**.

Table 9 Overview of Study Treatments

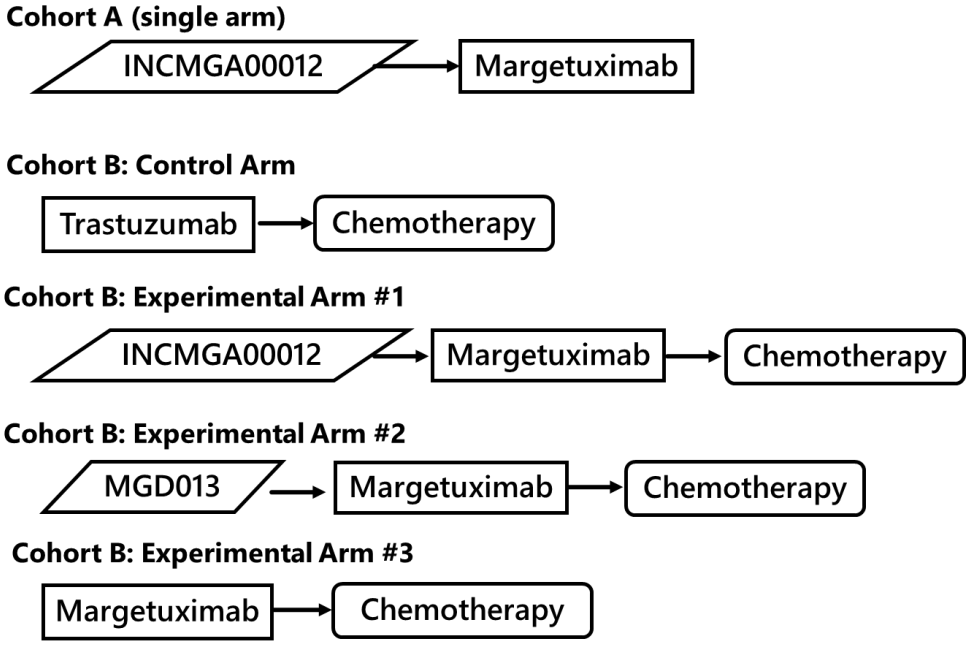
Cohort	Study Arm/Study Agent	Dose	Schedule	Route
Cohort A	**Single Experimental Arm**			
	INCMGA00012	375 mg	Q3W	IV
	margetuximab	15 mg/kg	Q3W	IV
Cohort B	**Control Arm**			
	trastuzumab	8 mg/kg loading dose then 6 mg/kg	Q3W	IV
	chemotherapy [a, b]			
	Experimental Arm 1			
	INCMGA00012	375 mg	Q3W	IV
	margetuximab	15 mg/kg	Q3W	IV
	chemotherapy [a, b]			
	Experimental Arm 2			
	MGD013	600 mg	Q3W	IV
	margetuximab	15 mg/kg	Q3W	IV
	chemotherapy [a, b]			
	Experimental Arm 3			
	margetuximab	15 mg/kg	Q3W	IV
	chemotherapy [a, b]			
	Chemotherapy: mFOLFOX-6 option [a, b]			
	leucovorin	400 mg/m^2	Q2W	IV
	oxaliplatin	85 mg/m^2	Q2W	IV
	5-FU bolus	400 mg/m^2	Q2W	IV
	5-FU 46 hr. continuous infusion	2400 mg/m^2	Q2W	IV
	Chemotherapy: XELOX option [a, b]			
	capecitabine	1000 mg/m^2	BID on Days 1-14 of each cycle	Oral
	oxaliplatin [c]	130 mg/m^2	Day 1 Q3W	IV

BID = twice daily; IV = intravenous infusion

a. The chemotherapy option selected must be approved for use per local regulations.
b. Chemotherapy must be used at the protocol-indicated starting doses and route of administration. Dosing modifications are permitted per local standard. Dose adjustments to improve tolerability and manage toxicities are permitted per local standard.
c. All chemotherapy will be capped at approximately 6 months of treatment (XELOX = 8 cycles, mFOLFOX-6 =12 cycles).

All changes in study drug infusions, including interruptions and their duration, as well as reductions in rate and duration, must be recorded. The actual date, and infusion start time and end time will be recorded on the case report form (CRF).

Figure 5 Sequence of Study Drug Administration for Each Cohort/Arm



6.1.1 Method of Assigning Patients to Treatment Groups

Cohort A is a nonrandomized, uncontrolled cohort evaluating margetuximab plus INCMGA00012. Patients will be assigned sequentially.

Cohort B Part 1 will enroll 200 patients in a 1:1:1:1 randomization for trastuzumab plus chemotherapy (Control Arm), INCMGA00012 plus margetuximab plus chemotherapy (Experimental Arm 1), MGD013 plus margetuximab plus chemotherapy (Experimental Arm 2), or margetuximab plus chemotherapy (Experimental Arm 3). The stratification factors are chemotherapy regimen (XELOX vs mFOLFOX-6) and results of local HER2 testing (IHC2+/FISH+ vs IHC3+).

6.2 Blinding

Not applicable. This is an open-label study.

6.3 Emergency Unblinding

Not applicable. This is an open-label study.

6.4 Study Drug and Supplies

Requests for additional study drug should be made to MacroGenics, Inc., via IRT at least 2 weeks in advance.

Normal saline in 100-mL or 250-mL IV bags will be obtained from the institution's usual commercial supplier for the dilution of study drugs in solution for IV administration.

6.4.1 Margetuximab

Margetuximab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow or pale brown solution, essentially free from visible foreign particles, but may contain proteinaceous particles. Margetuximab is supplied at a nominal protein concentration of 25 mg/mL in a single-dose vial containing 250 mg/10 mL. The product is formulated in a sterile solution of 1.1 mg/mL sodium phosphate monobasic monohydrate, 0.58 mg/mL sodium phosphate dibasic heptahydrate, 2.9 mg/mL sodium chloride, 11 mg/mL L-arginine hydrochloride, 30 mg/mL sucrose, and 0.1 mg/mL polysorbate 80, pH 6.1.

6.4.2 INCMGA00012

INCMGA00012 is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution,

6.4.3 MGD013

[redacted]

6.5 Other Study Treatments

6.5.1 Trastuzumab

HERCEPTIN® will be provided by MacroGenics, or its corporate business partners in China, except Taiwan.

The use of trastuzumab biosimilars in this study is strictly prohibited.

6.5.2 Chemotherapy

All treatment arms in Cohort B will include XELOX or mFOLFOX-6 chemotherapy. The choice of chemotherapy (as it is widely approved and available therapy) will be made by the treating physician prior to randomization and is not considered as investigational medicinal product. The chemotherapy regimen selected must be allowed for use per local regulations

and will be supplied locally unless an alternate source for the selected agent is needed. The choice of therapy should be made based on the patient's co-morbidities and the physician's best judgment about the most appropriate chemotherapy for a given patient. Chemotherapies must be used at the protocol-indicated starting doses, schedule, and route of administration (see **Table 9**); however, dose adjustments to improve tolerability and manage toxicities are permitted. Changes in chemotherapy will not be allowed following patient randomization (see **Section 6.1.1**). Substitution of generic equivalents for branded products is acceptable if such products have been approved by local regulatory authorities for use in the treatment of human diseases.

6.6 Study Treatment Preparation and Administration

Information on the packaging, labeling, storage, preparation and administration of study treatments, and active comparator, may be found in the Pharmacy Manual.

6.7 Treatment Compliance

All study treatments will be administered by healthcare professionals under the supervision of the Investigator. Records of dose calculation, administration, and dosing regimen will be accurately maintained by site staff. The monitor will review dose calculation, administration, and regimen as well as medication accountability during study site visits and at the completion of the study.

6.8 Storage and Accountability

Accurate accounting of all study drug must be maintained. The Investigator agrees to keep an inventory of study drugs using the institution's drug accountability logs or logs provided by MacroGenics. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

A Pharmacy Manual will be provided to the Investigator or designee. When the study is completed, copies of all study drug accountability records must be provided to the Sponsor. Original drug accountability records must be maintained with the rest of the documentation at the site for inspection by the study monitors and auditors.

6.9 Investigational Product Disposition at End of Study

Upon completion or termination of the study, sites whose drug destruction SOP or Clinical Trial Management Destruction Survey has been submitted and approved by MacroGenics may destroy all unused, used, and expired study drug on-site upon receipt of written authorization from MacroGenics. All sites who have not been approved for on-site destruction must return all unopened, expired, and used vials of study drug to the applicable clinical supply depot. All drug returns must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. If MacroGenics approves the destruction of drug at the site, the Investigator must ensure arrangements are made for proper disposal and that appropriate records of disposal, and any

corresponding documentation, are filed with the Pharmacy study records, and copies provided to the Sponsor for filing.

7 POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1 Infusion Related Reactions Including Cytokine Release Syndrome

Infusion reactions (including CRS) associated with mAbs, or DARTs administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section. However, severe reactions may require more intensive interventions (e.g., steroids, anti–TNF-α antibodies, and/or IL-6 inhibitors).

Patients should be monitored closely for the development of IRRs during infusions. Medications and supportive measures for the treatment of severe hypersensitivity reactions should be available for immediate use for an infusion reaction during study drug administration.

7.1.1 Premedication and Prophylaxis

The following are suggested guidelines for the Investigator regarding prophylactic pre-infusion measures to be followed to mitigate the occurrence or severity of potential infusion reactions. Equivalent medications may be substituted based on local medical practice and availability.

