CLINICAL TRIAL PROTOCOL: CP-MGAH22-05
PROTOCOL AMENDMENT 6

Study Title:	A Phase 1b/2, Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesophageal Junction or Gastric Cancer
Study Number:	CP-MGAH22-05
Study Phase:	Phase 1b/2
Product Name:	Margetuximab in combination with pembrolizumab (KEYTRUDA®)
Product Number:	MGAH22
IND Number:	
Indication:	Relapsed/refractory advanced, metastatic HER2+ gastroesophageal junction (GEJ) or gastric cancer (GC)
Coordinating Principal Investigator:	
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 USA
Sponsor's Medical Monitor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 USA

Confidentiality Statement

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Study Number: CP-MGAH22-05

This clinical study protocol has been approved by the Sponsor:

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

Vice President, Clinical Development

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
Anti-CTLA-4	Cytotoxic T lymphocyte associated protein 4 antibody
Anti-PD-1	Programmed cell death protein 1 antibody
Anti-PD-L1	Programmed death ligand 1antibody
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BUN	Blood urea nitrogen
°C	Degrees Celsius
Ca	Calcium
CBC	Complete blood count
CDR	Complimentary-determining region
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl	Chloride
CL	Plasma clearance
CNS	Central nervous system
cCR	Confirmed complete response
CR	Complete response

CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating Tumor DNA
CTLA-4	Cytotoxic T lymphocyte antigen 4
DBP	Diastolic blood pressure
dL	Deciliter
DLT	Dose-limiting toxicity
DRAE	Drug-related adverse event
ECG	Electrocardiogram
EAP	Expanded access program
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
EU	European Union
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
GC	Gastric cancer
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction cancer
GLP	Good Laboratory Practice
HC	Heavy chain
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HEENT	Head, eyes, ears, throat, neck
Hgb	Hemoglobin

HIPAA	Health Insurance Portability and Accountability Act
HPV	Human papilloma virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
irAE	Immune-related adverse event
irCR	Immune-related complete response
irPD	Immune-related progressive disease
irPR	Immune-related partial response
irRC	Immune-related response criteria
IRB	Institutional Review Board
IRE	Immediately Reportable Event
ISH	In-situ hybridization
IUD	Intrauterine device
IV	Intravenous
K	Potassium
Kg	Kilogram
LC	Light chain
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAD	Maximum administered dose
mcg or µg	Microgram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

Mg	Milligram
MHC	Major histocompatibility class
mL	Milliliter
Mm	Millimeter
Msec	Millisecond
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
Na	Sodium
NCI	National Cancer Institute
NK	Natural Killer
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall Survival
Pap	Papanicolaou
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamics, or Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Orally
PR	Partial response
PT	Prothrombin time
Q	Inter-compartment clearance
Q3W	Every 3 weeks
QW	Every week

RANK-L	Receptor-activator of nuclear factor kappa B ligand
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SCCHN	Squamous cell cancer of the head and neck
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
$T_{1/2\alpha}$	Distribution half-life
$T_{1/2\beta}$	Terminal half-life
T4	Thyroxine
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
Tregs	Regulatory T-cells
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
V_c	Central volume
V_1	Volume of distribution of the central compartment
V_p	Peripheral volume
V_{SS}	Volume of distribution at steady state
WBC	White blood cell

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:**
Name of Finished Product: Margetuximab (MGAH22)	
Study Title: A Phase 1b/2, Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesophageal Junction or Gastric Cancer.	
Study Number: CP-MGAH22-05	
Investigator(s)/Centers: This study will be executed at approximately 29 institutions in North America and Asia experienced in cancer immunotherapy and/or the conduct of Phase 1 studies in patients with gastroesophageal junction (GEJ) or gastric cancer (GC).	
Study Phase: Phase 1b/2	
Primary Objectives: The primary objectives of this study are: • To characterize the safety, tolerability, dose-limiting toxicities (DLT), and maximum tolerated dose (MTD) or maximum administered dose (MAD) (if no MTD is defined) of margetuximab when administered intravenously (IV) every 3 weeks in combination with 200 mg pembrolizumab administered IV every 3 weeks to patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or gastric cancer (GC). • To investigate the preliminary anti-tumor activity, as measured by objective response rate (ORR) and response duration, of margetuximab when administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks using both conventional Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (**Appendix 7**) and immune-related response criteria (irRC) (**Appendix 8**), in patients that have failed first-line trastuzumab-containing regimens.	
Secondary Objectives: Secondary objective of this study are: • To investigate the preliminary effect on overall survival (OS) and progression-free survival (PFS) of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks. • To characterize the pharmacodynamic (PD) activity of margetuximab when administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks. • To characterize the pharmacokinetics (PK) and immunogenicity of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks.	

Study Design:

General Study Design

This study is a Phase 1b/2, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary antitumor activity of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks in patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or gastric cancer (GC).

The study consists of a **Dose Escalation Phase (Part A)** to determine the MTD or MAD (if no MTD is defined) of escalating doses of margetuximab administered in combination with a fixed dose of 200 mg pembrolizumab, followed by a **Cohort Expansion Phase (Parts B-C)** to further define safety and initial efficacy of the combination with the margetuximab dose established in the first phase. As of Amendment 2, up to approximately 25 additional patients with gastric cancer (GC) only will be added to the Cohort Expansion Phase (**Part C** - see "Study Population" below). Both margetuximab and pembrolizumab will be administered once every 3 weeks. Both agents will be administered on the same day, with pembrolizumab administered first, followed by margetuximab. Each cycle of therapy is defined as 3 weeks, in which margetuximab and pembrolizumab will be given on Day 1. Tumor assessments will be performed every 6 weeks (i.e., following 2 cycles of treatment [prior to dosing for Cycles 3, 5, 7, etc.]) for the first 6 months on treatment; thereafter, tumor assessments will be performed every 12 weeks until documented progression, initiation of alternative anti-cancer therapy, lost to follow-up, withdrawal of informed consent, death, or end of study.

Assuming patients remain clinically stable, have not experienced immune-related progressive disease (irPD), and do not experience unacceptable toxicity that necessitates permanent discontinuation of both study drugs, treatment with the combination may continue for up to 2 years. Following up to 2 years of combination treatment, therapy will be discontinued and patients will be followed in Efficacy Follow-up Period.

For patients who are otherwise clinically stable but have met conventional criteria for progressive disease (PD), therapy may be continued at the discretion of the investigator pending confirmation of progression at the next scheduled tumor assessment. This approach allows for limited treatment of patients beyond initial radiographic documentation of disease progression, assuming that patients are tolerating therapy adequately and remain otherwise clinically stable despite this initial radiographic evidence of disease progression, and that the investigator feels the patient may still derive benefit from continuation of therapy.

For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for irPD will have been met, and treatment with margetuximab and pembrolizumab should be discontinued. The patient should be removed from study participation after completion of protocol-specified follow-up (see **Section 8.3** and **Appendix 1**, and **Appendix 2**).

Following the last dose of both study drugs, each patient will be followed for both PFS and OS during an **Efficacy Follow up Period**.

Dose Escalation Phase (Part A):

The goal of the Dose Escalation Phase (Part A) is to initially characterize the safety and tolerability of margetuximab and pembrolizumab administered in combination, and more specifically to describe the DLTs for each dose level studied and to define the MTD or MAD (if no MTD is defined) based on the frequency of the occurrence of dose-limiting toxicities (DLTs) in each cohort during the **DLT Evaluation Period**.

For the purposes of guiding decisions regarding dose escalation, the **DLT Evaluation Period** is defined as the time following administration of the first dose of pembrolizumab up to the day of the second planned administration of pembrolizumab (i.e., 21 days following first dose of pembrolizumab – the end of Cycle 1).

Margetuximab will be evaluated in two sequential escalating doses, 10 mg/kg and 15 mg/kg, in combination with 200 mg pembrolizumab in cohorts of 3 to 6 patients each. If it is determined that the MTD is exceeded in the first dose cohort, a dose de-escalation cohort to evaluate a lower dose of margetuximab (6 mg/kg) in combination with 200 mg pembrolizumab will be enrolled. The dose escalation schema is outlined below:

Cohort	Margetuximab Dose	Pembrolizumab Dose
Cohort -1 [a]	6 mg/kg	200 mg
Cohort 1 [b]	10 mg/kg	200 mg
Cohort 2	15 mg/kg	200 mg

a To be evaluated only if the starting dose is determined to exceed the MTD.
b Starting dose level

An intermediate dose of margetuximab may be explored during the dose escalation portion of the study, based on review of cumulative safety, efficacy, and/or PK data on respective arms and based upon agreement between investigators and Sponsor. The Regulatory Agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any additional dose level to be evaluated.

Cohort Expansion Phase (Part B):

The goals for this expansion portion of the study include the following:

1. Provide a preliminary assessment of the antitumor activity of margetuximab in combination with pembrolizumab in patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or gastric cancer (GC) post-trastuzumab
2. Further characterize the safety of margetuximab at the MTD (or MAD) in combination with pembrolizumab; and
3. Further evaluate the PK, PD, and immunogenicity of margetuximab in combination with pembrolizumab.

Cohort Expansion Phase - Gastric Cancer Only (Part C):

The goals for the expansion portion of the study include the following:

1. Provide a preliminary assessment of the antitumor activity of margetuximab in combination with pembrolizumab in patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ (3+ by immunohistochemistry [IHC3+]) GC only (as defined in AJCC Cancer Staging Manual, 8th Edition) post-trastuzumab
2. Further characterize the safety of margetuximab at the MTD (or MAD) in combination with pembrolizumab; and
3. Further evaluate the PK, PD, and immunogenicity of margetuximab in combination with pembrolizumab.

Efficacy Follow-up Period:

Following the final dose of study drug (pembrolizumab or margetuximab, whichever is last), each patient will be followed for both PFS and OS during an **Efficacy Follow up Period**. During this time, patients will undergo disease assessments and be followed at 12-week intervals for monitoring of PFS and overall survival.

Dose Limiting Toxicity:

For the purposes of safety management and defining DLTs (limited to Cycle 1 of the Dose Escalation Phase [Part A]), the combination of margetuximab and pembrolizumab will be treated as one entity during Cycle 1 of the **Dose Escalation Phase (Part A)** (i.e., the **DLT Evaluation Period**). If a DLT is considered related to one of the study drugs during this period, administration of both agents will be stopped. One exception to this rule will be in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab infusion and before the first margetuximab administration. In this case, the toxicity will be attributed to pembrolizumab alone and will not count as a DLT of the combination of study drugs and the patient will be replaced by another patient in the dose cohort.

In general, for patients who experience an adverse event (AE) that may meet the criteria for a DLT, subsequent administration of the study drugs should be held pending management and/or resolution of the event and assessment of attribution to the study drugs. Criteria for subsequent continuation of therapy are outlined below. No intra-patient dose reductions of either margetuximab or pembrolizumab are allowed during the study.

Definitions

Dose limiting toxicities will be based on treatment-emergent, drug-related AEs (or clinically significant laboratory abnormalities) occurring during the **DLT Evaluation Period** (defined as the time following administration of the first dose of pembrolizumab to the day of the second planned administration of pembrolizumab [i.e., 21 days following first dose of pembrolizumab – end of Cycle 1]). The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (NCI CTCAE v4.03).

Dose limiting toxicities are defined separately for hematologic and non-hematologic events as follows.

Hematologic Dose Limiting Toxicity

Hematologic DLT will be defined as follows:

- Grade 4 neutropenia lasting > 5 days
- ≥ Grade 3 febrile neutropenia lasting > 48 hours or any ≥ Grade 3 febrile neutropenia associated with hemodynamic compromise or objective evidence of infection
- Grade 4 thrombocytopenia, irrespective of duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- ≥ Grade 3 hemolysis

The following events will be specifically excluded from the definition of hematologic DLT:

- ≥ Grade 3 lymphopenia
- Grade 3 anemia that is not associated with other clinically significant complications

Non-Hematologic Dose Limiting Toxicity

Non-hepatic non-hematologic DLT will be defined as any ≥ Grade 3 non-hematologic event with the following **exceptions**:

- Grade 3 electrolyte abnormality that lasts less than 72 hours, is not otherwise associated with clinical complications, and responds to medical intervention

- Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
- Grade 3 nausea or vomiting that lasts < 72 hours and responds to medical intervention
- Grade 3 or 4 amylase and/or lipase elevation that is not associated with either clinical or radiographic evidence suggestive of pancreatitis
- Grade 3 diarrhea that lasts < 48 hours and responds to medical intervention
- Grade 3 gastrointestinal AEs of constipation, abdominal pain, cramping, dyspepsia or dysphagia that resolves to ≤ Grade 1 within 14 days with medical therapy
- Grade 3 fatigue that lasts < 7 days
- Grade 3 infusion-related reaction or cytokine release syndrome that lasts < 12 hours and responds to medical intervention.
- Grade 3 or 4 endocrinopathy that is adequately controlled with hormone supplementation
- Grade 3 skin toxicity that resolves to ≤ Grade 2 within 14 days of initiation of oral corticosteroids
- Grade 3 inflammatory reaction (e.g., with associated pain, swelling) attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.) that resolves to ≤ Grade 2 within 7 days with medical intervention.

Note: The following Grade 2 or greater non-hematologic AE may also be considered as DLT:

- Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of study drug(s) due to patient intolerance.
- Any ≥ Grade 2 drug-related AE that results in > 7-day treatment delay would be considered a DLT.
- Any hepatic laboratory abnormalities meeting all three Hy's law criteria (described within hepatic non-hematologic DLTs).
- Any Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 within 14 days of the initiation of topical therapy, or that requires systemic treatment.

Hepatic Non-Hematologic Dose Limiting Toxicity

- Any elevation of one or more transaminases > 8 × the institutional upper limit of normal (ULN) irrespective of duration
- Any Grade 3 elevation of one or more transaminases > 5.0 – 8.0 × ULN that does not resolve to Grade 2 (i.e., > 2.5 – 5.0 × ULN) within 7 days and Grade 1 (i.e., > ULN – 2.5 × ULN) within 14 days. In addition, steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day, by Day 14. Please see **Section 6.5.2.2** for further management guidelines.
- A Grade 3 elevation of total bilirubin that is > 5 × ULN, irrespective of duration.
- Any Grade 3 elevation of total bilirubin > 3.0-5.0 × ULN that does not resolve to Grade 2 (i.e., > 1.5-3.0 × ULN) within 7 days and Grade 1 (i.e., > ULN-1.5 × ULN) within 14 days. In addition, steroids must be tapered to ≤ 10 mg of prednisone or equivalent per day, by Day 14. Please see **Section 6.5.2.2** for further management guidelines.
- Any event meeting the criteria for Hy's law as follows (all three features):
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × ULN.