Cycle 1, guidelines – Recommendations prior to first infusion of study treatment:

- Acetaminophen 650-1000 mg orally (PO) or ibuprofen 400 mg PO
- Diphenhydramine 50 mg PO or IV
- Ranitidine 300 mg PO or IV
- Dexamethasone 10-20 mg IV

No pre-infusion prophylactic steroid administration is required for subsequent infusions. Non-steroidal premedication may be administered prior to the subsequent infusion, if warranted.

For patients who had infusion reactions following the first dose of margetuximab, INCMGA00012, or MGD013 that were not adequately or only moderately controlled with acetaminophen, diphenhydramine, or ranitidine, IV corticosteroids may be added to the premedication for subsequent administration of the given study drug. Dexamethasone (10 to 20 mg IV) may be used as premedication in addition to acetaminophen, diphenhydramine, and ranitidine if the patient experiences a Grade ≥ 2 infusion reaction with the first infusion. Permanently discontinue study treatment if there are continued IRR after use of recommended prophylaxis.

7.1.2 Management of Observed Infusion Reactions

The following are treatment guidelines (which may be modified as needed by the Investigator according to the best practices of medicine) for infusion reactions. Equivalent medications may be substituted based on local medical practice and availability.

Grade	Description	Treatment	Subsequent Infusions
1	Mild reaction: treatment intervention not indicated.	Interrupt or slow the rate of infusion. Monitor vital signs closely until medically stable.	Consider premedication with an antipyretic (eg, acetaminophen/paracetamol 500-1000 mg PO) and a histamine blocker (eg, diphenhydramine 50 mg PO) for participants who have had previous systemic reactions to protein-product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, histamine blockers, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate treatment (eg, IV fluids, histamine blockers, NSAIDs, antipyretics, narcotics) per institutional preferences. Monitor vital signs closely until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. Subsequent occurrences (after recommended prophylaxis): Permanently discontinue study treatment.	Premedicate at least 30 minutes before infusion with a histamine blocker (eg, diphenhydramine 50 mg PO) and an antipyretic (eg, acetaminophen/paracetamol 500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increased by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate treatment (eg, IV fluids, histamine blockers, NSAIDs, antipyretics, narcotics, oxygen, pressors, epinephrine, corticosteroids) per institutional preferences. Monitor vital signs closely until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment. Note for NCI CTCAE (v5.0) Grade 3 infusion-related reaction: if rapidly responsive to symptomatic medication and/or to brief interruption of infusion, study drug does not need to be permanently discontinued.

All changes in the infusion of any of the study drugs, including interruption of the infusion and its duration as well as reductions in infusion rate and duration, must be recorded.

7.2 Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs of unknown etiology, associated with drug exposure, and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxic, or other etiologic causes before labeling an AE as an irAE.

Recommendations for the management of specific irAEs known to be associated with INCMGA00012, MGD013 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in **Table 10**. If treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after the last dose of study drug, or if the corticosteroid dose cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, study drug should be permanently discontinued. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral corticosteroids. Other immunosuppressive treatment should begin if irAEs are not controlled by corticosteroids.

For management of irAEs not specifically mentioned in Section 7.2, refer to current National Comprehensive Cancer Network Guidelines for the Management of Immune-related Toxicities (https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf**).**

Temporary interruptions of study drugs may be required in the event of treatment-related, immune-related toxicity. General guidelines for specific toxicity regarding dosing and treatment are provided below. All toxicities will be graded according to NCI CTCAE v5.0.

Table 10 Toxicity Management Guidelines for Immune Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Study Treatment	Adverse Event Management
Pneumonitis	Grade 1	No action	None
	Grade 2	Withhold for at least 2 weeks and until ≤ Grade 1	Evaluate participants with suspected pneumonitis with radiographic imaging and administer systemic corticosteroids per local practice followed by taper Add prophylactic antibiotics for opportunistic infections
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue	
Diarrhea/colitis	Grade 1	No action	None
	Grades 2 or 3	Withhold until ≤ Grade 1	Consider prompt initiation of standard antidiarrheal agents and other necessary supportive care as needed (eg, oral and/or IV fluids) Administer systemic corticosteroids per local practice followed by taper Consider prophylactic antibiotics per local practice Consider gastrointestinal consultation and performing endoscopy to rule out colitis Consider stool sample evaluation to rule out Clostridioides difficile and infectious etiologies
	Grade 4 or recurrent Grade 3	Permanently discontinue	
AST/ALT elevation and/or increased total bilirubin/hepatitis	Grade 1	No action	None
	Grade 2 ALT or AST increase or Total bilirubin increases to > 1.5 × and up to 3 × ULN	Withhold until ≤ Grade 1	Administer systemic corticosteroids per local practice followed by taper Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable Consider monitoring total bilirubin, direct bilirubin, and alkaline phosphatase weekly (or more frequently)
	Grades 3 or 4 ALT or AST increase or In participants with liver metastases with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week or Total bilirubin increases to > 3 × ULN	Permanently discontinue	

Table 10 Toxicity Management Guidelines for Immune Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Study Treatment	Adverse Event Management
Endocrinopathies Hypothyroidism Hyperthyroidism Type 1 diabetes mellitus Hyperglycemia	Grades 1 or 2	No action	None
	Grades 3 or 4 hypothyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable	Initiate thyroid replacement hormones (eg, levothyroxine, liothyronine) per SOC
	Grades 3 or 4 hyperthyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable	Initiate symptomatic management
	Grades 3 or 4 Type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤ Grade 1 or is otherwise clinically stable	Initiate treatment with antihyperglycemics or insulin as clinically indicated
Endocrinopathies (continued) Adrenal insufficiency	Grade 1	No action	None.
	Grade 2	Withhold until ≤ Grade 1 or otherwise clinically stable	Initiate treatment with hormone replacement therapy as clinically indicated
	Grades 3 or 4	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or is otherwise clinically stable	Administer prednisone or equivalent at initial dose of 1-2 mg/kg/day followed by a taper and initiate treatment with hormone replacement therapy as clinically indicated
Endocrinopathies (continued) Hypophysitis	Grade 1	No action.	None.
	Grade 2 (asymptomatic)	Withhold until ≤ Grade 1 May restart study drug after controlled by hormone replacement therapy	Initiate treatment with hormone replacement therapy
	Grade 2 (symptomatic, eg, headaches, visual disturbances)	Withhold until ≤ Grade 1 May restart study drug after controlled by hormone replacement therapy, if indicated, and corticosteroid taper is complete	Administer corticosteroids at initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper and initiate treatment with hormone replacement therapy as clinically indicated Consult with endocrinologist as needed

Table 10 Toxicity Management Guidelines for Immune Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Study Treatment	Adverse Event Management
	Grades 3 or 4 (symptomatic)	Permanent discontinuation should occur if after withholding study drug, the toxicity does not resolve to ≤ Grade 1 within 12 weeks after last dose of study drug, or if corticosteroid dose cannot be reduced to ≤ 10 mg/day prednisone or equivalent within 12 weeks Permanent discontinuation of study drug should take place earlier, at the investigator's discretion, if corticosteroids and/or hormone replacement therapy cannot balance the participant's pituitary function	
Nephritis and renal dysfunction	Grade 1	No action	None
	Grades 2 or 3 increased blood creatinine	Withhold until ≤ Grade 1	Administer corticosteroids per local practice followed by taper
	Grade 4 increased blood creatinine	Permanently discontinue	
Skin (Eg, SJS, TEN)	Grade 1	No action	None
	Grade 2	No action	Manage with topical corticosteroids with or without drug interruption.

Table 10 Toxicity Management Guidelines for Immune Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Study Treatment	Adverse Event Management
	Grade 3a, persistent Grade 2 (≥ 2 weeks), or suspected SJSb	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	Administer corticosteroids per local practice followed by taper. Additionally, oral histamine blockers such as diphenhydramine or famotidine (per institutional preference) may be utilized as needed Refer to dermatology consult if no resolution with these measures Refer to dermatology consult if SJS or TEN is suspected
	Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, not requiring systemic corticosteroids, and resolving or improving to ≤ Grade 1 within 14 days do not have to interrupt study drug/treatment. Permanent discontinuation of study drug/treatment may be necessary if there is recurrence of Grade 3 rash after resuming study drug/treatment		
	Grade 4 or confirmed Grade 4 SJS or TEN	Permanently discontinue	Administer prednisone or equivalent at initial dose of 1-2 mg/kg/day followed by a taper Refer to dermatology consult
Myocarditis	Grade 2-4	Permanently discontinue	Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg/day of prednisone or equivalent). Taper as appropriate. Refer to cardiology consult Manage cardiac symptoms according to SOC and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
Important nervous system events (eg, Guillain-Barré syndrome, auto-immune encephalitis, myasthenia gravis, autonomic neuropathy, transverse myelitis)	Grade 2	Withhold until ≤ Grade 1	Refer to neurology consult Initiate treatment with systemic corticosteroids (initial dose of 1-2 mg/kg/day of prednisone or equivalent). Taper as appropriate. For Grade 2 transverse myelitis, consider permanent discontinuation Manage symptoms according to SOC and with guidance from neurology
	Grades 3 or 4	Permanently discontinue	

Table 10 Toxicity Management Guidelines for Immune Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken with Study Treatment	Adverse Event Management
All other irAEs	Grades 2 or 3 based on severity and type of reaction	Withhold until ≤ Grade 1	Based on severity of AE, administer corticosteroids Ensure adequate evaluation to confirm etiology or exclude other causes.
	Recurrent Grade 3 or persistent Grades 2 or Grade 3	Permanently discontinue	
	Grade 4 (excluding endocrinopathies)	Permanently discontinue	

8 CONCOMITANT THERAPY AND RESTRICTIONS

8.1 Concomitant Therapy

All concomitant medications, including prophylactic pre-infusion medications, and blood products administered during the patient's participation in the study until the End of Treatment Visit (EOTV) must be recorded in the source document. All changes in infusions, including interruptions and their duration as well as reductions in rate and duration, must be recorded.