- Concurrent elevation of total bilirubin > 2 × ULN without initial evidence of cholestasis (e.g., elevated serum alkaline phosphatase [ALK-P]).
- No alternative etiology can be identified.

Dose Escalation Rules

The **Dose Escalation Phase (Part A)** of this trial will proceed using a conventional 3 + 3 approach, and will begin with enrollment of 3 patients at a dose of 200 mg pembrolizumab administered as an IV infusion once every 3 weeks and an initial dose of 10 mg/kg margetuximab administered as an IV infusion once every 3 weeks. Successive dose escalation cohorts will be enrolled as outlined below. The MTD or MAD will be determined based on the assessment of DLTs during the DLT evaluation period. Patients who are not evaluable for safety for the full DLT evaluation period for reasons other than study drug-related toxicity will be replaced in the same dose-level cohort.

- If 0 of the first 3 patients treated at a given dose level experience a drug-related DLT during the DLT evaluation period, the dose will be escalated and 3 patients will be enrolled and treated at the next higher dose level.
- If 1 of the first 3 patients treated at a given margetuximab dose level experiences a drug-related DLT, then 3 additional patients will be enrolled at that dose level (thus making a total of 6 patients in this cohort) to further assess the safety of the combination.
- If ≥ 1 of these 3 additional patients enrolled in the cohort experience a DLT (that is, ≥2 out of 6), it will be concluded that the MTD has been exceeded, and 3 patients will be enrolled and treated at the next lower dose level. If 0 of the 3 additional patients experiences a DLT (that is only 1 of 6 patients has experienced a DLT), then the dose will be escalated, and 3 patients will be enrolled at the next higher dose level.
- If ≥ 2 patients out of the first 3 patients treated at a given dose level, or ≥ 2 of 6 patients treated at a given dose level, experience a drug-related DLT, then it will be concluded that the MTD for margetuximab in combination with pembrolizumab has been exceeded at that dose level, and all subsequent patients will be treated at the next lower dose level.
- Note that in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab infusion and before the first margetuximab administration, the toxicity will be attributed to pembrolizumab alone and will not count as a DLT of the combination of study drugs at the dose level under study. In this case the patient will be replaced by another patient in the dose cohort.
- A total of 6 patients were treated at the RP2D prior to enrolling in the Cohort Expansion Phase of the study.

Following these rules for dose escalation, the MTD/MAD for the combination of margetuximab and pembrolizumab will be defined as the dose level at which < 33% of patients experience a drug-related DLT during the DLT evaluation period. If no MTD is defined for the combination of margetuximab and pembrolizumab after escalation to the maximum protocol-specified dose, that dose level will be designated as the MAD.

Dose escalation to the next dose level is permitted only after the patients enrolled in the current dose cohort have competed the DLT evaluation period and safety data have been reviewed.

At the discretion of the Sponsor, dose escalation may be stopped before an MTD is reached. In this case, the MAD may be chosen based on an assessment of PK, pharmacodynamics, biomarker, safety, and response data. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.

As noted above, a total of 6 patients were treated at the recommended phase 2 dose (RP2D) prior to enrolling in the Cohort Expansion Phase of the study.

Rules for Treatment Discontinuation:

Patients who tolerate treatment with pembrolizumab and margetuximab may continue to receive additional treatment with the study drugs as specified above until any one of the following conditions are met:

- After documentation of a confirmed complete response (cCR), the combination of margetuximab and pembrolizumab are continued for one more treatment cycle.
- Patient meets criteria for irPD (**Appendix 8**)
- Occurrence of drug-related DLT
- The Sponsor, investigator, or Regulatory Agency terminates the study
- Withdrawal of patient due to an AE or serious adverse event (SAE)
- Withdrawal of patient consent
- Completion of protocol defined therapy
- Investigator discretion
- Pregnancy
- Death
- Two years of pembrolizumab and margetuximab combination treatment

Study Population:

The patient population to be enrolled in this study will consist of adult patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or gastric cancer (GC).

The number of patients enrolled in the Dose Escalation Phase (Part A) cannot be precisely determined in advance and could range up to 12 patients depending on results during the course of the trial and the number of margetuximab doses explored. This patient number does not take into account patient replacement for non-evaluable patients.

The Cohort Expansion Phases of the trial will enroll up to 85 patients.

The first expansion cohort (Part B) includes 30 patients in North America and 30 patients in Asia with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC.

Part C will enroll up to 25 patients in North American and/or Asia with relapsed/refractory unresectable locally advanced or metastatic HER2+ (IHC 3+) GC (as defined below under "Inclusion Criteria").

Inclusion/Exclusion Criteria:

To be eligible for study participation, patients must meet all the inclusion criteria. No exceptions will be granted by the Sponsor. Patients will be excluded from the study if they meet any exclusion criteria.

Inclusion Criteria:

General

1. Ability to provide informed consent and documentation of informed consent prior to initiation of any study-related tests or procedures that are not part of standard of care for the patient's

disease. Patients must also be willing and able to comply with study procedures, including the acquisition of specified research specimens.

2. Age ≥ 18 years old (minimum age dependent upon local regulations).
3. Patients may be male or female.
4. Sixty patients in Part B: Have histologically proven unresectable locally advanced or metastatic HER2+ gastroesophageal junction (GEJ) or gastric cancer (GC), determined as 3+ by IHC or 2+ by IHC and in situ hybridization– (ISH-) amplified (≥2.0) (as per College of American Pathologists/American Society of Clinical Oncology 2016 Guidelines) in the most recent tumor biopsy.

   Twenty-five patients in Part C (GC only): As of Amendment 2, up to 25 additional patients with histologically proven unresectable locally advanced or metastatic HER2+ GC (as defined in AJCC Cancer Staging Manual, 8th Edition) determined as 3+ by IHC (as per College of American Pathologists/American Society of Clinical Oncology 2016 Guidelines) in the most recent tumor biopsy.
5. Have received prior treatment with trastuzumab.
6. Have received treatment with one line of cytotoxic chemotherapy in the metastatic setting which includes trastuzumab. Prior adjuvant therapy that resulted in relapse within 6 months of completion of therapy will be considered a line of treatment for metastatic disease. Eligible patients must have documented progression on/after the most recent line of therapy. Patients who discontinue trastuzumab for other reasons (i.e., financial) are eligible if they have documented progression on/after trastuzumab without receiving alternate treatment.
   a. In Parts B and C, only one prior line of treatment that includes trastuzumab is allowed.
7. Resolution of all chemotherapy or radiation-related toxicities to ≤ Grade 1 (with exception of ≤ Grade 2 alopecia, stable sensory neuropathy, or stable electrolyte disturbances that are managed by supplementation).
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**Appendix 6**)
9. Life expectancy ≥ 12 weeks.
10. Measurable disease as per RECIST 1.1 criteria (**Appendix 7**) and documented by computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients with evaluable disease only will not be enrolled on this study. Note: Lesions to be used as measurable disease for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.
11. Patients should have a formalin-fixed, paraffin embedded tumor specimen or unstained slides identified and available for analysis, to enable determination of the expression of HER2 and programmed death ligand 1 (PD-L1) within tumor specimens using IHC staining.

Laboratory Features

12. Acceptable laboratory parameters as follows:
    a. Platelet count ≥ $100 \times 10^3/\mu L$ without transfusion within 2 weeks prior to the initiation of study drug.
    b. Absolute neutrophil count (ANC) ≥ $1.5 \times 10^3/\mu L$ in the absence of any growth factor support within 2 weeks prior to the initiation of study drug.
    c. Hemoglobin (Hgb) ≥ 9 g/dL
    d. ALT/AST ≤ 3.0 × ULN; for patients with hepatic metastases, ALT and AST ≤ 5 × ULN

e. Total bilirubin ≤ 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.

f. Creatinine < 2 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.

Reproductive Features

13. Female patients of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause) must have a negative urine pregnancy test performed within 72 hours prior to the initiation of study drug administration. Further, female patients of childbearing potential must agree to use highly effective contraceptive measures from the time of consent through 120 days after discontinuation of study drug administration.

    For Canadian patients only: Female patients of childbearing potential must have a negative pregnancy test prior to each cycle of pembrolizumab.

    a. Highly effective methods of contraception include hormonal contraceptives, intrauterine device or system, vasectomy, or tubal ligation. If a highly effective method is not achievable then a "double barrier" method is an effective alternative in which the male partner must use a condom with spermicide and the female partner must use a diaphragm or cervical cap concurrently.

14. Male patients with partners of childbearing potential must use barrier contraception. In addition, male patients should also have their partners use another method of contraception from the time of consent through 120 days after discontinuation of study drug administration.

15. Is not pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the prescreening or screening visit through 120 days after the last dose of trial treatment.

Tumor Biopsy

16. At least 20 of the 60 patients enrolled in the Cohort Expansion Phase (Part B) under the Original Protocol and Protocol Amendment 1 must have one lesion considered to be potentially accessible to biopsy and be willing to provide consent for biopsy samples. An attempt at a tumor biopsy of locally accessible lesions will be made for at least 20 of the 60 patients. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Tumor biopsies should only be obtained from lesions that are felt to be accessible with acceptable clinical risk in the judgment of the investigator and should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Lesions to be biopsied should not have been previously irradiated, unless the lesion has grown in size beginning at least 14 days since the last radiation dose. Note that multiple lesions may be used to obtain the biopsy sample.

    - The 25 patients enrolled into Part C will not be required to have pre- and on-treatment biopsies.
    - Diagnostic biopsy sample performed as standard of care will be collected from all patients on study. Patients enrolled on this study will be required to have an identified archival tumor specimen.

Previous Checkpoint Inhibitor Therapy

17. Patients who have previously received an immune checkpoint inhibitor (e.g., programmed-death ligand 1 antibody [anti-PD-L1], programmed cell death protein 1 antibody [anti-PD-1], cytotoxic T-lymphocyte-associated protein 4 antibody [anti-CTLA-4]) prior to enrollment must have toxicities related to the checkpoint inhibitor resolved to ≤ Grade 1 or baseline (prior to the checkpoint inhibitor) to be eligible for enrollment.

Exclusion Criteria:

1. Patients with symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic, and meet the following at the time of enrollment:
    a. No concurrent treatment for the CNS disease (e.g., surgery, radiation, corticosteroids ≥ 10 mg prednisone/day or equivalent)
    b. No progression of CNS metastases on MRI or CT for at least 21 days after last day of prior therapy for the CNS metastases
    c. No concurrent leptomeningeal disease or cord compression
2. Patients who experienced the following immune checkpoint inhibitor-related AEs (i.e., the following AEs make the patient ineligible despite the AE resolving to ≤ Grade 1 or baseline):
    a. ≥ Grade 3 ocular AE
    b. Changes in liver function tests that met the criteria for Hy's Law (> 3 × ULN of either ALT/AST with concurrent > 2 × ULN of total bilirubin and without alternate etiology)
    c. ≥ Grade 3 neurologic toxicity
    d. ≥ Grade 3 colitis or pneumonitis
3. 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 that are now clinically stable with replacement therapy and by laboratory testing.
    a. Patients with history of psoriatic arthritis are excluded.
4. History of prior allogeneic bone marrow, stem-cell or solid organ transplantation.
5. Treatment with any systemic anti-neoplastic therapy, or investigational therapy within the 3 weeks prior to the initiation of study drug administration. Adjuvant hormonal therapy for treatment of prostate or breast cancer is allowed.
6. Treatment with radiation therapy within 3 weeks prior to the initiation of study drug administration.
7. Treatment with corticosteroids (≥ 10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to the initiation of study drug administration. Steroids for topical, ophthalmic, inhaled or nasal administration are allowed.
8. History of 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 drug.
    b. Stroke or transient ischemic attack within 6 months prior to the initiation of study drug.
    c. Clinically significant cardiac arrhythmias.
    d. Uncontrolled hypertension: systolic blood pressure (SBP) >180 mmHg, diastolic blood pressure (DBP) >100 mmHg.
    e. Congestive heart failure (New York Heart Association [NYHA] class III-IV).
    f. Pericarditis or clinically significant pericardial effusion.
    g. Myocarditis.

h. Left ventricle ejection fraction (LVEF) < 50% by echocardiogram or multi-gated acquisition (MUGA) scan.

9. Clinically significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation.
10. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
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. History of clinically significant gastrointestinal bleeding within 4 weeks prior to the initiation of study drug.
    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. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study drug. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than one week prior to the initiation of study drug.
13. Known positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome.
14. Known history of hepatitis B or hepatitis C infection or known positive test for hepatitis B surface antigen, hepatitis B core antigen, or hepatitis C polymerase chain reaction (PCR).
15. History of another malignancy or a concurrent malignancy. Exceptions include patients who have been disease free for two years, or successfully treated for non-melanoma skin cancer, localized prostate cancer (Gleason Score <6) or carcinoma in situ, for example cervical cancer in situ, are eligible.
16. History of trauma or major surgery within 4 weeks prior to the initiation of study drug administration.
17. Any serious underlying medical or psychiatric condition that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site.
18. Known hypersensitivity to recombinant proteins, polysorbate 80 or any excipient contained in the drug or vehicle formulation for margetuximab or pembrolizumab **(Section 6.1)**.
19. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
20. 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 120 days after the last dose of trial treatment.
21. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
22. Employees of MacroGenics, Inc., and Merck & Co., Inc., unless approved by institutional review board (IRB) and principal investigator.
23. Prisoners or other individuals who are involuntarily detained.
24. Any issue that in the opinion of the investigator, would contraindicate the patient's participation in the study or confound the results of the study.

Study Drugs:

Margetuximab: Margetuximab is a sterile, clear-to-slightly-opalescent, colorless-to-pale-yellow or pale-brown, preservative-free solution for IV administration. Some visible, translucent, proteinaceous, margetuximab particles may be present. Margetuximab is supplied in single-use, 10-mL clear glass vials with FluroTec® coated gray butyl rubber serum stoppers and aluminum seals with plastic overseals. Each vial contains 250 mg margetuximab (25 mg/mL) in 10 mL of solution. The product is formulated in a buffer containing 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, in Sterile Water for Injection, pH 6.1.

Margetuximab will be administered as a 120-minute (2-hour) IV infusion after pembrolizumab administration. A sterile, low protein binding polyethersulfone (PES) 0.2 micron filtered administration set must be used for IV administration of margetuximab.

Pembrolizumab: Pembrolizumab is supplied as lyophilized powder in a single-use vial for reconstitution, or as solution for infusion in a single-use vial.

Pembrolizumab lyophilized powder is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted with 2.3 mL Sterile Water for Injection, USP and diluted for IV infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is a preservative-free, latex free solution which is essentially free of extraneous particulates.

Pembrolizumab will be administered by IV infusion over 30 minutes through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

Duration of Treatment and Study Duration:

Margetuximab and pembrolizumab will be administered in combination once every 3 weeks for up to 2 years. Disease status will be evaluated every two cycles (every 6 weeks) for the first six (6) months and then every twelve (12) weeks thereafter using CT and/or MRI as appropriate for the sites of disease, accompanied by physical examination. Although response assessment will be performed according to both conventional and immune-related response criteria (irRC) (**Appendix 7** and **Appendix 8**, respectively), patients will be managed according to irRC principles. This approach allows for the limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that the investigator feels that the patients are tolerating therapy adequately.

Patients who receive treatment and who achieve an objective response status of stable disease (SD), unconfirmed partial response (uPR), confirmed partial response (cPR), unconfirmed complete response (uCR), confirmed complete response (cCR), or unconfirmed progressive disease (uPD) according to immune-related response criteria (irRC) at the Week 6 radiographic disease assessment will be eligible to receive subsequent cycles of treatment, assuming that they remain clinical stable and have not experienced DLTs that necessitate permanent discontinuation of study drugs. Radiographic disease assessments will occur every 6 weeks (i.e., following 2 cycles of treatment [specifically prior to Cycles 3, 5, 7 etc.]). Patients who have experienced PD as evidenced by $\geq$ 20% increase in the dimensions of target lesions or the occurrence of new lesions may continue therapy at the discretion of the investigator pending confirmation of the PD at the next planned tumor assessment and satisfaction of criteria for irPD. Subsequent cycles of therapy after an initial documentation of PD should be administered to patients who have demonstrated

acceptable tolerance to treatment, who remain otherwise clinically stable, and who, in the assessment of the investigator, may derive clinical benefit from the continuation of treatment.

It is expected that enrollment of Part A of the study will occur over approximately 6 months, and enrollment of Parts B – C will take approximately 9 – 18 months.

The total time for conduct of the trial is expected to be approximately 60 months. These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

Treatment Schedule (Procedure): see Time and Events (**Appendix 1**, and **Appendix 2**).

Criteria for Evaluation:

Safety Assessments:

- The safety assessment will be based on the evaluation of treatment-emergent AEs that occur from the time of initiation of administration of either study drug through the End of Treatment Visit, 28 days after the last dose of study drug, or the initiation of another anti-cancer treatment (whichever is later) and will be determined based on signs, symptoms, physical examination findings and/or laboratory test results from enrolled patients as appropriate
- AEs and serious adverse events (SAEs) will be collected from the time the patient receives the first dose of study drug until the End of Treatment Visit, 28 days after the last dose of study drug, or the initiation of another anticancer treatment (whichever is later). Protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation.
- AEs reported between the time the patient signed the informed consent and the administration of the first dose of study drug will be captured as medical history.
- SAEs considered related to study drug may be reported at any time, even after the patient's final visit.
- Progression of the underlying neoplasm resulting in hospitalization or death (e.g., patient hospitalized for or dies from PD only, without any other SAE) will be documented as an antitumor activity outcome and not as an SAE. If an SAE occurs in a patient and it is unclear whether the event is related to PD, the SAE should be reported.
- The reporting of laboratory/vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:
    - Any criterion for an SAE is fulfilled
    - The laboratory/vital signs abnormality causes the patient to discontinue from the study treatment
    - The laboratory/vital signs abnormality causes the patient to interrupt the study treatment
    - The laboratory/vital signs abnormality requires intervention
    - The laboratory/vital signs are deemed clinically significant, based on medical judgment.

Efficacy Assessments:

Tumor assessments will be obtained at screening using CT and/or MRI scans at time intervals as specified in **Appendix 1** (Time and Events Table: Dose Escalation) and **Appendix 2** (Time and Events Schedule: Cohort Expansion). Radiographic disease assessments will occur every 6 weeks (i.e., following 2 cycles of treatment [Cycles 3, 5, etc.]) for the first 24 weeks and then every 12 weeks thereafter until documented progression, initiation of alternative anti-cancer therapy, lost to follow-up, withdrawal of informed consent, death, or end of study. Treatment will continue until patients have completed study therapy and required follow-up,

experienced disease progression according to irRC, or have been withdrawn from the study. At each on-treatment tumor assessment time point, the objective response status will be determined.

For patients who demonstrate acceptable tolerability of treatment with pembrolizumab and margetuximab and achieve an objective response assessment of irCR, irPR or irSD, or unconfirmed clinically stable irPD, therapy may be continued (see **Section 4.4** and **Section 5.3**).

For patients who are otherwise clinically stable, but have met conventional criteria for PD, therapy may be continued at the discretion of the investigator pending confirmation of progression at the next scheduled tumor assessment. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression and that the investigator feels the patient may still derive benefit from continuation of therapy. Treatment of patients according to irRC principles is supported by well-documented evidence that in some patients treated with T cell directed, immune-modulatory agents, their tumors can evolve to an objective response after an initial period characterized by either apparent radiographic growth of target lesions or the development of new target lesions that would otherwise meet the criteria for disease progression using conventional response criteria (**Appendix 7**). In the context of the statistical analysis for this trial, objective response determination and the assessment of best overall response (BOR) will be defined using both conventional RECIST 1.1 (**Appendix 7**) as well as an adaptation of these criteria, designated as immune-related response criteria (irRC) (**Appendix 8**). Patient management decisions, however, will be made solely based on the immune-related response criteria (**Appendix 8**).

For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for irPD will have been met, and treatment with margetuximab and pembrolizumab should be discontinued. The patient should be removed from study participation after completion of protocol specified follow-up (see **Section 8.3**, **Appendix 1** and **Appendix 2**). For patients who experience an objective response of immune-related complete response (irCR) or immune-related partial response (irPR), responses will be considered unconfirmed until the response has been documented by a subsequent confirmatory scan obtained no less than 4 weeks after the initial scan demonstrating an objective response.

Efficacy Assessments:

Objective Response and Response Duration

Target and non-target lesions will be designated and evaluated using both conventional RECIST 1.1 criteria (**Appendix 7**) and irRC (**Appendix 8**) for the purposes of statistical analysis. Objective responses will be categorized as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) for conventional RECIST 1.1 criteria and irCR, irPR, irSD, and irPD for the immune-related response criteria. Determination of the objective response rate will be calculated based on the proportion of response evaluable patients achieving CR or PR using the respective criteria, when such responses are confirmed by a subsequent scan obtained at least 28 days after the initial documentation of objective response. Response evaluable patients will include those patients who have measurable disease and have had a baseline tumor assessment and received one dose of either margetuximab or pembrolizumab (see **Appendix 1** and **Appendix 2**). Objective responses that are not subsequently documented with a confirmatory CT or MRI scan (e.g., unconfirmed responses) will not be included as an objective response for the purpose of calculating overall objective response rates. Response duration will be calculated from the time of initial response (CR or PR) documentation (in patients who have a subsequent confirmation of objective response) to the time of progressive disease or death, whichever occurs first. A patient's response duration will be censored if at the time of last antitumor assessment response is ongoing.

Progression-free survival (PFS)

PFS will be calculated as the time from the first dose of study drug until documented disease progression or death from any cause. (**Appendix 5**). A patient's PFS will be censored if at the time of last assessment for

progression, the patient remains progression free. PFS will be determined using conventional RECIST 1.1. In addition, PFS rate at 3 and 6 months will be evaluated.

Overall survival (OS)

OS will be calculated as the time from the first dose of study drug until death due to any cause. A patient's OS will be censored if at the time of last contact, the patient remains alive. In addition, OS rate at 1 and 2 years will be evaluated.

Pharmacokinetic Assessments:

Serum concentrations of margetuximab will be monitored using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA). Single and multiple dose PK parameters for margetuximab (e.g., C_{max}, T_{max}, AUC_{tau}, AUC_{inf}, C_{trough}, CL, V_{ss}, and T_{half}) will be derived from margetuximab serum concentration versus time data. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Immunogenicity Assessments:

The generation of anti-drug antibodies (ADA) directed against margetuximab will be assayed using ELISA. Samples positive for ADA will be evaluated for neutralizing activity.

Pharmacodynamics/Biomarkers:

Tests to be performed may include the following:

- Determination of Fc receptor genotypes for *CD16A, CD32A* and *CD32B*
- Characterization of alterations in serum cytokine levels including, but not limited to, interleukin (IL) IL-2, IL-6, IL-10, IFN-γ and TNF-α.
- Enumeration of lymphocyte subsets, natural killer (NK) cells and other activation markers and activation status over time via multi-parameter flow cytometry flow cytometry; evaluation of the T-reg population over time
- Determination of the potentiation of HER2 specific adaptive humoral and cellular immune responses: Plasma samples analyzed by ELISA to measure endogenous anti-HER2 IgG levels; peripheral blood mononuclear cell (PBMC) samples analyzed by ELISpot to measure HER2-specific T-cell activity
- Determination of PD-L1 expression will be explored via IHC staining of archival tumor biopsy specimens (unless fresh tumor sample submitted and used to determine PD-L1 expression and no archived sample obtained)

Limited to Cohort Expansion Phases (Parts B-C) only (unless otherwise noted):

- Determination of mutational burden (on ctDNA determined by Guardant 360 assay), as well as mismatch repair status by microsatellite instability (from pathology reports, when available).
- Determination of PD-L1 tumor cell membranous expression and T cell infiltration (including but not limited to CD4+ and CD8+ T cells) into the tumor bed via IHC staining of paired pre- and on-treatment tumor biopsy specimens.
- Part B only: Determination of HER2 tumor cell membranous expression via IHC staining of pre-treatment and/or on-treatment tumor biopsy specimens.
- Determination of gene expression signatures (i.e., nanostring technology) in tissues, which may be indicative of immunotherapy responses associated with the agents on trial.

Analysis Populations:

Two general populations will be used for the purposes of data analysis - the Safety Population and the Response Evaluable Population as defined below:

- **Safety Population:** All patients who received at least one dose of either margetuximab or pembrolizumab. This population will be used for safety analysis and for analysis of PFS and OS. Patients who receive at least one dose of margetuximab will be included in PK, PD, and immunogenicity analyses.
- **Response Evaluable Population:** All patients who have baseline measurable disease and received at least one dose of either margetuximab or pembrolizumab. This population will be used for analysis of ORR.

Statistical Methods:

Response will be categorized as CR, PR, SD, or PD and evaluated using RECIST 1.1 criteria and as irCR, irPR, irSD, or irPD using the irRC. The ORR will be the proportion of patients in the response evaluable population achieving CR or PR when such responses are confirmed at least 28 days after the initial observation of an objective response. A two-sided 95% exact binomial confidence interval will be calculated around the ORR for each expansion region and also by tumor type.

Response duration will be calculated for responders as the time from initial response (CR or PR) to the time of PD or death. Kaplan-Meier methods will be used to estimate response duration over time and the median response duration. Responders who complete the study without documented PD will be censored at the date of their last tumor assessment.

PFS will be calculated as the time from the initial infusion of pembrolizumab or margetuximab until documented disease progression or death from any cause. Patients with no PFS event (disease progression or death from any cause) will be censored at the date of their last tumor assessment. In addition, PFS rates will be calculated at 3 and 6-month time points from the first dose of study drug. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. The method of Brookmeyer and Crowley (**9**) will be used to construct 95% CIs around PFS estimates of the median and other quartiles for each expansion region and also by tumor type.

Incomplete and missing data can complicate interpretation of PFS. **Appendix 5** describes the handling of these data for the PFS analysis.

Overall survival is defined as the time from the initial infusion of pembrolizumab or margetuximab to death from any cause. Patients who are alive at last contact will be censored at the date that the patient was last known to be alive. Kaplan-Meier methods will be used to estimate the overall survival function. In addition, OS rate will be calculated at 1 year and 2-year time points from the first dose of study drug.

In Part B, after 15 patients were enrolled in each region under the Original Protocol and Protocol Amendment 1 and after each patient has at least one post-baseline tumor assessment, a futility rule was applied and enrollment in that region was continued. The enrollment could have been stopped if there was no more than one response. One response out of 15 patients will have 80% confidence to rule out the response rate of 20% or higher (the upper limit of one-sided 80% CI for response rate < 20%).

2 BACKGROUND INFORMATION

2.1 Disease Background

2.1.1 Gastroesophageal Junction Cancer and Gastric Cancer

Although the incidence of gastroesophageal junction cancer (GEJ) and gastric cancer (GC) has been declining in recent decades, it remains a global health problem. It is a disease associated with high mortality and poor prognosis, as it is often diagnosed at an advanced stage **(15, 52)**. If identified at an early stage, surgery is the primary treatment for patients with GC, with a 5-year survival of 36% in patients with operable disease who also receive perioperative chemotherapy **(16)**. Five-year survival among patients with advanced or metastatic GC, however, has been reported to range between 5-20%, with median overall survival (OS) rates of less than 1 year **(69)**.

Globally, GC is the fifth most common malignancy, with half the total 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), it is estimated that over 24,500 people will be diagnosed with GC and 10,720 individuals will die from this disease in 2015 **(69)**. For patients with advanced-stage GC, treatment typically consists of a fluoropyrimidine-based combination chemotherapy and is associated with a median overall survival of 7-10 months **(52, 78)**. The introduction of targeted treatments for GC has improved overall survival rates for specific populations. In the ToGA trial **(3)**, trastuzumab, a monoclonal antibody against HER2, in combination with chemotherapy, increased median overall survival by approximately 3.5 months and is now used for the first-line treatment of HER2+ advanced gastric or GEJ. In patients with previously treated disease, ramucirumab, a VEGFR-2 antibody, administered as single agent or in combination with paclitaxel, demonstrated increases in median overall survival of 1.4 months and 2.2 months, respectively **(26, 81)**. Although newer therapies have improved survival for advanced cases of GEJ and GCs, there remains a significant medical need for continued improvement in therapies for this disease.