8.1.1 Prohibited Therapy

The following rules concerning concurrent treatment(s) will apply in this study:

- Any other anti-neoplastic therapies other than the assigned study treatment including other small molecules, biologics, or radiotherapy are not allowed.
- Patients may not receive other investigational drugs during the period of study participation.
- Live vaccines within 4 weeks prior to the first dose of study treatment and while participating in the study are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
- Because INCMGA00012 and MGD013 have a mechanism of action dependent upon the engagement of T lymphocytes, the use of corticosteroids should be limited to the extent possible. Chronic doses of corticosteroids more than 10 mg/day prednisone or equivalent are prohibited other than for the management of drug-related adverse experiences. Steroids may be employed in the treatment of suspected INCMGA00012- or MGD013-associated irAEs in consultation with the Sponsor's Medical Monitor. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed.
- Trastuzumab biosimilar products are not allowed.
- Capecitabine or 5-FU precautions
    - Per the EMA direct healthcare professional communication (DHPC), as treatment of patients with 5-FU or capecitabine-containing medicinal products is contraindicated in patients with known complete DPD deficiency, DPD testing is recommended during screening (https://www.ema.europa.eu/en/documents/dhpc/5-fluorouracil-ivcapecitabine-tegafur-containing-products-pre-treatment-testing-identify-dpd_en.pdf). These tests can be conducted locally where available.

- Patients receiving concomitant capecitabine or 5-FU and oral coumarin-derivative anticoagulants such as warfarin and phenprocoumon should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters have been reported during concomitant use.
- Phenytoin: Monitor phenytoin levels in patients taking capecitabine concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- CYP2C9 substrates: Care should be exercised when capecitabine is co-administered with CYP2C9 substrates.

- Oxaliplatin
  - Since platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds. Exercise caution in coadministration with other nephrotoxic compounds.

8.1.2 Permitted Therapies

Patients may receive the following concurrent therapies:

- Antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease.
- Transfusions such as red blood cells and platelets are permitted to treat symptoms or signs of anemia or thrombocytopenia.
- Bisphosphonates or RANK-L inhibitors provided such agents are approved in the local jurisdiction and treatment with the agent is begun before the start of study treatment.
- Use of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, or other growth factors is allowed per local practice.

8.1.3 Contraception

Male and female patients are required to use highly effective contraceptive measures as specified below. Male patients are required to use a condom regardless of his WOCBP partner's method of contraception.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral

- Intravaginal
- Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

8.2 Restrictions

8.2.1 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study.

8.2.2 Patient Activity Restrictions

There are no restrictions on patient activities and no requirement for patient confinement during the study.

9 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. The timing of the study procedures is presented in **Appendix 1**.

9.1 Informed Consent

The Investigator is responsible for ensuring that the patient provides informed consent prior to performing any study-related assessments, evaluations, or procedures that are not part of standard of care for the patient's disease. Informed consent for this study must be provided by signing an IRB/Independent Ethics Committee (IEC) approved informed consent document (Consent for Study Participation). A copy of the relevant signed informed consent document must be provided to the patient and the original maintained according to institutional procedures. The patient's medical records will include documentation of the informed consent process.

9.2 Screening Period

Patients may receive the first dose of study treatment up to 28 days after signing the informed consent. This period is defined as the screening period. At the screening visit, patients will enter the study upon signing the informed consent document. No screening activities outside of usual standard of care should be performed prior to obtaining informed consent from the patient. However, medical testing that is performed according to local standard of care may be used to qualify patients for participation in the study.

9.3 Medical History

A complete medical history should be obtained during the screening visit. All concurrent medical conditions in the last 60 days and any significant past medical conditions (e.g., hospitalizations, surgeries, chronic conditions, prior cancer history, etc.) should be collected. Any untoward event that occurs prior to the first dose of study treatment should be recorded as medical history and not as an AE, unless it is due to a protocol-related-procedure.

9.4 Prior and Concomitant Medications

Changes to concomitant medications, blood products, and procedures should be evaluated in light of potential AEs, and do not need to be recorded on the CRF. If a change to concomitant medications or procedures is related to an AE, record the AE on the eCRF.

Prior courses of systemic cancer therapy (e.g., chemotherapy, immunotherapy, etc.) will be documented in the medical records and on the eCRF.

9.5 Physical Examination

The Investigator will perform physical examination of all patients; the examination will be conducted as specified in **Appendix 1**. Full physical examination will be performed at screening, and it will include height (screening only), weight, and examination of skin,

HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system. All other physical examinations will be directed physical examinations based on patient symptoms and tumor location, as clinically indicated.

9.6 Vital Signs

Vital signs are obtained as clinically indicated according to the local standards and best practices and **not** recorded on the eCRF.

9.7 Pulse Oximetry

Pulse oximetry is strongly recommended prior to each treatment cycle. Clinically significant out of range values should be reported as an AE.

9.8 Clinical Laboratory Tests

Blood and urine samples will be collected at the times specified in **Appendix 1**. Hematology, serum chemistry, pregnancy, urinalysis, coagulation time, and endocrine evaluation tests will be collected and processed, according to instructions in the Laboratory Manual. Safety laboratory tests should be performed and reviewed before study treatment administration. Laboratory values are **not** entered on the eCRF. Clinically significant laboratory values should be reported as AEs, according to the criteria in **Section 12.2.1**, "Clinical Laboratory Changes."

9.8.1 Local HER2 Testing

In Cohort B, tissue must be tested for HER2 and documented from a reference laboratory that conforms to standards set for accreditation by (CAP/CLIA), or an equivalent accreditation organization. Per recognized guidelines such as CAP, American Society of Clinical Pathologists, and American Society of Clinical Oncology, HER2 status for GC or GEJ cancer should be based on the most recently available tumor biopsy collected from the gastric or GEJ cancer patient.

The HER2 IHC and FISH test kit must be HercepTest™, and HER2 FISH pharmDx™ for use in GC. Use of test kits only approved for breast cancer is not permitted. Patients with IHC 2+ require confirmation with HER2 FISH pharmDx™. If the investigative site does not have access to specified test kits, samples may be sent to the central laboratory for testing. If patient samples are sent to the central lab for eligibility testing, the patient may not be enrolled in the study until the central laboratory results are communicated to the site.

Refer to the Laboratory Manual for preparation, handling and shipping instructions.

Patients who are enrolled based on the local HER2 test, and later do not meet protocol criteria based on central confirmation can continue in the study.

9.9 Central Laboratory Assays

Clinical laboratory tests to be performed are presented in **Appendix 2**. Centralized testing of HER2, PD-L1, LAG-3, and MSI status, will be conducted at a central laboratory designated by the Sponsor. FDA-approved tests will be used for HER2 and PD-L1. See the Laboratory Manual for details regarding the collection, preparation and shipping of study samples. Collection of samples for PK, PD and ADA are no longer required.

9.10 Pharmacodynamics/Biomarkers

Procedures for the acquisition, handling, and processing of pharmacodynamic biomarker specimens will be provided in the Laboratory Manual.

Patients enrolled on the study will be required to have an identified FFPE tumor specimen block. A minimum of 10 unstained slides of 4- to 5-micron sections on positively charged slides from an FFPE tumor specimen or contemporaneous biopsy available for submission for HER2, PD-L1, MSI, and LAG-3. If possible, include one hematoxylin and eosin stained slide of the same tumor specimen to assist in location of tumor cells.

Individual assay results of central MSI testing will not be provided to the Investigator and central radiology reviewers for tumor assessments.

9.11 Radiographic Assessments

Baseline tumor imaging consists of a CT or MRI scan for all patients. The subsequent tumor assessments on treatment should use the same imaging modality as that for the baseline assessment. Target and non-target lesions will be designated at screening and evaluated for disease progression only according to **Appendix 1**. No measurement of individual lesions is required. Only the RECIST 1.1 overall response will be recorded in the eCRF.

A CT or MRI scan of the brain will be performed in cases where brain metastasis is suspected to rule out metastatic spread to the brain.

9.12 Electrocardiography

Twelve-lead ECGs will be obtained at screening and as clinically indicated.

Actual times and other parameters of the ECG assessments will be recorded on the eCRFs.

9.13 MUGA/Echocardiogram

Multigated acquisition ventriculography scanning (MUGA) scans or echocardiograms will be obtained and analyzed locally in all patients according to the Time and Events Schedules (**Appendix 1**). The same modality should be used throughout the study for any given patient. All MUGA scans or echocardiography performed will be evaluated for the change in LVEF from baseline.

9.14 End of Treatment Visit

A list of evaluations to be performed for the EOTV is provided in **Appendix 1**. The EOTV should be performed within 30 days after the patient has met study treatment discontinuation criteria specified in **Section 5.3**.

9.15 Post-Treatment Follow-up Visit

The post-treatment follow-up period includes up to a 30-day follow-up after treatment discontinuation or initiation of subsequent anticancer therapy, whichever is earlier. Any patient currently in survival follow-up will be discontinued from study.

10 ASSESSMENT OF PHARMACOKINETICS AND PHARMACODYNAMICS

10.1 Pharmacokinetic Assessments

Serum concentrations of study drugs will be measured using respective validated assay methods in the Sponsor's designated laboratory. Descriptive PK summaries will be provided.

10.2 Pharmacodynamic/Biomarker Assessments

Pharmacodynamics/Biomarker Assessments

Biomarker assessments related to entry criteria will be performed prospectively prior to enrollment. Other biomarker assessments not related to entry criteria will be prospectively collected and retrospectively analyzed.

Cohort A

- MSI status performed by a central laboratory
- PD-L1 and HER2 expression by IHC will be conducted with FDA-approved assays by a central laboratory for eligibility.

Cohort B

- Determination of MSI status performed by a central laboratory
- LAG-3 expression based on FFPE tumor tissue
- Determination of PD-L1 and HER2 expression will be conducted with FDA-approved assays for central confirmation.

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Assessments

11.1.1 Disease Response Assessments

Tumor assessments will be obtained using CT and/or MRI scans and tumor response evaluated according to RECIST v1.1. Target and non-target lesions will be designated at screening and assessed every 3 cycles (± 7 days) for approximately 9 months. Beginning with Cycle 13, assessments will occur every 4 cycles (± 7 days) while on treatment.

Patients in Cohort A who have radiographic progression but are clinically stable may remain on study treatments until the next radiographic evaluation, upon Sponsor Medical Monitor consultation.

11.1.2 Survival Assessments

Survival assessments will no longer continue. Patients currently in survival follow up should be discontinued from the study.

11.2 Immunogenicity Assessments

The generation of ADA for margetuximab, INCMGA00012, and MGD013 will be monitored using validated assay methods. Blood samples will be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of blood sample for ADA assessment.

12 ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

12.1 Definitions

12.1.1 Adverse Event

Adverse event (AE): any untoward medical occurrence in a patient or clinical trial patient associated with use of a drug in humans, whether or not considered drug related. An AE can be:

- any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- any occurrence that is new in onset or aggravated in severity or frequency from baseline, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2 Adverse Drug Reaction

Adverse drug reaction (ADR): noxious and unintended response to the medicinal product related to any dose. As used herein, the phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

12.1.3 Adverse Event of Special Interest

An AESI is an event of scientific and medical interest or concern to the Sponsor’s product or program, for which ongoing monitoring and rapid communication to the Sponsor may be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it.

12.1.4 Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening (immediate risk of death)
- Inpatient hospitalization for longer than 24 hours or prolongation of existing hospitalization (even if the event is Grade 1)
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Important medical events

12.1.5 Attribution/Assessment of Causality

Attribution/Assessment of Causality is a determination that describes the relationship or association of the study product with an AE.

Assessment of causality or relationship of AEs to study drug is provided by the Investigator and is determined by the Investigator. Criteria include 1) temporal relationship of the AE to study drug administration, 2) whether an alternative etiology has been identified, and 3) biological plausibility.

Causality assessment categories used for this study are described below.

Causality assessments considered not related to study drug:

- None: The event is related to an etiology other than study drug. Alternative etiology should be documented.
- Unlikely: The event is unlikely related to study drug and likely related to factors other than study drug. An alternative explanation is more likely (e.g., concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

If an SAE is considered “unlikely” or “unrelated” to study drug, the Investigator should offer a clinical opinion factor(s), agent(s), or process(es) likely to be causative of the event.

Causality assessments considered related to study drug:

- Possible: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the patient’s clinical status or underlying disease.
- Probable: There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the patient’s clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug, causes other than the study drug are ruled out, and/or the event re-appeared on re-exposure to the study drug.

12.1.6 Severity Criteria

Assessment of AE severity will be by NCI CTCAE v5.0.

For events not contained in CTCAE, the Investigator may assign intensity according to the following generic CTCAE grading scale:

- Grade 1 = Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

12.2 Adverse Event Collection and Documentation

12.2.1 All Adverse Events

All patients who receive at least one dose of study drug are evaluable for safety. AEs will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled patients as appropriate.

All AEs whether serious or non-serious, will be reported from the time a signed and dated informed consent form (ICF) is obtained until 30 days following the last dose of study drug or until the start of a subsequent systemic anticancer therapy, if earlier.

Both protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation. AEs and SAEs reported between the time the patient signs the ICF and the administration of the first dose of study drug will be captured as concurrent medical history unless the events are attributed to protocol-specified procedures. Events attributed to protocol-specified procedures will be collected on the Adverse Event eCRFs as appropriate. AEs, regardless of seriousness, severity, or relationship to study drug, are documented on the eCRF, including:

- Duration, severity, and seriousness of each AE
- Action taken with respect to study drug(s)
- Investigator’s attribution/causality assessment
- Event outcome

When possible, diagnoses are given for signs and symptoms due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion reported as “upper

respiratory infection"). All treatment for AE management will be recorded. Non-serious AEs should be entered into the eCRFs within 10 business days of study site awareness.

Clinical Laboratory Changes: Safety laboratory assessments will be evaluated by the Investigator to ensure patient safety. Laboratory tests will be graded according to CTCAE v5.0. The Investigator is responsible for reviewing the results of all laboratory tests as they become available:

- Laboratory values that fall outside of a clinically accepted reference range or values that differ significantly from previous values must be evaluated by the Investigator for clinical significance. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.

A laboratory abnormality is reported as an AE if associated with an intervention including, but not limited to, discontinuation of treatment, dose reduction/delay, or concomitant therapy. Also, any laboratory abnormality may be reported as an AE at the Investigator's discretion, based on clinical significance. Examples include abnormalities for which there are no interventions yet abnormal value(s) suggest(s) disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, diagnosis or medical condition should be reported (e.g., renal failure, hematuria) not the laboratory abnormality (e.g., elevated creatinine, urine RBC increased).

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The Sponsor will also notify the Investigator of regulatory submissions, as appropriate. The Investigator is responsible for notifying the appropriate IEC or IRB that approved the protocol, unless otherwise required and documented by the IEC/IRB.

12.2.2 Serious Adverse Events

All SAEs occurring during the study must be reported to the Sponsor.

- Within 24 hours of becoming aware of an SAE, the Investigator should report the SAE to the Sponsor by completing the appropriate eCRF(s). Upon receipt of SAE follow-up information, the appropriate eCRFs should be completed within 24 hours of becoming aware of the follow-up information. In the event of a system outage, SAE form can be utilized as the back-up reporting method. The completed SAE form should be emailed to saereports@macrogenics.com or faxed to (301)-354-3800. The SAE information should be entered into the eCRF(s) within 24 hours of the system becoming available. SAEs related to study drug may be reported at any time, through 30 days after the last dose of study drug or until start of a subsequent anticancer therapy, if earlier.
- In those cases, in which the SAE is considered related to study drug, the study drug may be discontinued, and the patient will continue participation in the study for observational safety and analysis (except for cases where the patient is withdrawn from the study by the Investigator or withdrew the consent).

- After 30 days following the last dose of study drug administration, if an Investigator becomes aware of a SAE that s/he suspects is related to study drug, the Investigator should report the event to the Sponsor. Grade 3 or Grade 4 SAEs considered related to study drug are followed until recovery to ≤ Grade 1.
- The Investigator will follow all SAEs until resolution and record the date of resolution. Resolution is a return to pre-treatment status or stabilization of a chronic condition.
- Unresolved SAEs at study end or upon patient withdrawal must be followed until:
    - The event resolves
    - The event stabilizes
    - The event returns to baseline, if a baseline value/status is available
    - The event can be attributed to an etiology other than study drug
    - It becomes unlikely additional information can be obtained due to patient or health care practitioner refusal, or LTFU after due diligence efforts.

- Any event requiring hospitalization or its prolongation during study drug will be reported as a SAE, except hospitalization:
    - A standard hospitalization for administration of study drug
    - For a protocol/disease-related procedure e.g., surgery, scans, endoscopy, and sampling of marrow, blood, or other tissue.
    - Hospitalizations not intended to treat an acute illness or AE, including social reasons such as pending placement in long-term care or hospice facility.
    - Documented surgery or procedure planned before study entry.

- Any SAE of suspected transmission of an infectious agent via a medicinal product will be reported.

Disease progression or events deemed related to disease progression resulting in hospitalization or death without other SAE criteria will be documented as an antitumor activity outcome, **not reported** as a SAE; they will be collected as efficacy endpoints. **Conversely,** SAEs should be reported if it is unclear if the event is due to PD.

12.2.3 Protocol-Specific Adverse Events of Special Interest

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities by the Sponsor. The Sponsor must be notified of these events regardless of seriousness (i.e., serious and nonserious AEs). A list of protocol-specific AESIs are displayed in **Table 11**.