2.1.2 HER2+ Gastroesophageal Junction Cancer or Gastric Cancer

HER2 positivity has been observed in 7 – 35% of GC tumors **(3)**. The ToGA trial established HER2 as a validated target in patients with GEJ or GC and demonstrated that patients with overexpression of HER2 benefitted from receiving trastuzumab in addition to standard (frontline) fluoropyrimidine/cisplatin chemotherapy. Median overall survival (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+ positive by immunohistochemistry (IHC) with amplified by fluorescence in situ hybridization [FISH]), 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 HER2+ GEJ or GC patients.

Treatment of patients with advanced HER2+ gastric or GEJ cancer who have progressed after frontline fluoropyrimidine/cisplatin chemotherapy plus trastuzumab is not well defined. However, single-agent taxane or irinotecan therapy is frequently employed **(1, 13, 33, 37, 44)**. Response rates resulting from the use of weekly paclitaxel in this patient population ranged from 16% to 24%, while median PFS ranged from approximately 2.1 to 2.6 months and median OS from approximately 5.0 to 7.8 months **(33, 41, 44, 81)**. Irinotecan produced similar results in a similar patient population **(41)**. Recently, the RAINBOW study demonstrated an improvement in overall survival to 9.6 months with the addition of ramucirumab in combination with paclitaxel in second-line setting for GEJ or GC **(81)**.

Additional anti-HER2 therapies have been and are being tested in the second-line treatment of patients with advanced GEJ or gastric cancers overexpressing HER2. Although the TyTAN trial failed to demonstrate a statistically significant improvement in survival for the combination of paclitaxel plus lapatinib **(63)**, the point estimates for survival favored the combination (OS = 11.0 months) vs. the paclitaxel alone arm (OS = 8.9 months), suggesting that a more potent anti-HER2 therapy might be useful in this setting. In addition, a large multinational trial is underway involving the second-line treatment of patients with gastric or GEJ cancer comparing the anti-HER2 drug conjugate ado-trastuzumab emtansine to taxane alone. A second trial examines the activity of the combination of capecitabine plus ado-trastuzumab emtansine in patients with advanced HER2+ gastric or gastroesophageal cancer without regard to prior treatment. Applying the paradigm developed in the treatment of HER2-overexpressing metastatic breast cancer **(27, 38)**, it may be reasonable to continue anti-HER2 therapy following disease progression while moving to another backbone chemotherapy regimen. However, no specific anti-HER2 treatment is currently part of the standard treatment algorithm for HER2 overexpressing gastric or GEJ cancers after trastuzumab. Recent literature suggests that progression post-trastuzumab and failure of other HER2 targeted agents is due to loss of HER2 overexpression **(18, 39, 65)**. Furthermore, there is high heterogeneity of HER2 expression in gastric and GEJ cancers **(31, 84)** indicating a need for tests with higher specificity **(66)**. Guardant 360 is a digital sequencing panel for quantitative analysis of cell-free circulating tumor DNA with high specificity, which can be used to monitor HER2 gene amplification level longitudinally as well as overall tumor mutational burden **(45)**. The NEXT-2 trial has shown non-inferiority to tissue biopsy and advantage of real-time predictive treatment in refractory tumors **(46)**. Although a large body of literature supports the notion that trastuzumab acts by alteration of signaling from the HER2 oncoprotein and resulting subsequent growth inhibition and/or apoptosis **(35, 85)** there is a growing realization that an important mechanism of trastuzumab's action is the mediation of antibody dependent cellular cytotoxicity (ADCC). Clynes et al. **(14)** demonstrated that the tumor inhibition effects of trastuzumab on human tumor xenograft models were dependent upon expression in the mouse of receptors for the Fc portion of the anti-HER2 monoclonal antibody. This observation was followed by the demonstration by Musolino et al. **(51)** of prolonged PFS for patients with metastatic breast cancer treated with trastuzumab in high affinity vs. low affinity carriers of alleles of the gene for the activating Fc receptor CD16A.

2.2 Background on PD-1

2.2.1 PD-1

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades **(19)**. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies **(6, 8, 22, 29, 48, 55, 56, 62, 64, 68, 75, 77)**. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in many solid malignancies, such as ovarian, colorectal, and pancreatic cancers; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma **(12, 20, 43, 47, 55, 58, 86)**. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma **(21, 30, 36)**.

Programmed death protein-1 (PD-1) is an immune-modulatory receptor expressed on activated T-cells. The physiological role of PD-1 is to limit the inflammatory response to infection and prevent autoimmunity by limiting the activity of T cells in the periphery **(5, 25, 42)**. The basis for this physiology is that the ligands for PD-1, namely programmed death-ligand 1 (PD-L1) (B7-H1) and programmed death-ligand 2 (PD-L2) (B7-DC), are up-regulated on many cell types — hematopoietic, endothelial and epithelial — in response to pro-inflammatory cytokines, notably interferon gamma. In addition, PD-L2 is up-regulated on dendritic cells and macrophages in response to different pro-inflammatory cytokines such as interleukin (IL) IL-4 **(67, 80)**.

Cancer cells, to avoid antitumor response, co-opt the normal physiology of the PD-1 pathway used to prevent collateral normal tissue damage that would occur in an unchecked inflammatory immune response. Expression of PD-L1 as an adaptive response to antitumor immunity likely occurs because this ligand is induced on most epithelial cancers in response to interferon-gamma, similarly to epithelial and stromal cells in normal tissues **(76)**. In addition, PD-1 is highly expressed on induced regulatory T-cells (T-regs), and PD-1: PD-L1 interactions appear to promote the induction, conversion and maintenance of T-regs, suggesting an additional mechanism for immunosuppression in a tumor microenvironment rich in PD-1 ligands **(2, 24)**.

Blockade of negative regulatory signals to T cells, such as CTLA-4 and PD-1/PD-L1, is an area of active investigation in gastric cancer. Expression of PD-L1 on gastric tumors has been documented in a number of studies **(10, 83)**. Collectively, these studies included 725 patients and demonstrated expression with an average frequency of 43%, ranging from 42% to 67%, suggesting that the PD-L1 pathway is active in this setting and that blockade of PD-L1 activity could have therapeutic benefit. Complete responses in gastric cancer have been anecdotally reported with anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) and anti-PD-1/PD-L1 antibodies **(59, 74)**. Indeed, the recent report demonstrating an improvement in survival among heavily pre-treated advanced metastatic gastric and GEJ cancers that were treated with monotheraphy pembrolizumab clinically validates the approach of inhibiting this pathway. In this study, the KEYNOTE-012 study, 39 advanced metastatic gastric or GEJ cancer patients that were refractory to standard treatments were treated with monotherapy pembrolizumab. An objective

response rate (ORR) of 22.2% was noted, along with a 1.9-month median progression-free survival and an 11.4-month median overall survival **(4)**.

2.3 Study Agent Background

2.3.1 Margetuximab

Margetuximab **(54)** is derived from 4D5, the murine precursor to the humanized therapeutic antibody, trastuzumab. Chimeric 4D5 (ch4D5) is generated by fusing the mouse light chain (LC) and heavy chain (HC) complementarity-determining region (CDR) and framework sequences of 4D5 to a human immunoglobulin (Ig) G1 backbone. Margetuximab is generated from ch4D5 by removal of an N-glycosylation site in the LC variable region (modification of one amino acid residue) and by optimization of the Fc domain (modification of five amino acid residues). Margetuximab binds the HER2 oncoprotein with affinity similar to that of trastuzumab, and preserves the direct anti-proliferative properties of trastuzumab. The optimized Fc domain of margetuximab, however, confers enhanced binding to the activating low-affinity and high affinity Fc receptors, CD16A. In particular, binding to the lower-affinity isoform of CD16A (CD16A-158F) is enhanced in a proportionally greater fashion than binding to the higher-affinity isoform (CD16A-158V). In addition, the optimized Fc domain of margetuximab exhibits reduced binding to the inhibitory receptor, CD32B, a feature expected to further enhance the cell-directed cytotoxic properties of margetuximab. In preclinical models, margetuximab exhibits enhanced anti-tumor activity compared to a trastuzumab surrogate against HER2-expressing tumor cell lines in in vitro ADCC assays and in human tumor xenograft models in human CD16A+ transgenic mice.

2.3.1.1 Margetuximab Clinical Experience

Margetuximab has been, or is currently being evaluated in three other clinical studies, CP-MGAH22-01 (study closed, CSR final), CP-MGAH22-02 (CSR preparation ongoing) and CP-MGAH22-04 (study is ongoing).

Study CP-MGAH22-01 is a Phase 1, open-label, single-arm, multicenter dose-escalation study to define the toxicity profile, maximum tolerated dose (MTD), immunogenicity, pharmacokinetic (PK), and potential anti-tumor activity of margetuximab in patients with refractory HER2+ breast cancers, HER2+ gastric or GEJ cancers, and patients with other carcinomas that overexpress HER2 for whom no standard therapy is available. The study evaluated 2 regimens of margetuximab (administered via intravenous [IV] infusion): three of every four-week dosing (0.1 – 6.0 mg/kg) and every 3-week dosing (10.0, 15.0, and 18.0 mg/kg). The CSR for this study has been completed.

Study CP-MGAH22-02 is a single-arm, open-label, Phase 2 study of margetuximab in patients with relapsed or refractory breast cancer whose tumors express HER2 at a 2+ level by IHC and lack evidence of *HER2* gene amplification by FISH or express HER2 at a 1+ level by IHC and have a value of >10.5 by HERmark® testing. The original margetuximab dose and schedule evaluated was 6.0 mg/kg via IV infusion weekly on Days 1, 8, and 15 of a 28-day cycle. The study protocol was subsequently amended to evaluate margetuximab at a dose and schedule of

15 mg/kg via IV infusion every 3 weeks, consistent to that being evaluated in the CP-MGAH22-01 study. This study is closed, and the CSR is being completed.

Study CP-MGAH22-04 is a Phase 3, randomized, open-label, controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy, for the treatment of patients with advanced HER2+ breast cancer who have received prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine in the neoadjuvant, adjuvant, or metastatic settings and have received at least one, and no more than three, lines of therapy in the metastatic setting. Patients must have progressed on or following the most recent therapy. Eligible patients will be assigned to chemotherapy of the investigator's choice to be chosen from capecitabine, eribulin, gemcitabine, or vinorelbine. Study treatments (study drugs and chemotherapies) to be administered during this study are summarized in the following table.

Agent	Starting Dose	Schedule	Mode of Administration
Chemotherapy			
Capecitabine	1000 mg/m2 BID	BID for 14 days in a 21-day cycle	Oral
Eribulin	1.4 mg/m2	Day 1 and 8 of a 21-day cycle	IV
Gemcitabine	1000 mg/m2	Day 1 and 8 of a 21-day cycle	IV
Vinorelbine	25-30 mg/m2	Day 1 and 8 of a 21-day cycle	IV
Study Drugs			
Trastuzumab	8 mg/kg loading dose then 6 mg/kg	Every 21 days	IV
Margetuximab	15 mg/kg	Every 21 days	IV

BID = twice daily; IV = intravenous

Approximately 530 patients will participate in this study.

As of 30 September 2017, 276 patients have been treated in trials investigating margetuximab, including 274 patients treated in 4 MacroGenics-sponsored clinical studies and 2 patients being treated in a non-MacroGenics-sponsored expanded access program (EAP) trial as follows:

- CP-MGAH22-01: n = 66 patients enrolled and treated
- CP-MGAH22-02: n = 25 patients enrolled and treated
- CP-MGAH22-04: n = 119 patients enrolled and treated with margetuximab. (Note: data remain blinded to the Sponsor; therefore, the safety summaries presented herein include data from patients treated with the comparator agent, trastuzumab.)
- CP-MGAH22-05: n = 64 patients enrolled and treated
- EAP: n = 2 patient enrolled and treated (non-MacroGenics-sponsored trial)

Margetuximab has been tolerable, and the overall safety profile has remained unchanged with no occurrence of concerning safety signals. Refer to the **margetuximab investigator's brochure** for details on its safety profile.

2.3.2 Pembrolizumab Background and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities **(7, 17, 32, 57, 70, 71, 79)**. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma **(17, 53, 57, 71, 87)**. In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo **(17)**. Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the pembrolizumab Investigator's Brochure.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in patients with NSCLC, head and neck squamous cell carcinoma, urothelial cancer, GC, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details, please refer to the pembrolizumab IB.

Pembrolizumab is currently indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (Combined Positive score [CPS] ≥1) as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. The recommended dose of pembrolizumab is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression (please refer to the KEYTRUDA® [pembrolizumab] package insert).

Study KEYNOTE-059 was a multicenter, non-randomized, open-label multi-cohort trial that enrolled 259 patients with gastric or GEJ adenocarcinoma who progressed on at least 2 prior

systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy.

The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 259 patients with GC enrolled in Study KEYNOTE-059, the median duration of exposure to pembrolizumab was 2.1 months (range: 1 day to 21.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical examination were ineligible. Adverse reactions occurring in patients with GC were similar to those occurring in patients with melanoma or non-small cell lung cancer (NSCLC).

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 (IHC 22C3 pharmDx Kit) with a combined positive score (CPS) of greater than or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. Median age was 64 years; 77% were male; 82% were White and 11% Asian; 85% had M1 disease; and 7% had M0 disease. Fifty-one percent had 2 and 49% had 3 or more prior lines of therapy in the recurrent or metastatic setting.

For the 143 patients, the ORR was 13.3% (95% CI: 8.2, 20.0); 1.4% had a complete response and 11.9% had a partial response. Among the 19 responding patients, the duration of response ranged from 2.8+ to 19.4+ months, with 11 patients (58%) having responses of 6 months or longer and 5 patients (26%) having responses of 12 months or longer.

Among the 259 patients enrolled in KEYNOTE-059, 7 (3%) had tumors that were determined to be MSI-H. An objective response was observed in 4 patients, including 1 complete response. The duration of response ranged from 5.3+ to 14.1+ months.

2.3.2.1 Safety

Safety data are available for a total of 2461 patients with melanoma or NSCLC in 8 Merck-sponsored clinical trials as available in the investigator's brochure dated May 2016.