Table 11 Adverse Events of Special Interest

AESI	Reporting Requirement
Potential Hy's Law: AST or ALT > 3 × ULN **and** total bilirubin > 2 × ULN and without any alternate etiology	Within 24 hours of the study site's awareness of the event
≤ Grade 2 IRRs or CRS events	Within 10 days of the study site's awareness of the event.
≥ Grade 3 IRRs or CRS events	Within 24 hours of the study site's awareness of the event
≥ Grade 3 immune-related AEs	Within 24 hours of the study site's awareness of the event
Decreased LVEF defined as: ≥ 16% absolute decrease from the pre-treatment value, or < institutional normal limits (or 50% if no limits are available) and ≥ 10% absolute decrease from pre-treatment values	Within 24 hours of the study site's awareness of the event

12.2.4 Pregnancy

Pregnancy in a female patient or partner of a male patient must be reported on the Pregnancy Exposure Form (from the Study Procedures manual) within 24 hours of study site awareness. The reporting period is from consent through 7 months after the last dose of study treatment, or initiation of subsequent anticancer therapy. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, to be reported on the SAE Report Form by email, SAEReports@macrogenics.com, or by fax, (301) 354-3800. SAEs should be entered into the eCRFs within 5 calendar days of the site's awareness. Patients becoming pregnant during the study must discontinue study drug.

The Investigator must attempt to follow the pregnancy to term or termination in order to report the outcome and health status of the mother and child. The Investigator should discuss with and encourage the pregnant partner to allow collection of follow up information. The Pregnant Partner Consent Form must be signed prior to collecting follow-up information. Follow-up information will be collected for all live newborns at birth and 6 months after birth. Information will be collected to assess study drug effects on the newborn. If appropriate, follow-up will be extended.

12.2.5 Special Reporting Situations

12.2.5.1 Overdose

If an event of clinical consequence occurs due to the overdose an AE and needs to be reported to MacroGenics within 24 hours of awareness. All AEs associated with an overdose should be recorded in the eCRF.

12.2.5.1.1 INCMGA00012

Retifanlimab has been safely administered at doses up to 750 mg Q4W. In case of overdose, participants should be closely monitored for signs or symptoms of adverse reactions, and treatment should consist of general supportive measures.

12.2.5.1.2 MGD013 and Margetuximab

Overdose is any accidental administration of study drug ≥ 20% of the assigned dose. In the event of an overdose, the patient should be closely monitored for potential AEs.

12.2.5.2 Product Quality Issues

Any suspected transmission of an infectious agent via a medicinal product, or other product quality issue that results in an event of clinical consequence are considered AEs. The AE resulting from a product quality issue should be reported within 24 hours of awareness of the event.

12.2.5.3 Discontinuation of Study Therapy Due to an Adverse Event

Any AE not related to disease progression that results in the discontinuation of the patient from study therapy must be reported to MacroGenics **within 24 hours** of the discontinuation. Follow up of the AE will continue until resolution or stabilization of the AE unless the patient withdraws consent for further follow up.

13 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patient's, Investigators, and the Sponsor and are mandated by regulatory agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

13.1 Procedures

All initial PQCs must be reported to the Sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the Sponsor according to the SAE reporting timelines (refer to **Section 12.2.2**). A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.

13.2 Contacting Sponsor Regarding Product Quality

Product quality issues should be reported via e-mail to:
Quality.complaints@macrogenics.com.

14 STATISTICAL ANALYSIS

This section outlines the statistical methodology and principles which will be used for data analysis in this study. A separate statistical analysis plan (SAP) and statistical programming plan will further describe the details regarding statistical methods and will govern the analysis.

14.1 Determination of Sample Size

The planned sample sizes are described below. The study enrollment was closed. At the time of this protocol amendment, there are 48 patients treated in Cohort A. There were 34 patients randomized, of which 33 patients were treated in Cohort B Part 1. Cohort B Part 2 has never started.

Cohort A

The sample size of approximately 100 non-MSI-H patients is based on a Simon two-stage design to provide approximately 83% power to test ORR of at a 2-sided alpha level of 0.05. The first stage (Part 1) will enroll and treat 40 response evaluable non-MSI-H patients. If at least 21 (53%) responders (CR or partial response [PR]) are observed, the study will move to the second stage (Part 2) with enrollment of approximately 60 additional response evaluable non-MSI-H patients. Other efficacy data such as DoR and PFS will be considered as well in enrollment decision-making. If the study continues to enroll an additional 60 patients, the null hypothesis H_0: ORR = would be rejected at 1-sided alpha level of 0.025 (or equivalently, 2-sided 0.05) if the observed ORR from all 100 response evaluable non-MSI-H patients is ≥ . However, the totality of the data will be assessed to determine not only statistical significance but a clinically meaningful effect. The total number of patients to be enrolled in Cohort A is expected to be approximately 110 in order to obtain approximately 100 non-MSI-H patients.

Cohort B

The sample size for Cohort B is determined based on a Phase 2/3 design. The sample size will consist of patients that are HER2+ by central confirmation. Entry criteria for HER2 may be based on a local test, however, enrollment will continue until the sample size is accrued based on central confirmation. The total planned sample size for Cohort B is approximately 750, consisting of two parts:

- In the Cohort B Part 1, a total of approximately 250 patients with centrally confirmed HER2+ will be enrolled as follows. First, approximately 200 patients will be randomized in a 1:1:1:1 ratio to 1 of 4 arms (one control arm and three margetuximab-containing arms). The randomization will be stratified by two stratification factors: chemotherapy regimen (XELOX or mFOLFOX-6) and results of local HER2 testing (IHC 2+/FISH+ vs IHC 3+). Selection of which of 2 margetuximab and CPI-containing arms to move to the Phase 3 part of the study (Cohort B Part 2) for further testing will be primarily based on ORR but will also take into consideration PFS and safety. After this randomization portion of

enrollment is complete, enrollment of up to approximately 50 additional non-randomized patients will continue into the margetuximab + chemotherapy arm only.

- In Cohort B Part 2, approximately 500 patients with centrally-confirmed HER2+ will be randomized in a 1:1 ratio between the control arm and the selected margetuximab arm. The randomization will be stratified by two stratification factors: chemotherapy regimen (XELOX vs. mFOLFOX-6) and results of local HER2 testing (IHC 2+/FISH+ vs IHC 3+).

By applying the closed testing procedure (**27**) and the inverse normal p-value combining method (**5**) to test primary endpoint OS at the end of Cohort B Part 2, the sample size of approximately 650 patients planned enrollment [Cohort B Part 1: control arm (50 patients), 2 margetuximab and CPI-containing arms (100 patients) and 500 patients from Cohort B Part 2] will provide approximately 80% power to detect OS HR = (median OS increase from months for control arm to months for either margetuximab and CPI-containing arm) at 1-sided 0.025 (or equivalently, 2-sided 0.05) alpha level. The total sample size for Cohorts A and B is approximately 860.

14.2 Independent Data Monitoring Committee

An IDMC will oversee the ongoing monitoring and interpretation of the safety and efficacy data from this study. An IDMC charter will be created, reviewed, and approved by the committee prior to study initiation.

The IDMC will evaluate aggregate safety data for the relevant treatment arms, and also evaluate efficacy for the specified analyses. Frequency of IDMC meetings may be adjusted in accordance with the consensus of the IDMC and reflected in the IDMC Charter.

- For Cohort A, the first IDMC meeting will take place after the first 12 patients have completed at least 1 cycle of study treatment, or at 6 months from first enrollment, whichever comes first. Reviews will continue in 6-month intervals (± 1 month).

- In Cohort B, the first evaluation will take place after 20 patients in each arm have been enrolled and completed at least 1 cycle of treatment, or approximately 6 months from first enrollment, whichever comes first. The IDMC may meet at any time if evolving safety data warrant a safety review. Reviews will continue in 6-month intervals (± 1 month).

- Once the first assessment in Cohort B is completed, to the extent possible, safety and efficacy data from Cohort A and Cohort B will be reviewed at the same meeting.

The IDMC will also review safety and efficacy data for each of the cohorts. When approximately 40 patients (Cohort A) or 200 patients (Cohort B Part 1) have at least one CT scan to evaluate response or discontinued study treatment prior to first tumor assessment, the IDMC will be asked to make a recommendation regarding continuation of full enrollment for the cohort or suspending enrollment pending Sponsor final decision.

The committee will be provided with safety and efficacy tables and data listings for these reviews. Additional details on the IDMC monitoring, and administration may be found in the IDMC Charter.

14.3 Analysis Populations

The study analyses will be performed on the following populations:

- Safety Population: All patients who receive 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, respectively. Patients enrolled in Cohort B will be analyzed according to the actual treatment received rather than the treatment group they were assigned. This population will also be used to summarize baseline data for Cohort A.

- PK Evaluable Population: All patients who received at least one dose of study drug, date and time of dose administration and relative PK sample collection are known and have sufficient concentration data to derive at least one PK parameter.

- ADA Evaluable Population: All patients who received at least one dose of study treatment, date and time of dose administration and relative PK sample collection are known and have sufficient concentration data to derive at least one PK parameter.

- ITT Population: All patients who are assigned to treatment in Cohort A and all patients who are randomized into Cohort B of the study. Patients will be analyzed according to the treatment assigned. This population will be used to summarize baseline data and evaluate PFS.

- Response Evaluable Population (REP): All patients who received at least one dose of study treatment and had baseline radiographic tumor assessment. This population will be used for objective response related efficacy analyses for Cohort A and Cohort B, respectively, and will be analyzed according to the actual treatment received.

14.4 Demographics and Baseline Characteristics

Patient disposition, demographics, baseline characteristics, disease history, medical history, and prior cancer treatment will be summarized using descriptive statistics.

14.5 Study Drug Exposures and Concomitant Medications

Study drug exposures and concomitant medications will be summarized by descriptive statistics. The summary of study drug exposure will include descriptive statistics as well as frequency counts for the number of doses or cycles received, the total dose administrated as well as the total dose intended, and the dose intensity which is calculated as percentage of total dose administered divided by total dose intended during whole treatment period.

14.6 PK/PD and Immunogenicity Analysis

14.6.1 Pharmacokinetics Analysis

Serum samples from patients with positive ADA results will be analyzed for concentrations of relevant study treatments. Concentration data will be summarized accordingly to evaluate the relationship between study drug exposure and ADA positivity.

14.6.2 Immunogenicity Analysis

The proportion of patients who are negative for study drug-specific ADA (i.e., margetuximab, INCMGA00012, or MGD013) at baseline and have a study drug-specific ADA-positive after administration of study treatment(s), the proportion of patients who are negative at baseline and remain negative, and the proportion of patients who have a positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized.

14.6.3 Pharmacodynamic Analysis

Summary statistics for pharmacodynamic parameters, such as, but not limited to, those listed under in **Section 10.2** and corresponding changes from baseline, will be summarized and/or may also be presented graphically as will possible associations between changes in pharmacodynamic measures of interest and study drug and exposure may be explored.

14.7 Efficacy and Endpoint Analyses

14.7.1 Primary Efficacy Endpoints and Analyses for Cohort A

The primary efficacy endpoint for Cohort A is ORR per RECIST v1.1, defined as the proportion of non-MSI-H patients in the response evaluable population who achieve the BOR of CR or PR (called responders) per RECIST v1.1. The 2-sided 95% exact binomial CI of ORR will be calculated.

For RECIST v1.1, the BOR will be categorized as CR, PR, stable disease (SD), PD, or NE. To be qualified as an objective response, CR and PR require confirmation at least 4 weeks after initial observation of such response, and SD requires an observation at least once after 6 weeks. BOR will be evaluated from the start of study treatment.

The analysis of ORR will be based on investigator review determined response data.

14.7.2 Secondary Efficacy Endpoints and Analyses for Cohort A

The secondary efficacy endpoints for non-MSI-H patients in Cohort A are:

- PFS, defined as the time from start of study treatment to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. For patients who are not known to be dead or progressed at time of data cut-off for PFS analysis, the PFS will be censored at the last tumor assessment. Specifically, the following censoring rules will be applied as the analysis of PFS (**Table 12**).

Table 12 Censoring Rules for PFS Analysis

Situation	Date	Outcome
No baseline tumor assessments	First dose date	Censored
Death prior to first scheduled tumor assessment	Date of death	Progressed
No post-baseline tumor assessments in absence of death prior to first scheduled tumor assessment	First dose date	Censored
Documented progression	Date of progression	Progressed
Initiation of alternative anticancer treatments in absence of documented progression	Date of last tumor assessment prior to initiation of such treatment	Censored
Death or documented progression immediately after missing two or more consecutive scheduled tumor assessments	Date of last tumor assessment prior to missed assessments	Censored

- DoR, defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first. The DoR is calculated only for the responders. For responders who are not known to be dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. Specifically, the last 3 situations described in **Table 12** will be applied. The DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

- DCR, defined as the percentage of response evaluable patients who experienced response of CR, PR, or SD for at least 3 months.

The 2-sided 95% exact binomial CI of DCR will be calculated. The Kaplan-Meier method will be applied to estimate PFS, DoR, curves; their median times; PFS rates at 6, 9, and 12

months. The method of Brookmeyer and Crowley (9) will be used to construct 95% CIs for median time of each time-to-event endpoint. The 95% CIs for PFS rates at each time point of interest will be calculated by normal approximation after log(-log) transformation. The analyses of PFS and DoR will be performed using investigator assessed response data.

Note that all primary and secondary efficacy endpoints will be analyzed only for non-MSI-H patients.

14.7.3 Efficacy Endpoints and Analyses for Cohort B Part 1

The efficacy endpoints include ORR and DCR, defined in the same way as for Cohort A, based on investigator assessments. The BOR, ORR, and DCR will be summarized in the REP.

14.7.4 Analysis of Tumor Size Change Over Time

The tumor size is defined as the sum of diameters of the target lesions. The tumor size change from baseline over time will be summarized and may be presented by spider plot. The best tumor size change from baseline will be presented by waterfall plot.

14.8 Safety Endpoints and Analyses

14.8.1 Adverse Events

Only TEAEs will be summarized. The following TEAEs will be provided in summary tables as well as displayed in listings:

- All TEAEs
- TEAEs by CTCAE ≥ Grade 3
- TRAEs
- TRAEs by CTCAE ≥ Grade 3
- TEAEs related to each individual study drug
- Any SAEs
- Treatment-related SAEs
- SAEs related to each individual study drug
- TEAEs that result in study treatment discontinuation
- TRAEs that result in study treatment discontinuation
- TEAEs which lead to interruption of each individual study drug

- TEAEs that lead to withdrawal of each individual study drug
- Fatal AEs
- AESIs

All of these tables will display the number and percent of patients that experience the given event and will display events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Events will be displayed alphabetically for SOC and PT. An overall summary of AEs will display the number and percent of patient/patients who experience at least one event of each of the above types.

14.8.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by lab panel (hematology, blood chemistry, and urinalysis) and will be displayed by visit for each lab parameter. Shift tables may be produced.

14.8.3 Other Safety Endpoints

ECGs and LVEF will be collected and analyzed for evidence of cardiac toxicity. Vital signs will be summarized with descriptive statistics at each visit and time point where they are collected. Shift tables may be performed.

14.9 Interim Analysis

Cohort A

There is a planned interim analysis after 40 patients in the REP have been enrolled and their responses have been assessed by independent review. As described in **Section 14.1**, if at least 21 (53%) responders (CR or PR) per independent review are observed, then enrollment will continue. The Investigator assessed response, PFS based on both independent review and Investigator assessment, and safety data will also be summarized to assist in decision making.

14.10 Final Analysis

The final analysis will occur after all patients have completed treatment and the 30-day follow-up.

14.11 Other Assessments or Analyses

No other analyses are planned.

15 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. MacroGenics and/or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session (Investigator Meeting or Study Initiation Visit) to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site to monitor protocol compliance and general Good Clinical Practice (GCP) compliance.
- Be available for consultation and stay in contact with the study site personnel by mail, e-mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

15.1 Monitoring, Auditing and Inspections

To ensure the safety of patients in the study, compliance with applicable regulations, and ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as source documents for the study.

MacroGenics or its designee will monitor the study on a regular basis throughout the study period according to the study Monitoring Plan. The Investigator will allocate adequate time for such monitoring activities. The study monitor periodically will conduct a cross-check of the patient data recorded on eCRFs against source documents at the study site. The Investigator will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media) and study-related facilities (e.g., investigational pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The Investigator and study site personnel must address all queries in a timely manner.

Participation as an Investigator in this study implies acceptance of the potential for inspection by the study Sponsor/Representatives, US or non-US government regulatory authorities, IRB/IEC and applicable compliance and quality assurance offices. The Investigator will permit study-related audits and inspections and will provide access to all study-related documents (e.g., source documents, regulatory documents, data collection instruments,

study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

15.2 Data Collection and Management

The Investigator is responsible for maintaining accurate, complete, and up-to-date records for each patient. The Investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, or other media containing data pertaining to this protocol.

The anonymity of participating patients must be maintained. For data collection, and management purposes, patients are to be identified by a patient number only. Documents that identify the patient beyond patient number (e.g., patient initials) will not be submitted to the Sponsor (e.g., the signed informed consent document) and must be maintained in strict confidence by the Investigator, except to the extent to allow auditing by the regulatory authorities, study monitor, or Sponsor representatives.

Site personnel record all data for each patient through eCRFs using the Medidata RAVE™, an Electronic Data Capture (EDC) system provided and approved by the Sponsor. Refer to the Study Procedures Manual for additional information regarding eCRFs, if any that will be used as source documentation. Study sites must complete eCRFs for each patient in a timely manner shortly after each patient visit. As the person ultimately responsible for the accuracy of all eCRF data, the Investigator must sign the Investigator's Statement in each patients eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system to ensure data accuracy, quality, consistency, and completeness. Manual queries resulting from review by monitors, medical coders, and Data Management staff are also generated from within the EDC system, where they are tracked. Study sites resolve the queries and correct the entered data accordingly. Every change to data is captured in the EDC system audit trail. AEs are coded using MedDRA, whereas concomitant medications are coded using the WHO Drug Dictionary. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for analysis and reporting. Upon completion of the study, each study site will be provided with the eCRFs for each of their patients.

16 ADMINISTRATIVE CONSIDERATIONS

16.1 Institutional Review Board or Independent Ethics Committee Approval

The Investigator should provide the Sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and ICH. Any documents that the IRB/IEC may need to fulfill its responsibilities, such as the protocol and any amendments, Investigator's Brochures, and information concerning patient recruitment, payment or compensation procedures, or information from the Sponsor, will be submitted to the IRB/IEC. The IRB/IEC's written approval of the study protocol and the ICFs will be in the possession of the Investigator and the Sponsor before the study drug is initiated at the Investigator's site. The Investigator will transmit the IRB/IEC's approval statement to the Sponsor. This approval must include the date of review and refer to the study by protocol title and/or study number and version number and refer to the ICFs by version number or date. If the IRB/IEC or institution uses its own unique number for the protocol instead of the Sponsor's number, that unique number should be noted on the approval statement. If approval of the ICFs is stamped on the forms (instead of documented in the IRB/IEC approval statement) the date of approval and/or expiration must be included.