In the pembrolizumab monotherapy trials, in general, the most commonly reported AEs included fatigue, diarrhea, decreased appetite, nausea, dyspnoea, and anaemia. The incidence of drug-related AEs (DRAEs) ranged from 39.8% to 80.0%. The incidence of Grade 3-5 DRAEs across studies ranged from 6.8% to 12.0%. The most commonly reported Grade 3-5 DRAEs were anaemia, alanine aminotransferase increased, aspartate aminotransferase increased, and colitis.

In the pembrolizumab monotherapy trials, most patients who experienced an adverse event (AE) continued in the study, with the incidence of AEs leading to discontinuation ranging from 4.2% to 12.3%. The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a DRAE were infrequent and ranged from 0% to 4.5%. The most commonly reported DRAE leading to discontinuation was pneumonitis. Refer to the

pembrolizumab investigator's brochure [See **KEYTRUDA® (pembrolizumab) investigator's brochure**] for further details on its safety profile.

2.4 Rationale for Combining Margetuximab and Pembrolizumab

Despite current treatment options for patients with GEJ or GC, substantial unmet medical need remains for patients with advanced disease. This study evaluates a novel combination of immunotherapies in patients with advanced cancer and is designed to investigate whether combined administration of margetuximab and pembrolizumab may result in enhanced antitumor activity.

The blockade of individual immune checkpoint inhibitors has demonstrated antitumor activity in a variety of cancers and has now been validated in GEJ and gastric cancer **(50)**. Nonetheless, the vast majority of tumors among these patients eventually progress, escaping immune detection and destruction. Therefore, strategies that combine immune checkpoint blockade through non-redundant immune checkpoints and/or other mechanisms are being actively investigated and are beginning to demonstrate even greater potential antitumor activity than monotherapy-based treatments **(73)**.

The simultaneous blockade of HER2 with margetuximab and PD-1 with pembrolizumab represents an attractive opportunity to potentially enhance and focus the immune system against HER2 overexpressing cancer cells to mediate antitumor effects more pronounced than blocking either single target alone. Aside from coordinately targeting the distinct functions mediated by HER2 and PD-1 axis with combined administration of margetuximab and pembrolizumab, additional lines of evidence suggest that these agents may be combined to more effectively enhance the antitumor response compared to blocking either target alone. Margetuximab is an Fc-optimized monoclonal antibody modified to increase Fc-receptor-mediated effector activity, and thus may enhance potential ADCC immune attack on HER2-expressing tumor cells. Enhanced ADCC activity may result in increased tumor antigen presentation and an improved adaptive immune response **(54)**. Combining the two distinct mechanisms of action of enhanced ADCC and release of the PD-1 checkpoint inhibition against T-effector cells may provide increased anti-tumor activity compared to that observed with blocking either target alone. In conclusion, treating patients with two agents that may have monotherapy anti-tumor activity is an effective rationale for combining margetuximab and pembrolizumab, especially given their complementary mechanisms of action. Furthermore, possible coordinated engagement of both innate and adaptive immunity also serves as scientific rationale for combining these agents.

2.5 Rationale for Dose Selection

2.5.1 Dose Escalation Phase (Part A)

2.5.1.1 Pembrolizumab

The dose of pembrolizumab administered during the study will be 200 mg given once every 3 weeks via 30-minute IV infusion. In Study KEYNOTE-001 (KN001), two randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2 mg/kg versus

10 mg/kg Q3W have been completed, while one randomized cohort evaluation of 10 mg/kg Q3W versus 10 mg/kg Q2W is ongoing. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, an observed objective response rate (ORR) of 26% (21/81) and 26% (25/79) was observed among advanced melanoma patients who had received prior ipilimumab treated with pembrolizumab 2 mg/kg and 10 mg/kg, respectively. The proportion of patients with drug-related AE, Grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group **(61)**.

Per the **KEYTRUDA® (pembrolizumab) investigator's brochure**, PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days), thus supporting a Q3W dosing schedule.

A population PK analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight-based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W versus the dose regimen of 2 mg/kg Q3W (i.e., 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the non-small cell lung cancer (NSCLC) and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

In conclusion, the above data indicates that the 200 mg Q3W fixed dose regimen planned to be used in this trial is likely similar, with regard to efficacy and tolerability, to the 10 mg/kg Q2W dose regimen used in KN012, and supports its use in this study. No dose reduction is allowed for pembrolizumab in this study. A 200 mg Q3W pembrolizumab fixed dose regimen is currently employed in several ongoing pembrolizumab studies (NCT02494583, NCT02335411, and NCT02370498).

2.5.1.2 Margetuximab

The dose for margetuximab in the Dose Escalation Phase (Part A) will begin at 10 mg/kg IV (120-minute infusion), with a proposed escalation to 15 mg/kg, given on a once every 3-weeks schedule. There will be a dose de-escalation to 6 mg/kg margetuximab if the starting dose of 10 mg/kg in combination with pembrolizumab is found to exceed the MTD.

The initial margetuximab dose proposed, 10 mg/kg, is based on the PK and safety profile of margetuximab from the two ongoing clinical studies.

Clinical PK were evaluated in the Phase 1 study. A two-compartment model with parallel linear and Michaelis-Menten elimination adequately described the observed (interim) data. Model parameters were generally in agreement with those commonly expected for a monoclonal antibody. Single dose exposure was predicted to be approximately dose proportional at doses > 3 mg/kg when dosed weekly for 3 weeks in 4-week cycles and ≥ 15 mg/kg when dosed every 3 weeks. The terminal half-life was estimated at 12.7 days.

Table 1 **Margetuximab Pharmacokinetics at Steady State – 6 mg/kg, 10 mg/kg, 15 mg/kg, 18 mg/kg – CP-MGAH22-01**

Parameter (unit)		Margetuximab Dose and Schedule			
		6 mg/kg QW [a] N=19	10 mg/kg Q3W [b] N=6	15 mg/kg Q3W [b] N=6	18 mg/kg Q3W [b] N=6
C_{trough} (µg/mL)	Mean (SD)	73.0 (38.2)	42.3 (25.5)	69.9 (42.9)	86.1 (47.9)
	Median (95% CI)	66.9 (20.5 - 169)	37 (6.86 – 101)	61 (15.8 - 180)	77.6 (20.8 - 207)
C_{max} (µg/mL)	Mean (SD)	217 (58.1)	236 (16.8)	360 (93.9)	429 (103)
	Median (SD)	211 (125 - 355)	227 (136 – 380)	345 (222 - 590)	417 (263 - 660)
AUC (µg/mL*h)	Mean (SD)	84700 (30000)	49500 (16500)	72200 (27200)	87500 (30300)
	Median (95% CI)	80500 (40700 - 15800)	43100 (20400 – 84400)	66800 (35300 - 139000)	82200 (43600 - 160000)

a Dosed once weekly (QW) for 3 weeks in 4-week (28-day) cycles

b Dosed once every 3 weeks in 3-week (21-day) cycles.

Steady state exposure estimates are shown in **Table 1** for margetuximab when dosed at 6.0 mg/kg weekly for 3 of every 4 weeks (n=19), 10 mg/kg every 3 weeks (n=6), 15.0 mg/kg every 3 weeks (n=6), and 18.0 mg/kg every 3 weeks (n=6) in Study CP-MGAH22-01. At steady state, these doses and regimens are estimated to have similar exposure. Serum trough concentrations (C_{trough}) for the 6 mg/kg, 15 mg/kg, and 18 mg/kg doses are nearly identical, are at or above those reported for trastuzumab in patients with breast cancer **(28)** and are above that required for inhibition of HER2 signaling as demonstrated for trastuzumab **(11)**. Similarly, area under the concentration-time curve (AUC) values are also very similar.

There are no obvious differences in the safety profiles of each margetuximab dose evaluated to date that suggest a dose-toxicity relationship. (Details of the number and kind of AEs reported both in aggregate and by dose are available in the margetuximab IB). The frequency, type, and severity of AEs observed did not differ and although the maximum serum concentration (C_{max}) differs for these three dose groups in a dose-related manner, no obvious difference in the safety profile was observed between patients treated at 6.0 mg/kg (the lowest C_{max}), 15.0 mg/kg, and 18.0 mg/kg (the highest C_{max}). No increase in AEs was noted with prolonged exposure, and none of these patients have been discontinued from treatment because of toxicity. Based on the PK and

safety data available to date, 10 mg/kg margetuximab administered every 3 weeks is a reasonable starting dose for this study.

The doses and schedule of margetuximab selected for evaluation in the Dose Escalation Phase (Part A) of this study, 10 mg/kg and 15 mg/kg given every 3 weeks, is based on the observed safety and efficacy profile of margetuximab at all doses tested to date and the predictable PK characteristics in the ongoing Phase 1 study. As noted, the top dose for this study (15.0 mg/kg) is also the dose being studied in the Phase 3 randomized HER2+ breast cancer study (CP-MGAH22-04).

2.5.2 Cohort Expansion Phase (HER2+ GEJ/GC and HER2+ GC-IHC3+) (Parts B – C)

The recommended phase 2 dose (RP2D) of margetuximab as determined during the Dose Escalation Phase (Part A) (15 mg/kg Q3W) is used in combination with the fixed dose (200 mg) of pembrolizumab during the Cohort Expansion Phases (Parts B – C).

3 STUDY PURPOSE AND OBJECTIVES

This study is an open-label, dose escalation, Phase 1b/2 study designed to characterize the safety, tolerability, PK, pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of margetuximab administered IV once every 3 weeks in combination with 200 mg pembrolizumab administered IV once every 3 weeks in patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC.

3.1 Primary Objectives

The primary objectives of this study are:

- To characterize the safety, tolerability, DLT, and MTD or MAD (if no MTD is defined) of margetuximab when administered IV every 3 weeks in combination with 200 mg pembrolizumab administered IV every 3 weeks to patients with relapsed/refractory advanced HER2+ GEJ or GC.
- To investigate the preliminary anti-tumor activity, as measured by objective response rate (ORR) and response duration, of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks using both conventional Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (**Appendix 7**) and immune-related response criteria (irRC) (**Appendix 8**), in patients that have failed first-line trastuzumab-containing regimens.

3.2 Secondary Objectives

Secondary objectives of this study are:

- To investigate the preliminary effect on OS and PFS of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks
- To characterize the PD activity of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks.
- To characterize the PK and immunogenicity of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks.

3.3 Exploratory Objectives

- To explore the relationships between PK, PD, patient safety and antitumor activity of margetuximab when administered in combination with pembrolizumab.
- To investigate the immune-regulatory activity of margetuximab in combination with pembrolizumab by analysis of peripheral blood samples for potentiation of HER2 specific adaptive humoral and cellular immune responses.

- To determine the relationships between membranous expression of PD-L1 on tumor cells, immune cell infiltration within biopsy specimens (including but not limited to CD4+ and CD8+ T cells), PD-L1 expression on the immune cell infiltrate, and clinical response via IHC staining of paired pre- and on-treatment tumor biopsy specimens.
- To determine the relationship of allelic variation in *CD16A, CD32A* and *CD32B* to anti-tumor activity.
- Determination of mutational burden (on ctDNA determined by Guardant 360 assay), as well as mismatch repair status by microsatellite instability (from pathology reports, when available).
- To determine of gene expression signatures in tissues, which may be indicative of immunotherapy responses associated with the agents on trial.
- To validate ctDNA *ERBB2,* determined by circulating tumor DNA Guardant 360 assay amplification as a surrogate of HER2 expression in patients with GC; to be performed at Guardant Laboratories.

The results of exploratory objectives may not be included in the Clinical Study Report or final data tables and listings unless they represent meaningful findings.

4 TRIAL DESIGN

4.1 Overall Study Design and Plan

4.1.1 General Study Design

This study is a Phase 1b/2, open-label, dose escalation and cohort expansion study designed to characterize the safety, tolerability, PK, PD, immunogenicity, and preliminary antitumor activity of margetuximab administered IV every 3 weeks in combination with pembrolizumab administered IV every 3 weeks in patients with relapsed/refractory, unresectable locally advanced or metastatic HER2+ GEJ or GC.

The study consists of a **Dose Escalation Phase (Part A)** to determine the MTD or MAD (if no MTD is defined) of escalating doses of margetuximab administered in combination with a fixed dose of 200 mg pembrolizumab, followed by a **Cohort Expansion Phase (Parts B – C)** to further define the safety and initial efficacy of the combination with the margetuximab dose established in the first phase. As of Protocol Amendment 2, up to 25 additional patients with GC only will be added to Cohort Expansion Phase (Part C). See **Section 4.1.3**.

Both margetuximab and pembrolizumab will be administered once every 3 weeks (one cycle). Both agents will be administered on the same day, with pembrolizumab administered first, followed by margetuximab. Each cycle of therapy is defined as 3 weeks, in which margetuximab and pembrolizumab will be given on Day 1. Tumor assessments will be performed every 6 weeks (i.e., following 2 cycles of treatment [prior to dosing for Cycles 3, 5, 7, etc.]) for the first 6 months on treatment; thereafter, tumor assessments will be performed every 12 weeks.

Assuming the patient remains clinically stable, has not experienced immune-related progressive disease (irPD), and does not experience unacceptable toxicity that necessitates permanent discontinuation of both study drugs, treatment with the combination treatment may continue for up to 2 years (**Section 4.4** and **Section 5.3**). Combination therapy with pembrolizumab and margetuximab will be discontinued after 2 years.

For patients who are otherwise clinically stable but have met conventional criteria for PD, therapy may be continued at the discretion of the investigator pending confirmation of progression at the next scheduled tumor assessment. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression, and that the investigator feels the patient may still derive benefit from continuation of therapy.

For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for irPD will have been met, and treatment with margetuximab and pembrolizumab should be discontinued. The patient should be removed from study participation after completion of protocol specified follow-up (see **Section 8.3** and **Appendix 1** and **Appendix 2**).

Efficacy Follow-up Period: Following the last dose of combination therapy, all patients will be followed for PFS and OS for up to 2 years or until 3 months after the last patient completes or discontinues study treatment.

4.1.2 Dose Escalation Phase (Part A)

The goal of the **Dose Escalation Phase (Part A)** is to initially characterize the safety and tolerability of margetuximab and pembrolizumab administered in combination, and more specifically to describe the DLTs for each dose level studied and to define the MTD or MAD (if no MTD is defined) based on the frequency of the occurrence of DLTs in each cohort during the **DLT Evaluation Period**.