Protocol modifications or changes may not be initiated without approval from the Sponsor and prior written IRB/IEC approval (when required), except when necessary to eliminate immediate hazards to the patients. Such modifications will be submitted to the IRB/IEC; and written verification that the modification was submitted should be obtained.

The Investigator must, where required by local regulations, submit to the IRB/IEC the following:

- The protocol and the Investigator's Brochures and any amendments or updates.
- The ICF(s) and any amendments or changes.
- Any documents given to patients or potential patients (e.g., recruitment materials, diary cards) and the plan for distribution/use.
- Revisions of other documents originally submitted for review or for notification.
- Serious and/or unexpected AEs occurring during the study.
- New information that may adversely affect the safety of patients or conduct of the study.
- At minimum, an annual update and/or request for re-approval of study, unless otherwise specified by IRB/IEC.
- Protocol deviations.

- Notification when the study has been completed.
- Proof of indemnity/liability insurance.
- Other documents required by the IRB/IEC.

16.2 Ethical Conduct of the Study

The investigational study will be conducted according to the Protection of Human Patients (21 CFR [Code of Federal Regulations] 50), Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312.60 – 312.69), and/or the current ICH Guideline for Good Clinical Practice (ICH E6) and all other applicable regulations.

16.3 Patient Information and Consent

It is the responsibility of the Investigator to obtain and document written informed consent from the patient. Informed consent in compliance with the principles of informed consent in ICH E6 and all applicable local regulations should be obtained before any protocol-specified procedures or interventions are conducted. The Sponsor reserves the right to delay initiation of the study at a site where ICFs do not meet the standards of applicable local regulations or ICH E6.

Information should be given to the patient in both oral and written form, and patients must be given ample opportunity to inquire about details of the study.

The consent form generated by the Investigator must be approved by the IRB/IEC. The Investigator will provide the Sponsor with a copy of the IRB/IEC-approved consent forms and a copy of the IRB/IEC's written approval before the start of the study.

Consent forms must be written (and appropriately translated in the patient's native language or language in which the patient has fluency) so as to be understood by the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC. The form must be signed and dated by the patient, and by the person who conducted the discussion of the informed consent.

All versions of each patient's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and/or authorized MacroGenics monitoring and regulatory compliance persons. The patient should receive a copy of the signed and dated written ICF and any other written information provided to the patients.

16.4 Patient Confidentiality

To maintain confidentiality of patients, all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number. Clinical information will not be released without written permission of the patient, or an individual with legal decision-making

authority for the patient or the patient's interests, except as necessary for monitoring by the relevant regulatory authorities, the Sponsor of the clinical study, or the Sponsor's representative. The Investigator must also comply with all local applicable privacy regulations [e.g., US Health Insurance Portability and Accountability Act of 1996 (HIPAA) or the General Data Protection Regulation (GDPR)], on protection of individuals with regard to personal data.

16.5 Case Report Forms and Study Records

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the patient's medical file, original laboratory reports, histology, and pathology reports (as applicable). The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered into the eCRFs designed to capture data pertinent to the clinical investigation. Data should be recorded on paper source documents or electronic in an electronic medical records system. Electronic CRFs should be completely in their entirety by the Investigator or his/her designee. Prior to eCRF database lock, the Investigator will verify the completeness and accuracy of the data and indicate that he/she has done so by providing an electronic signature on the appropriate eCRF. The Investigator will retain a copy of all source documents.

16.6 Access to Source Documentation

The Investigator and study center will permit the Sponsor, its representatives, IRB/IEC, and all relevant regulatory agencies access to all original source data and documents regardless of media, for study monitoring audits and inspections.

16.7 Retention of Data

Per ICH guidelines, all essential documents, including eCRFs, source documents (regardless of media), signed ICFs, and laboratory test results, should be retained by the Investigator for at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. There may be other circumstances for which MacroGenics is required to maintain study records for longer periods; therefore, MacroGenics should be contacted before study records are removed from the control of the study site for any reason. The Investigator must obtain written permission from MacroGenics prior to destruction of study documents.

16.8 Sample Retention

Samples acquired for protocol-specified assays are retained according to local and regional regulatory requirements. If the patient consents, to the use of their study samples for secondary research purposes, samples may be used for exploratory testing and retained up to

15 years from the end of study. Please refer to the Laboratory Manual for the address and contact information for sample retention laboratories, including long-term storage.

16.9 Financial Disclosure

The Investigator and Sub-Investigators will be required to disclose any applicable financial arrangement as defined in US regulation (i.e., 21 CFR 54).

The following information will be collected about the Investigators, their spouse and each dependent child: any significant payments of other sorts from MacroGenics, Inc., or any alliance partner, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in the study drug; and any significant equity interest in MacroGenics, Inc., as defined in 21 CFR 54. Investigators are obliged to update the Sponsor with any changes in reported information up to 1 year following the end of the study.

In addition, Investigators and Sub-Investigators will be required to disclose if they are an employee of MacroGenics, or an immediate family member of a MacroGenics employee, officer, or director. This is to assist MacroGenics with its compliance with Securities and Exchange Commission rules requiring disclosure of certain transactions with related persons as defined in 17 CFR 229.404. “Immediate family member of a MacroGenics employee” means a child, stepchild, parent, stepparent, spouse, sibling, mother-in-law, father-in-law, son-in-law, brother-in-law, or sister-in-law of any MacroGenics employee, officer, or director or any person sharing the household of such MacroGenics employee, officer, or director.

In consideration of participation in the study, MacroGenics, will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

Financial disclosure information will be documented in writing and signed and dated by the Investigator. This information will be collected prior to that Investigator taking part in the research.

16.10 Publication and Disclosure Policy

Data collected in this clinical study belong to the study Sponsor. The publication terms regarding use of the study data will be noted in the Clinical Trial Agreement. This includes authorship: scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

16.11 Discontinuation of the Study or Study Sites

16.11.1 Discontinuation of the Study

The study may be discontinued by a regulatory authority or at the discretion of the Sponsor.

The Investigator maintains the right to discontinue his/her participation in the study should his/her clinical judgment so dictate. The Investigator will notify the IRB/IEC of any study discontinuation. Study records must be retained as noted above.

16.11.2 Discontinuation of Study Sites

Site participation may be discontinued if MacroGenics, the Investigator, a regulatory authority, or the IRB/IEC of the study sites deems it necessary for any reason.

17 REFERENCE LIST

Note: *Newly added literature references are in colored text. Previously cited submitted literature references are in black text.*

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Appendix 1 Time and Events Schedules

Time and Events Schedule, Cohort A

EVALUATION/ PROCEDURE	Screening D (-28 to -1)	Cycle 1	Subsequent Cycles	EOTV	Follow-Up
		D1	D1 (± 3d) [a]		
INCMGA00012		X	X		
Margetuximab		X	X		
Informed Consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical/Cancer History	X				
Blood sample for MSI status	X				
FFPE Tissue [b]	X				
Eligibility Review	X				
Registration	X				
Physical Exam	X	X	X	X	
ECG (12-lead)	X				
MUGA/ Echocardiogram [c]	X		X	X	
Vital Signs [d]	X	X			
Clinical Laboratory Tests [e]	X	X	X	X	
TSH and free T4 [e]	X	X	X		
PT or INR [f]	X	X			
Urinalysis [f]	X	X			
Pregnancy Test [g]	X	X	X	X	
Tumor Assessment [h]	X		X		
Adverse Events	Continuous				

a. A cycle is 21 days ± 3 days is from the previous dosing day. There should be at least 18 days between administrations.

b. FFPE tissue from the original diagnosis is required. If the patient has received perioperative anti-HER2 therapy, FFPE from a subsequent biopsy is required to confirm HER2 status.

c. Echocardiogram or MUGA scan is obtained every 12 weeks (± 7 days) from Cycle 1 Day 1, and as clinically indicated.

d. Vital signs are according to the local standard of care.

e. See **Appendix 2** for a list of required laboratory assessments. Laboratory assessments may be drawn up to 3 days in advance of Day 1 of subsequent cycles.

f. TSH and free T4 are required at Screening, C1D1, every odd cycle, and as clinically indicated. Tests performed at screening and Cycle 1 Day 1, then as clinically indicated.

g. Serum or urine pregnancy test for WOCBP. Serum pregnancy test is required at screening.

h. Tumor assessments are performed every 3 cycles (± 7 days) for the first 9 months, beginning at Cycle 13 every 4 cycles (± 7 days) for disease progression are performed until treatment discontinuation. Only RECIST 1.1 overall response will be recorded in the eCRF.