For the purposes of guiding decisions regarding dose escalation, the **DLT Evaluation Period** is defined as the time following administration of the first dose of pembrolizumab up to the day of the second planned administration of pembrolizumab (i.e., 21 days following first dose of pembrolizumab - end of Cycle 1). DLTs are defined in **Section 4.2** and Dose Escalation Rules described in **Section 4.3**.

Margetuximab will be evaluated in two sequential escalating doses, 10 mg/kg and 15 mg/kg, in combination with 200 mg pembrolizumab in cohorts of 3 to 6 patients each. If it is determined that the MTD is exceeded in the first dose cohort, a dose de-escalation cohort to evaluate a lower dose of margetuximab (6 mg/kg) in combination with 200 mg pembrolizumab will be enrolled.

The dose escalation schema is outlined below:

Table 2 Margetuximab Dose Escalation Cohorts

Cohort	Margetuximab Dose	Pembrolizumab Dose
Cohort -1 [a]	6 mg/kg	200 mg
Cohort 1 [b]	10 mg/kg	200 mg
Cohort 2	15 mg/kg	200 mg

a To be evaluated only if the starting dose is determined to exceed the MTD.
b Starting dose level

An intermediate dose of margetuximab may be explored during the dose escalation portion of the study, based on review of the cumulative safety, efficacy, and/or PK data on the respective arms and based upon agreement between the investigators and the Sponsor. The Regulatory Agencies and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any additional dose level to be evaluated.

4.1.3 Cohort Expansion Phase

4.1.3.1 Cohort Expansion Phase (Part B)

During Part B of the Cohort Expansion Phase, 60 patients (30 each in North America and Asia) with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC will be

enrolled under the Original Protocol and Protocol Amendment 1 to receive margetuximab at the RP2D established from the **Dose Escalation Phase (Part A)** of the study (15 mg/kg) in combination with 200 mg pembrolizumab. The goals for this portion of the study will be to:

1. Provide a preliminary assessment of the antitumor activity of margetuximab in combination with pembrolizumab in patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC.
2. Further characterize the safety of margetuximab in combination with pembrolizumab at the MTD (or MAD); and
3. Further evaluate the PK, PD, and immunogenicity of margetuximab in combination with pembrolizumab.

4.1.3.2 Cohort Expansion Phase (Part C)

During Part C of the Cohort Expansion Phase, up to 25 patients in North America and/or Asia with unresectable locally advanced or metastatic HER2+ (IHC 3+) GC will be enrolled under Protocol Amendment 2 (as further described in **Section 5.1**) to receive the same regimen of margetuximab in combination with pembrolizumab as described above. The goal for this portion of the study will be to:

1. Provide a preliminary assessment of the antitumor activity of margetuximab in combination with pembrolizumab in patients with relapsed/refractory unresectable locally advanced or metastatic HER2 3+ (IHC3+) GC only (as defined in AJCC Cancer Staging Manual, 8th Edition) post-trastuzumab
2. Further characterize the safety of margetuximab at the MTD (or MAD) in combination with pembrolizumab; and
3. Further evaluate the PK, PD, and immunogenicity of margetuximab in combination with pembrolizumab.

4.1.4 Efficacy Follow-up Period

Following a patient's final dose of study drug (pembrolizumab or margetuximab, whichever is last), each patient will be followed during the **Efficacy Follow up Period**. The **Efficacy Follow up Period** will end 3 months after the last patient completes or discontinues treatment. During this time, patients will be followed at 12-week intervals for monitoring of progression-free survival and overall survival. Disease assessments should be done at office follow-up visits if patients are agreeable.

Prior to database lock for final OS analysis, survival data will be requested for all patients still in **Efficacy Follow-up Period**, regardless of the interval since the prior assessment.

4.2 Dose Limiting Toxicity

For the purposes of safety management and defining DLTs, the combination of margetuximab and pembrolizumab will be treated as one entity during Cycle 1 of the **Dose Escalation Phase (Part A)** (i.e., the **DLT Evaluation Period**). If a DLT considered related to one of the study drugs occurs during this period, administration of both agents will be stopped. One exception to this rule will be in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab infusion and before the first margetuximab administration. In this case, the toxicity will be attributed to pembrolizumab alone and will not count as a DLT of the combination of study drugs, and the patient will be replaced by another patient in the dose cohort.

In general, for patients who experience an AE that may meet the criteria for a DLT at any time during the course of the study, subsequent administration of the study drugs should be held pending management and/or resolution of the event and assessment of attribution to the study drugs. Criteria for subsequent continuation of therapy are outlined below. No intra-patient dose reductions of either margetuximab or pembrolizumab are allowed during the study.

4.2.1 Definitions

Dose limiting toxicities will be based on treatment-emergent drug-related AEs (or clinically significant laboratory abnormalities) occurring during the **DLT Evaluation Period** (defined as the time following administration of the first dose of pembrolizumab up to the day of the second planned administration of pembrolizumab [i.e., 21 days following first dose of pembrolizumab – end of Cycle 1]). The severity of AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Dose limiting toxicities are defined separately for hematologic and non-hematologic events as outlined below.

4.2.2 Hematologic Dose Limiting Toxicity

Hematologic DLT will be defined as follows:

- Grade 4 neutropenia lasting > 5 days
- ≥ Grade 3 febrile neutropenia lasting > 48 hours or any ≥ Grade 3 febrile neutropenia associated with hemodynamic compromise or objective evidence of infection
- Grade 4 thrombocytopenia, irrespective of duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- ≥ Grade 3 hemolysis

The following events will be specifically **excluded** from the definition of hematologic DLT:

- ≥ Grade 3 lymphopenia
- Grade 3 anemia that is not associated with other clinically significant complications

4.2.3 Non-Hematologic Dose Limiting Toxicity

Non-hepatic non-hematologic DLT will be defined as any ≥ Grade 3 non-hematologic event **with the following exceptions**:

- Grade 3 electrolyte abnormality that lasts less than 72 hours, is not otherwise associated with clinical complications, and responds to medical intervention
- Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
- Grade 3 nausea or vomiting that lasts < 72 hours and responds to medical intervention
- Grade 3 or 4 amylase and/or lipase elevation that is not associated with either clinical or radiographic evidence suggestive of pancreatitis
- Grade 3 diarrhea that lasts < 48 hours and responds to medical intervention
- Grade 3 gastrointestinal AEs of constipation, abdominal pain, cramping, dyspepsia or dysphagia that resolves to ≤ Grade 1 within 14 days with medical therapy
- Grade 3 fatigue that lasts < 7 days
- Grade 3 infusion-related reaction or cytokine release syndrome that lasts < 12 hours and responds to medical intervention.
- Grade 3 or 4 endocrinopathy that is adequately controlled with hormone supplementation
- Grade 3 skin toxicity that resolves to ≤ Grade 2 within 14 days of initiation of oral corticosteroids
- Grade 3 inflammatory reaction (e.g., with associated pain, swelling) attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.) that resolves to ≤ Grade 2 within 7 days with medical intervention

Note: The following Grade 2 or greater non-hematologic AE may also be considered as DLT:

- Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of study drug(s) due to patient intolerance.
- Any ≥ Grade 2 drug-related AE that results in > 7-day treatment delay would be considered a DLT.

- Any hepatic laboratory abnormalities meeting all three Hy's law criteria (described within **Section 4.2.4** below).
- Any Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 within 14 days of the initiation of topical therapy, or that requires systemic treatment.

4.2.4 Hepatic Non-Hematologic Dose Limiting Toxicity

- Any Grade 3 elevation of one or more Please see **Section 6.5.2.2** for further management guidelines.
- A Grade 3 elevation of total bilirubin. Please see **Section 6.5.2.2** for further management guidelines.
- Any event meeting the criteria for Hy's law as follows (all three features):
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × ULN.
    - Concurrent elevation of total bilirubin > 2 × ULN without initial evidence of cholestasis (e.g., elevated serum alkaline phosphatase [ALK-P])
    - No alternative etiology can be identified.

4.3 Dose Escalation Rules

The **Dose Escalation Phase (Part A)** of this trial will proceed using a conventional 3 + 3 approach, and will begin with enrollment of 3 patients at a dose of 200 mg pembrolizumab administered as an IV infusion once every 3 weeks and an initial dose of 10 mg/kg margetuximab administered as an IV infusion once every 3 weeks. Successive dose escalation cohorts will be enrolled as outlined below. The MTD or MAD will be determined based on the assessment of DLTs during the DLT Evaluation Period. Patients who are not evaluable for safety for the full DLT evaluation period for reasons other than study drug-related toxicity will be replaced in the same dose-level cohort.

- If 0 of the first 3 patients treated at a given dose level experience a drug-related DLT during the DLT evaluation period, the dose will be escalated and 3 patients will be enrolled and treated at the next higher dose level.
- If 1 of the first 3 patients treated at a given margetuximab dose level experiences a drug-related DLT, then 3 additional patients will be enrolled at that dose level (thus making a total of 6 patients in this cohort) to further assess the safety of the combination.

- If ≥ 1 of these 3 additional patients enrolled in the cohort experience a DLT (that is, ≥ 2 out of 6), it will be concluded that the MTD has been exceeded, and 3 patients will be enrolled and treated at the next lower dose level. If 0 of the 3 additional patients experiences a DLT (that is only 1 of 6 patients has experienced a DLT), then the dose will be escalated, and 3 patients will be enrolled at the next higher dose level.
- If ≥ 2 patients out of the first 3 patients treated at a given dose level, or ≥ 2 of 6 patients treated at a given dose level, experience a drug-related DLT, then it will be concluded that the MTD for margetuximab in combination with pembrolizumab has been exceeded at that dose level, and all subsequent patients will be treated at the next lower dose level.
- Note that in the circumstance in which a DLT occurs during or immediately following the first pembrolizumab infusion and before the first margetuximab administration, the toxicity will be attributed to pembrolizumab alone and will not count as a DLT of the combination of study drugs at the dose level under study. In this case the patient will be replaced by another patient in the dose cohort.
- A total of 6 patients were treated at the RP2D prior to enrolling in the Cohort Expansion Phases of the study.

Following these rules for dose escalation, the MTD/MAD for the combination of margetuximab and pembrolizumab will be defined as the dose level at which < 33% of patients experience a drug-related DLT during the DLT evaluation period. If no MTD is defined for the combination of margetuximab and pembrolizumab after escalation to the maximum protocol-specified dose, that dose level will be designated as the MAD.

Dose escalation to the next dose level is permitted only after the patients enrolled in the current dose cohort have competed the DLT evaluation period and safety data have been reviewed.

At the discretion of the Sponsor, dose escalation may be stopped before an MTD is reached. In this case, the MAD may be chosen based on an assessment of PK, PD, biomarker, safety, and response data. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.

4.4 Rules for Treatment Discontinuation

Patients who tolerate treatment with pembrolizumab and margetuximab may continue to receive additional treatment with the study drugs as specified in the protocol (see **Section 4.1.1**), until any one of the following conditions are met:

- After documentation of a confirmed complete response (cCR), the combination of margetuximab and pembrolizumab is continued for one more treatment cycle.
- Patient meets criteria for immune-related disease progression (irPD) (**Appendix 8**)
- Occurrence of drug-related DLT

- The Sponsor, investigator, or regulatory agency terminates the study
- Withdrawal of patient due to an AE or SAE
- Withdrawal of patient consent
- Completion of protocol defined therapy
- Investigator discretion
- Pregnancy
- Death
- Two years of pembrolizumab and margetuximab combination treatment

4.5 Guidelines for Dose Modifications

No intra-patient dose escalation will be allowed. No dose reductions will be allowed. Infusion rate reduction is allowed during re-challenge for patients experiencing an infusion reaction (**Section 6.5.1**). Patients who experience a DLT that is considered related to either study drug should be withdrawn from further pembrolizumab or margetuximab administration but will be followed-up for safety purposes.

4.5.1 Dose Delays

Patients who experience toxicity that is potentially dose-limiting should have study drug held pending assessment, management, and resolution of the toxicity. Specific guidance for the management of known toxicities associated with pembrolizumab and margetuximab treatment, including infusion-related reactions, immune-related adverse events (irAEs), and cardiotoxicities of special interest is provided in **Section 6.5**. For patients in whom the toxicity is assessed to be unrelated to study drug or for whom the toxicity does not meet the criteria for DLT or meet criteria for the known toxicities, therapy may be re-instituted at the same dose and schedule that was administered prior to the event, presuming the toxicity has resolved to ≤ Grade 1 in severity. Reinstitution of therapy shall be conducted as follows:

- For patients in whom the toxicity is assessed to be related to study drug, dose delays of up to 14 days are allowed (see exception for cardiotoxicities of special interest described in **Section 6.5.3**). This may include up to one missed dose. However, the procedures at the original scheduled missed visit should be performed as soon as possible and resumed as Day 1 of next cycle with treatment reinstituted after recovery from toxicity.
- For patients in whom the toxicity is assessed to be related to study drug, dose delays > 14 days will result in discontinuation of treatment (see exception for cardiotoxicities of special interest described in **Section 6.5.3**).

4.6 Rationale for Study Design

As described in **Section 2.4**, there is a strong rationale to evaluate the antitumor activity of the margetuximab and pembrolizumab combination in HER2+ GEJ and GC. The study is designed to determine the MTD or MAD (if no MTD is defined) of the combination in the Dose Escalation Phase (Part A) of the study. The DLT Evaluation period occurs within the first 3-week treatment cycle; patients who do not experience a DLT or other unacceptable toxicity, or clinically significant progressive disease (PD) (i.e., immune-related progressive disease [irPD]), will then be allowed to continue receiving combination margetuximab and pembrolizumab for up to two years. Once an MAD or MTD is defined, patients will be enrolled into a Cohort Expansion Phase. In this portion of the study, the combination of margetuximab and pembrolizumab will be evaluated in up to 85 evaluable patients (60 patients with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC enrolled in Part B [30 each in North America and Asia], and 25 patients in North America and/or Asia with unresectable locally advanced or metastatic HER2+ (IHC 3+) GC enrolled in Part C, using the MAD or MTD determined in the Dose Escalation Phase (Part A).

4.7 Study Duration

Margetuximab and pembrolizumab will be administered in combination once every 3 weeks for up to 2 years. It is expected that enrollment of Part A of the study will occur over approximately 6 months and that enrollment of Parts B - C of the study will take approximately 9-18 months.

The total time for conduct of the trial is expected to be approximately 60 months. These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

4.7.1 Patient Accrual

The number of patients enrolled in **the Dose Escalation Phase (Part A)** cannot be precisely determined in advance and could range up to 12 patients depending on results in the course of the trial and the number of margetuximab doses explored. This patient number does not take into account patient replacement for non-evaluable patients.

The **Cohort Expansion Phases (Parts B – C)** of the trial will enroll up to 85 patients. This includes 30 patients in North America and 30 patients in Asia with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC (Part B), and 25 additional patients in North America and/or Asia with unresectable locally advanced or metastatic HER2+ (IHC 3+) GC (Part C).

4.7.2 Definition of End of Trial

The end of study will occur after the last patient completes the **Efficacy Follow Up Period** (see **Section 4.1.4**) and the data collection process is complete (time of study database lock).

5 SELECTION AND WITHDRAWAL OF PATIENTS

Inclusion and exclusion criteria are designed to properly define the target population for study participation and to identify those patients who may not be appropriate candidates for study participation based on specific co-morbidities or other clinicopathologic features of their disease. 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

General:

1. Ability to provide informed consent and documentation of informed consent prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the patient's disease. Patients must also be willing and able to comply with study procedures, including the acquisition of specified research specimens.
2. Age ≥ 18 years old (minimum age dependent upon local regulations).
3. Patients may be male or female.
4. **Sixty patients in Part B:** Have histologically proven unresectable locally advanced or metastatic HER2+ gastroesophageal junction (GEJ) or gastric cancer (GC) determined as 3+ by IHC or 2+ by IHC and in situ hybridization– (ISH-) amplified (≥2.0) (as per College of American Pathologists/American Society of Clinical Oncology 2016 Guidelines) in most recent tumor biopsy.

   Twenty-five patients in Part C (GC only): As of Amendment 2, up to 25 additional patients will have histologically proven unresectable locally advanced or metastatic HER2+ GC (as defined in AJCC Cancer Staging Manual, 8th Edition) determined as 3+ by IHC (as per College of American Pathologists/American Society of Clinical Oncology 2016 Guidelines) in the most recent tumor biopsy.

5. Have received prior treatment with trastuzumab.
6. Have received treatment with one line of cytotoxic chemotherapy in the metastatic setting, which includes trastuzumab. Prior adjuvant therapy that resulted in relapse within 6 months of completion of therapy will be considered a line of treatment for metastatic disease. Eligible patients must have documented progression on/after the most recent line of therapy. Patients who discontinue trastuzumab for other reasons (e.g., financial) are eligible if they have documented progression on/after trastuzumab without receiving alternate treatment.
   - In Parts B and C, only one prior line of treatment that includes trastuzumab is allowed.
7. Resolution of all chemotherapy or radiation-related toxicities to ≤ Grade 1 (with exception of ≤ Grade 2 alopecia, stable sensory neuropathy, or stable electrolyte disturbances that are managed by supplementation).

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**Appendix 6**).
9. Life expectancy ≥ 12 weeks.
10. Measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (**Appendix 7**) and documented by computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients with evaluable disease only will not be enrolled on this study. Note: Lesions to be used as measurable disease for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.
11. Patients should have a formalin-fixed, paraffin embedded tumor specimen or unstained slides identified and available for analysis, to enable determination of the expression of HER2 and PD-L1 within tumor specimens using IHC staining.

Laboratory Features:

12. Acceptable laboratory parameters as follows:
    a. Platelet count ≥ $100 \times 10^3/\mu L$ without transfusion within 2 weeks prior to the initiation of study drug.
    b. Absolute neutrophil count (ANC) ≥ $1.5 \times 10^3/\mu L$ in the absence of any growth factor support within 2 weeks prior to the initiation of study drug.
    c. Hemoglobin (Hgb) ≥ 9 g/dL.
    d. ALT/ AST ≤ 3.0 × ULN; for patients with hepatic metastases, ALT and AST ≤ 5 × ULN.
    e. Total bilirubin ≤ 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
    f. Creatinine < 2 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.

Reproductive Features:

13. Female patients of childbearing potential (not surgically sterilized and between menarche and 1 year postmenopause) must have a negative urine pregnancy test performed within 72 hours prior to the initiation of study drug administration. Further, female patients of childbearing potential must agree to use highly effective contraceptive measures from the time of consent through 120 days after discontinuation of study drug administration.

For Canadian patients only: Female patients of childbearing potential must have a negative pregnancy test prior to every cycle of pembrolizumab.

- Highly effective methods of contraception include hormonal contraceptives, intrauterine device or system, vasectomy, or tubal ligation. If a highly effective method is not achievable then a "double barrier" method is an effective alternative in which the male partner must use a condom with spermicide and the female partner must use a diaphragm or cervical cap concurrently.

14. Male patients with partners of childbearing potential must use barrier contraception. In addition, male patients should also have their partners use another method of contraception from the time of consent through 120 days after discontinuation of study drug administration.
15. Is not pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the prescreening or screening visit through 120 days after the last dose of trial treatment.

Tumor Biopsy

16. At least 20 of the 60 patients enrolled in the Cohort Expansion Phase (Part B) under the Original Protocol and Protocol Amendment 1 must have one lesion considered to be potentially accessible to biopsy and be willing to provide consent for biopsy samples. An attempt at a tumor biopsy of locally accessible lesions will be made for at least 20 of the 60 patients. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be $\geq$ 2 cm in longest diameter. Tumor biopsies should only be obtained from lesions that are felt to be accessible with acceptable clinical risk in the judgment of the investigator.
    - The 25 patients enrolled into Part C will not be required to have pre- and on-treatment biopsies.
    - Diagnostic biopsy sample performed as standard of care will be collected from all patients on study.

Previous Checkpoint Inhibitor Therapy

17. Patients who have previously received an immune checkpoint inhibitor (e.g., anti-PD-L1, anti-PD-1 anti-CTLA-4) prior to enrollment must have toxicities related to the checkpoint inhibitor resolved to $\leq$ Grade 1 or baseline (prior to the checkpoint inhibitor) to be eligible for enrollment.

5.2 Exclusion Criteria

1. Patients with symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic, and meet the following at the time of enrollment:

a. No concurrent treatment for the CNS disease (e.g. surgery, radiation, corticosteroids ≥ 10 mg prednisone/day or equivalent).
b. No progression of CNS metastases on MRI or CT for at least 21 days after last day of prior therapy for the CNS metastases.
c. No concurrent leptomeningeal disease or cord compression.

2. Patients who experienced the following immune checkpoint inhibitor-related AEs (i.e., the following AEs make the patient ineligible despite the AE resolving to ≤ Grade 1 or baseline):
    a. ≥ Grade 3 ocular AE.
    b. Changes in liver function tests that met the criteria for Hy's Law (> 3 × ULN of either ALT/AST with concurrent >2 × ULN of total bilirubin and without alternate etiology).
    c. ≥ Grade 3 neurologic toxicity.
    d. ≥ Grade 3 colitis or pneumonitis.

3. 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 that are now clinically stable with replacement therapy and by laboratory testing.
    a. Patients with history of psoriatic arthritis are excluded.

4. History of prior allogeneic bone marrow, stem-cell or solid organ transplantation.
5. Treatment with any systemic anti-neoplastic therapy, or investigational therapy within the 3 weeks prior to the initiation of study drug administration. Adjuvant hormonal therapy for treatment of prostate or breast cancer is allowed.
6. Treatment with radiation therapy within 3 weeks prior to the initiation of study drug administration.
7. Treatment with corticosteroids (≥ 10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to the initiation of study drug administration. Steroids for topical, ophthalmic, inhaled or nasal administration are allowed.
8. History of 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 drug.
    b. Stroke or transient ischemic attack within 6 months prior to the initiation of study drug.
    c. Clinically significant cardiac arrhythmias.

d. Uncontrolled hypertension: systolic blood pressure (SBP) >180 mmHg, diastolic blood pressure (DBP) >100 mmHg.
e. Congestive heart failure (New York Heart Association [NYHA] class III-IV).
f. Pericarditis or clinically significant pericardial effusion.
g. Myocarditis.
h. Left ventricle ejection fraction (LVEF) < 50% by echocardiogram or multi-gated acquisition (MUGA) scan.

9. Clinically significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation.
10. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
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. History of clinically significant gastrointestinal bleeding within 4 weeks prior to the initiation of study drug.
    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. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study drug. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than one week prior to the initiation of study drug.
13. Known positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome.
14. Known history of hepatitis B or hepatitis C infection or known positive test for hepatitis B surface antigen, hepatitis B core antigen, or hepatitis C polymerase chain reaction (PCR).
15. History of another malignancy or a concurrent malignancy. Exceptions include patients who have been disease free for two years, or successfully treated for non-melanoma skin cancer, localized prostate cancer (Gleason Score <6) or carcinoma in situ, for example cervical cancer in situ, are eligible.
16. History of trauma or major surgery within 4 weeks prior to the initiation of study drug administration.

17. Any serious underlying medical or psychiatric condition that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site.
18. Known hypersensitivity to recombinant proteins, polysorbate 80 or any excipient contained in the drug or vehicle formulation for margetuximab or pembrolizumab (**Section 6.1**).
19. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
20. 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 120 days after the last dose of trial treatment.
21. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
22. Employees of MacroGenics, Inc., and Merck & Co., Inc., unless approved by institutional IRB and principal investigator.
23. Prisoners or other individuals who are involuntarily detained.
24. Any issue that in the opinion of the investigator, would contraindicate the patient's participation in the study or confound the results of the study.

5.3 Withdrawal of Patient from the Study

If the investigator decides that the patient should be withdrawn from the study or from dosing for any reason other than disease progression, the Sponsor or its designee must be alerted within 24 hours via an Immediately Reportable Event form (**Section 7.9.6**).

Patients who withdraw before Study Day 21 during the Dose Escalation Phase (Part A) for a reason unrelated to drug toxicity may be considered to have inadequate data to support dose escalation. In this case, replacement patients may be enrolled in the same dose level.

Procedures for handling patients who fail to appear for study visits and criteria regarding when to consider patients lost-to-follow-up will be defined in the Study Manual.

5.3.1 Guidelines for Study Discontinuation

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

- Completion of protocol defined follow-up period.
- Uncontrolled intercurrent illness unrelated to cancer that renders continuing study follow-up unsafe or regular study visits impossible.
- The Sponsor, investigator, or regulatory agency terminates the study.
- The patient requests to be discontinued from the study, i.e., withdrawal of consent.
- Noncompliance with protocol-required evaluations.
- The patient exhibits progression of disease (according to irRC).
- Death

6 STUDY TREATMENTS

6.1 Description of Treatments and Study Drug and Supplies

Both study drugs will be administered as an open-label IV solution, followed by observation.

Under no circumstances is the investigator allowed to release these clinical supplies for use by another physician not named on Form FDA 1572 (and/or country or region equivalent document) or to administer study drug to a patient who is not enrolled in this study. Study drug must be dispensed at an institution specified on Form FDA 1572 (or equivalent document).

6.1.1 Margetuximab

Margetuximab is a sterile, clear-to-slightly-opalescent, colorless-to-pale-yellow or pale-brown, preservative-free solution for IV administration. Some visible, translucent, proteinaceous, margetuximab particles may be present. Margetuximab is supplied in single-use, 10-mL clear glass vials with FluroTec® coated gray butyl rubber serum stoppers and aluminum seals with plastic overseals. Each vial contains 250 mg margetuximab (25 mg/mL) in 10 mL of solution. The product is formulated in a buffer containing 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, in Sterile Water for Injection, pH 6.1.

6.1.2 Pembrolizumab

Pembrolizumab (marketed as KEYTRUDA® by Merck & Co., Inc, Whitehouse Station, NJ 08889 U.S. License No. 0002) is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Pembrolizumab is supplied as lyophilized powder in a single-use vial for reconstitution or as solution for infusion in single-use vials.

Table 3 Pembrolizumab Product Descriptions

Product Name	Dosage Form and Strength
MK-3475	For Injection: 50 mg lyophilized powder in single-dose vial for reconstitution or Injection: 100 mg/4 mL solution in single-use vial

Pembrolizumab lyophilized powder is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted with 2.3 mL Sterile Water for Injection, USP and diluted for IV infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab solution for infusion is a sterile, non-pyrogenic aqueous solution supplied in a vial containing 100 mg/4 mL of pembrolizumab.

6.2 Drug Preparation

6.2.1 General Guidelines and Precautions

The calculated dose of margetuximab will be administered based on the patient's actual weight at Day 1. Significant (≥ 10%) change in body weight from baseline should prompt recalculation of dose.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis or infusion-related reactions (including CRS) should be observed during both margetuximab and pembrolizumab administration. Supportive measures may include, but are not limited to: epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. Please refer to **Section 6.5.1** for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

Separate infusion bags must be used for each infusion. Pembrolizumab is to be administered first.

An effort should be made to begin the margetuximab infusion within 30 minutes after the completion of the pembrolizumab infusion. It is understood that this window may not always be attainable, but is the preferred window of time to administer margetuximab.

6.2.2 Pembrolizumab Preparation

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

6.2.3 Margetuximab Preparation

The Pharmacy Manual contains specific instructions for the preparation of the margetuximab infusion and administration of infusion solution.

6.2.4 Placebo or Control

There will be neither placebo nor active control drug for this study.

6.3 Study Drug Administration

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (i.e. elective surgery, unrelated medical events, patient vacation, holidays, etc.) not related to study therapy.

6.3.1 Pembrolizumab Administration

The pembrolizumab infusion solution should be administered over 30 minutes through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter using an infusion pump. Do not co-administer other drugs through the same infusion line.

6.3.2 Margetuximab Administration

After pembrolizumab administration, margetuximab will be administered as a 120-minute (2-hour) IV infusion using a sterile PES 0.2 micron filtered administration set. *Margetuximab should not be administered as an IV push or bolus.*

Margetuximab should not be mixed or diluted with other drugs.

6.4 Selection and Timing of Dose for Each Patient

Patients will be assigned to successive dose cohorts as described in **Section 4.1.2** and **Section 4.1.3**. On each treatment day, pembrolizumab will be administered first, followed by margetuximab administration within 30 to 120 minutes following completion of pembrolizumab infusion.