Time and Events Schedule, Cohort B, Control Arm

EVALUATION/ PROCEDURE	Screening D (-28 to -1)	Cycle 1	Subsequent cycles	EOTV	Follow-Up
		D1	D1 (± 3d) [a]		
Investigator's choice chemotherapy [b]		X	X		
Trastuzumab		X	X		
Informed Consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical/Cancer History	X				
Blood sample for MSI status	X				
FFPE Tissue [c]	X				
Registration	X				
Physical Exam	X	X	X	X	
ECG (12-lead)	X				
MUGA/ Echocardiogram [d]	X		X	X	
Vital Signs [e]	X	X			
Clinical Laboratory Tests [f]	X	X	X	X	
TSH and free T4 [f]	X				
Urinalysis [g]	X	X			
Pregnancy Test [h]	X	X	X	X	
Tumor Assessment [i]	X		X		
Adverse Events	Continuous				

a. A cycle is 21 days ± 3 days from the previous dosing day and based on margetuximab dosing. There should be at least 18 days between administrations.

b. Investigator's choice of chemotherapy: XELOX or mFOLFOX-6. See **Table 9** for study treatments, and **Section 4.2** for duration of individual treatments.

c. FFPE tissue from the original diagnosis is required. If the patient has received prior perioperative anti-HER2 therapy, FFPE from a subsequent biopsy is required to confirm HER2 status.

d. Echocardiogram or MUGA scan is obtained every 12 weeks (± 7 days) from Cycle 1 Day 1, or as clinically indicated.

e. Vital signs are obtained according to the local standard of care.

f. See **Appendix 2** for a list of required laboratory assessments. Laboratory assessments may be drawn up to 3 days in advance of Day 1 of subsequent cycles. PT or INR collection is required while receiving capecitabine or 5-FU. Post-screening TSH and free T4 are not required for patients in the Control Arm.

g. Tests performed at screening and Cycle 1 Day 1, then as clinically indicated.

h. Serum or urine pregnancy test for WOCBP. Serum pregnancy test is required at screening.

i. Tumor assessments are performed every 3 cycles (± 7 days) for the first 9 months, beginning at Cycle 13 every 4 cycles (± 7 days) for disease progression are performed until treatment discontinuation. Only RECIST 1.1 overall response will be recorded in the eCRF.

Time and Events Schedule, Cohort B, Experimental Arms 1 and 2

EVALUATION/ PROCEDURE	Screening D (-28 to -1)	Cycle 1	Subsequent Cycles	EOTV	Follow Up
		D1	D1 (± 3d) [a]		
INCMGA00012 or MGD013		X	X		
Margetuximab		X	X		
Investigator's choice chemotherapy [b]		X	X		
Informed Consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical/Cancer History	X				
Blood sample for MSI status	X				
FFPE Tissue [c]	X				
Registration	X				
Physical Exam	X	X	X	X	
ECG (12-lead)	X				
MUGA/ Echocardiogram [d]	X		X	X	
Vital Signs [e]	X	X			
Clinical Laboratory Tests [f]	X	X	X	X	
TSH and free T4 [f]	X	X	X		
Urinalysis [g]	X	X			
Pregnancy Test [h]	X	X	X	X	
Tumor Assessment [i]	X		X		
Adverse Events	Continuous				

a. A Cycle is 21 days ± 3 days from the previous dosing day, and based on margetuximab dosing. There should be at least 18 days between administrations.

b. Investigator's choice of chemotherapy: XELOX or mFOLFOX-6. See **Table 9** for study treatments, and **Section 4.2** for duration of individual treatments

c. FFPE tissue from the original diagnosis is required. If the patient has received prior perioperative anti-HER2 therapy, FFPE from a subsequent biopsy is required to confirm HER2 status.

d. Echocardiogram or MUGA scan is obtained every 12 weeks (± 7 days) from Cycle 1 Day1, or as clinically indicated.

e. Vital signs are obtained according to the local standard of care.

f. See **Appendix 2** for a list of required laboratory assessments. Laboratory assessments may be drawn up to 3 days in advance of Day 1 of subsequent cycles. PT or INR collection is required while receiving capecitabine or 5-FU. TSH and free T4 are required at Screening, C1D1, every odd cycle, and as clinically indicated.

g. Tests performed at screening and Cycle 1 Day 1, then as clinically indicated.

h. Serum or urine pregnancy test for WOCBP. Serum pregnancy test is required at screening.

i. Tumor assessments are performed every 3 cycles (± 7 days) for the first 9 months, beginning at Cycle 13 every 4 cycles (± 7 days) for disease progression are performed until treatment discontinuation. Only RECIST 1.1 overall response will be recorded in the eCRF.

Time and Events Schedule, Cohort B, Part 1 Experimental Arm 3

EVALUATION/ PROCEDURE	Screening D (-28 to -1)	Cycle 1	Subsequent Cycles	EOTV	Follow Up
		D1	D1 (± 3d) [a]		
Investigator's Choice Chemotherapy [b]		X	X		
Margetuximab		X	X		
Informed Consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical/Cancer History	X				
Blood sample for MSI status	X				
FFPE Tissue [c]	X				
Registration	X				
Physical Exam	X	X	X	X	
ECG (12-lead)	X				
MUGA/ Echocardiogram [d]	X		X	X	
Vital Signs [e]	X	X			
Clinical Laboratory Tests [f]	X	X	X	X	
TSH and free T4 [f]	X				
Urinalysis [g]	X	X			
Pregnancy Test [h]	X	X	X	X	
Tumor Assessment [i]	X		X		
Adverse Events	Continuous				

a. A cycle is 21 days ± 3 days is from the previous dosing day and based on margetuximab dosing. There should be at least 18 days between administrations.

b. Investigator's choice of chemotherapy: XELOX or mFOLFOX-6. See **Table 9** for study treatments, and **Section 4.2** for duration of individual treatments.

c. FFPE tissue from the original diagnosis is required. If the patient has received prior perioperative anti-HER2 therapy, FFPE from a subsequent biopsy is required to confirm HER2 status.

d. Echocardiogram or MUGA scan is obtained every 12 weeks (± 7 days) from Cycle 1 Day 1, or as clinically indicated.

e. Vital signs are obtained according to the local standard of care.

f. See **Appendix 2** for a list of required laboratory assessments. Laboratory assessments may be drawn up to 3 days in advance of Day 1 of subsequent cycles. PT or INR collection is required while receiving capecitabine or 5-FU. Post-screening TSH and free T4 are not required for patients receiving Arm 3.

g. Tests performed at screening and Cycle 1 Day 1, then as clinically indicated.

h. Serum or urine pregnancy test for WOCBP. Serum pregnancy test is required at screening.

i. Tumor assessments are performed every 3 cycles (± 7 days) for the first 9 months, beginning at Cycle 13 every 4 cycles (± 7 days) for disease progression are performed until treatment discontinuation. Only RECIST 1.1 overall response will be recorded in the eCRF.

Appendix 2 Clinical Laboratory Tests

Pregnancy test: Blood or Urine Human chorionic gonadotropin (hCG). A repeat central pregnancy test is required for any positive local urine pregnancy test. **Hematology:** Hemoglobin Hematocrit Platelet count White blood cell count with absolute differential neutrophils, lymphocytes, and eosinophils* **Serum chemistry:** Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Total Bilirubin Reflex to Direct Bilirubin, if elevated Blood urea nitrogen Chloride Creatinine Glucose Potassium Sodium	**Coagulation*:** Prothrombin time (PT), or INR **Urinalysis:** Glucose Ketones Protein Occult blood **Endocrine** (after screening, for MGD013 or INCMGA00012 arms only) TSH Free T4

*according to local lab. PT or INR collection is required while receiving capecitabine or 5-FU in Cohort B.

Appendix 3 RECIST 1.1 Guidelines

Adapted from Eisenhauer 2009 (**14**).

All patients with be required to have at least 1 measurable lesion to be considered as having measurable disease at baseline for the determination of eligibility for this study. Measurable lesions are defined below.

1 Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion prior to study enrollment.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesions(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is

suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers *alone* cannot be used to assess *objective* tumor response.

2 Tumor Response Evaluation

2.1 Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

2.2 Baseline documentation of ‘target’ and ‘non-target’ lesions

Where more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. For example, in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in

which circumstance the next largest lesions which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters.* If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an

absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. However, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesions. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions(s).

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

2.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When a patient also has measurable disease. In this setting, to achieve 'unequivocal progression; on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. The same general concepts apply here as noted above, *however*, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 Evaluation of best overall response

The BOR is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table A-1** on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

2.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

The *BOR* is determined once all the data for the patient is known.

Table A-1 Time point response: patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR

Target lesions	Non-target lesions	New lesions	Overall response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Best response determination in trials where confirmation of complete or PR is required:
Complete or partial responses may be claimed only if the objective response is confirmed on a follow-up scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. In this circumstance, the BOR can be interpreted as in **Table A-2**.

Table A-2 Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a [a] If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Table A-1** and **Table A-2**.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5 Confirmation/Duration of response

2.5.1 Confirmation

Objective responses should be confirmed by CT and/or MRI scans obtained no less than 4 weeks after the original scan.

2.5.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.5.3 Duration of stable disease

Stable disease (SD) is measured from the start of the treatment until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

Appendix 4 Gastric Adenocarcinoma Sub-types

Patients with the following gastric cancer sub-types are eligible for enrollment into the study**.**

World Health Organization (2010)	Lauren Classification (1965)
Papillary adenocarcinoma	Intestinal type
Tubular adenocarcinoma	
Mucinous adenocarcinoma	
Signet-ring cell carcinoma, and other poorly cohesive carcinoma	Diffuse type
Mixed carcinoma	Indeterminate type

Appendix 5 Principal Investigator's Agreement

Study Title: A Phase 2/3 Trial to Evaluate Margetuximab in Combination with INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients with Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer

Study Number: CP-MGAH22-06

I have read the protocol described above.

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution of the ethical review of the study, without written authorization from MacroGenics, Inc. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Signed: _____

Date: _____

Name (printed): _____

Title: _____

Affiliation: _____

Address: _____

Phone Number: _____

CP-MGAH22-06 Protocol Amendment 5 (06-June-2022)
This is the electronic signature page for the above referenced document.

User Task: eSignatories Approval	Data Management/Statistics Approval (Intended or Designee) 14-Jun-2022 15:16:50 GMT+0000

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