6.5 Potential Adverse Events and Supportive Care Measures

6.5.1 Infusion-Related Reactions Including Cytokine Release Syndrome

Infusion reactions (including cytokine release syndrome [CRS]) associated with either margetuximab or pembrolizumab 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-TNFα antibodies, and/or IL-6 inhibitors).

Patients should be monitored closely for the development of infusion-related reactions during the pembrolizumab and margetuximab 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 and may include, but are not limited to: subcutaneous (SC) epinephrine (0.3 to 0.5 mL of a 1:1000 solution), antihistamines (e.g., diphenhydramine 25 to 50 mg IV), corticosteroids (e.g., dexamethasone 20 mg IV push or equivalent), IV fluids, vasopressors, oxygen, bronchodilators, and antipyretics. Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available. The patient should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal patient care will be provided throughout the study according to institutional standards.

Should symptoms of fever or chills develop it may be difficult to distinguish among potential causes of the symptoms including emerging infection, or infusion reaction. Patients should be evaluated carefully for the presence of infection, with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate based on the assessment of the

investigator. Please refer to **Section 6.5.1.3** for guidance regarding the management of infusion reactions.

If a patient has a Grade 1 or 2 infusion reaction with pembrolizumab and the investigator considers it prudent, based on medical judgment, for a delay of the patient's margetuximab drug administration at the scheduled infusion time, the margetuximab dose may be administered on the following day (the day after the pembrolizumab infusion). For Grade 3 infusion reactions with pembrolizumab that resolve completely or to Grade 1 within 12 hours, the scheduled dose of margetuximab may be administered the following day with premedications as listed below.

6.5.1.1 Grading of Infusion Reactions

Infusion reactions will be categorized as follows:

- Grade 1: mild reaction; infusion interruption not indicated, intervention not indicated; Note: although interruption in infusion is not indicated, temporary rate reduction indicated before resuming original rate, as patient tolerates (see **Section 6.5.1.3**);
- Grade 2: therapy or infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs (NSAIDS), narcotics, IV fluids]; prophylactic medications indicated for ≤ 24 hours;
- Grade 3: prolonged (e.g., not rapidly responsive to medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates);
- Grade 4: life-threatening consequences; pressor or ventilatory support indicated;
- Grade 5: death.

The above grading scale is the CTCAE v 4.03 grading scale for infusion reaction, which is nearly identical to the CTCAE v 4.03 grading scale for cytokine release syndrome and allergic reaction, and therefore considered appropriate for grading all infusion reactions in this study, irrespective of the underlying mechanism of the reaction. The Sponsor's Medical Monitor or designee should be contacted immediately if questions arise concerning the grade of the reaction.

6.5.1.2 Premedications and Prophylaxis

Premedication should be administered per institutional standards and investigator's criterion. 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.

Prior to first infusion of pembrolizumab (Cycle 1, guidelines to be followed):

- Acetaminophen 650-1000 mg orally (PO) or ibuprofen 400 mg PO
- Diphenhydramine 50 mg PO or IV or equivalent H1 antagonist

- Ranitidine 300 mg PO or IV or equivalent H2 antagonist
- Dexamethasone 20 mg IV

Only one dose of pre-infusion prophylaxis steroids administered prior to pembrolizumab may be required. Non-steroidal pre-medications may be administered prior to the subsequent margetuximab infusion if warranted.

If prophylaxis was used prior to pembrolizumab infusion, no steroidal prophylaxis is needed prior to margetuximab infusion; non-steroidal prophylaxis may be employed per clinical discretion of the investigator.

For all subsequent administrations of pembrolizumab and margetuximab, patients who had infusion reactions who were not adequately or only moderately controlled with acetaminophen, diphenhydramine, or ranitidine, IV dexamethasone at doses of 4 mg may be considered.

6.5.1.3 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. Note that these apply to both margetuximab and pembrolizumab:

- Grade 1:
  - Slow the infusion rate by 50%.
  - Monitor the patient for worsening of condition.
  - Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated to the initial rate. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
  - If a patient has an infusion reaction with pembrolizumab, the margetuximab infusion can be given (without prophylactic medications) on the same day if the infusion reaction resolves within 3 hours. For scheduling purposes, the margetuximab infusion may be given the next day if the reaction lasts greater than 3 hours.
  - If a patient has an infusion reaction with pembrolizumab, prophylactic preinfusion medications should be given prior to all subsequent pembrolizumab infusions as written below for Grade 1 infusion reactions.
  - If a patient has an infusion reaction with margetuximab, prophylactic preinfusion medications should be given prior to all subsequent margetuximab infusions as written below.

- The following prophylactic preinfusion medications are recommended prior to future infusions of margetuximab and/or pembrolizumab for patients who experience Grade 1 infusion reactions: diphenhydramine 50 mg PO or IV (or equivalent) and/or acetaminophen 650 mg PO at least 30 minutes before additional study drug administrations.
- Report as an Adverse Event of Special Interest (AESI) by completing the appropriate eCRF page.

- Grade 2:
  - Stop the infusion.
  - Administer diphenhydramine hydrochloride 25-50 mg IV, acetaminophen 650 mg PO for fever, and oxygen and bronchodilators for mild bronchospasm.
  - Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30 minutes, as tolerated. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
  - Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.
  - If a patient has an infusion reaction with pembrolizumab:
    - The margetuximab infusion can be administered on the same day if the infusion reaction resolves within 3 hours. The margetuximab infusion may be given the next day if the infusion reaction last longer than 3 hours.
    - Premedication of diphenhydramine hydrochloride 25-50 mg IV and acetaminophen 650 mg PO should be administered 30 minutes prior to the margetuximab dose. If no corticosteroids were given for the pembrolizumab infusion reaction, dexamethasone 20 mg IV may be considered prior to margetuximab administration.
    - Prophylactic pre-infusion medications should be given prior to all subsequent pembrolizumab infusions. Patients who experience a Grade 2 infusion reaction should be pre-medicated with diphenhydramine hydrochloride 25-50 mg IV and acetaminophen 650 mg PO for subsequent doses of pembrolizumab.
  - If a patient has an infusion reaction with margetuximab, prophylactic pre-infusion medications should be given prior to all subsequent margetuximab infusions.

- For patients with Grade 2 infusion reactions despite premedication with diphenhydramine and acetaminophen, corticosteroids (dexamethasone 20 mg IV) should be considered for acute management of the event and should be added to the premedication regimen for subsequent dosing of pembrolizumab and /or margetuximab.
- Report as an Adverse Event of Special Interest by completing the appropriate eCRF page.

- Grade 3:
  - STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
  - TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN.
  - Administer diphenhydramine hydrochloride 25-50 mg IV, dexamethasone 20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (e.g. methylprednisolone 2-4 mg/kg IV or the equivalent) may also be considered for acute management.
  - IV fluids, supplemental oxygen and bronchodilators should be considered as appropriate.
  - **Grade 3 infusion reaction:** If the Grade 3 infusion reaction occurs with pembrolizumab, both margetuximab and pembrolizumab will be discontinued for that day. If symptoms have resolved to baseline within 12 hours, margetuximab may be infused the next day. Pembrolizumab would be re-challenged at the next scheduled infusion cycle, with a 50% reduction of infusion rate. In addition, patients should be pre-medicated for this re-challenge and for any subsequent doses of pembrolizumab with the following: diphenhydramine hydrochloride 25-50 mg IV, oral acetaminophen 625 mg and dexamethasone 20 mg IV. Margetuximab dosing can be resumed with at the next scheduled infusion day if the pembrolizumab Grade 3 infusion reaction resolved to grade 1 within 12 hours. Patients who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further margetuximab or pembrolizumab treatment.
  - Patients who experience a second Grade 3 infusion reaction at the time of re-challenge of margetuximab or pembrolizumab (irrespective of duration of first Grade 3 reaction) will permanently discontinue margetuximab and pembrolizumab.
  - Report as an Adverse Event of Special Interest and an Immediately Reportable Event (IRE) within 24 hours.
  - Report the event as a SAE, if appropriate.

- Grade 4:
  - STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
  - TO AVOID EXACERBATION OF INFUSION REACTION OR CRS: DO NOT FLUSH THE TUBING.
  - Administer diphenhydramine hydrochloride 50 mg IV, methylprednisolone 2-4 mg/kg IV (or more as considered appropriate), and other medications/treatment as medically indicated (e.g., an IL-6 receptor inhibitor or IL-6 inhibitor, an IL-2 receptor inhibitor, and/or an anti-TNFα antibody).
  - Give epinephrine or bronchodilators as indicated.
  - Support ventilation and blood pressure as indicated.
  - Report as an Adverse Event of Special Interest and an IRE within 24 hours.
  - Report the event as an SAE.
  - Patients who have a Grade 4 infusion reaction will not receive further margetuximab or pembrolizumab.

- Grade 5:
  - Report as an IRE within 24 hours.
  - Report the event as an SAE.

All changes in the infusion of either margetuximab or pembrolizumab, including interruption of the infusion and its duration as well as reductions in infusion rate and duration, must be recorded.

6.5.2 Immune-Related Adverse Events

A high level of awareness for the possibility that an AE may be an immune-related AE (irAE) is necessary in the management of patients receiving pembrolizumab because the presentations of an irAE can be subtle, and other causes must be ruled out. An irAE can occur at any point during treatment with pembrolizumab. It is imperative to establish the correct diagnosis promptly, determining severity based on Common Terminology Criteria for Adverse Events (CTCAE) grading and initiating treatment with steroids, if necessary, and holding further pembrolizumab treatment is essential **(49)**.

Immune checkpoint blockade therapies have been associated with several syndromes resulting from the breaking of immunological tolerance in normal tissues **(34, 60, 72)**. These syndromes include but are not limited to: pneumonitis, colitis, autoimmune hepatitis, arthritis, glomerulonephritis, myocarditis and cardiomyopathy, hypophysitis, thyroiditis, or other autoimmune endocrinopathies. The occurrence of any of these syndromes dictates interruption and potentially discontinuation of study drug administration pending further evaluation and reporting them to the Sponsor as AESIs. Most low-grade immune-related AEs (irAEs) can be

managed symptomatically. Persistent low grade or moderate toxicities may require treatment with corticosteroids or in refractory cases other immune suppressing agents such as mycophenolate or infliximab. High-grade immune-related toxicities will, in almost all cases, require treatment with corticosteroids.

For the purposes of the safety management, no distinction should be made as to which drug is the causative agent and both agents stopped (temporarily held or discontinued).

Temporary interruptions of margetuximab and/or pembrolizumab 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 v4.03.

6.5.2.1 Diarrhea or Colitis

Diarrhea that develops in patients while receiving pembrolizumab may reflect immune reactivity against normal colonic epithelium and careful monitoring for potential immune related colitis should be instituted. Patients should be monitored closely for evidence of diarrhea or other change in bowel habits as well as other signs and symptoms suggestive of colitis. Patients who develop signs or symptoms including abdominal pain, bloating, nausea, vomiting, diarrhea or blood in the stools should be evaluated carefully for potential colitis.

- Grade 1 diarrhea
  - Closely monitor the diarrhea until resolution.
- Grade 2 diarrhea
  - Hold pembrolizumab and margetuximab
  - Increase frequency of monitoring until resolution
  - Symptomatic management
    - Loperamide/diphenoxylate
    - Consider low dose steroids, if clinically indicated.
  - Consider management as per Grade 3 diarrhea with prolonged Grade 2 event lasting more than 5 to 7 days or relapsed diarrhea.
- Grade 3 diarrhea
  - Hold pembrolizumab and margetuximab
  - Hospitalize patient promptly for further evaluation and management including:
    - Bowel rest
    - Supplemental IV fluids with close monitoring of fluid and electrolyte status.

- Monitoring of frequency of bowel movements
  - Consider imaging to rule out bowel obstruction or perforation
  - Consideration of colonoscopy as appropriate
  - Implementation of initial empiric immune suppression consisting of IV corticosteroids using methylprednisolone at a dosage of 2 mg/kg/day divided twice daily. As tolerated, patients may be converted to oral corticosteroids (i.e., prednisone 2 mg/kg/day divided twice daily) and tapered as appropriate guided by the patients' clinical status.
  - Taper corticosteroids as clinically indicated
  - For patients with severe colitis, or those who do not respond to corticosteroids, additional immune suppression with anti-TNF-α antibodies (i.e., infliximab) should be considered early in the course.
- Consider restarting pembrolizumab and margetuximab if:
  - It is determined there is no colitis and an alternative cause of diarrhea is found, and
  - Diarrhea resolves to ≤ Grade 1 within 14 days

- Grade 4 diarrhea
  - Discontinue pembrolizumab and hold margetuximab
  - Treat as for Grade 3

6.5.2.2 Hepatic Toxicity

6.5.2.2.1 Elevations in Transaminases

Management guidelines for patients experiencing hepatic toxicity are as follows:

- Grade 1 elevations
  - No specific therapy required
- Grade 2 elevations
  - For elevations in transaminases 3 to 5 × ULN (Grade 2), rule out viral and other etiologies, and consider immediate oral steroids such as prednisone 60 mg/day divided twice daily, and hold pembrolizumab and margetuximab.
  - If improvement to ≤ Grade 1 does not occur within 48 hours with oral steroids, consider IV steroids such as methylprednisolone at 2 mg/kg/day divided twice daily or oral steroids such as prednisone 60 to 120 mg per day, divided twice daily

- Resume pembrolizumab and margetuximab at the next scheduled dose if:
  - No more than one dose of pembrolizumab and margetuximab was missed
- If improvement to ≤ Grade 1 does not occur within 14 days, discontinue pembrolizumab and margetuximab.

- Grade 3 elevations
  - Discontinue pembrolizumab and margetuximab
    - Initiate IV steroids and,
    - If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate. Do not use infliximab in these cases because of a potential for autoimmune hepatitis **(40)**.
    - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
- Grade 4 elevation
  - Discontinue pembrolizumab and margetuximab
  - Treat as for Grade 3 elevation.

6.5.2.2.2 Elevations in Total Bilirubin

Management guidelines for patients experiencing elevations in total bilirubin are as follows:

- Grade 1 elevations
  - No specific therapy required
- Grade 2 elevations
  - Hold pembrolizumab and margetuximab until improvement to ≤ Grade 1.
  - Consider oral steroids
  - If improvement to ≤ Grade 1 does not occur within 14 days, discontinue pembrolizumab and margetuximab and begin oral steroids.
- Grade 3 elevations
  - Discontinue pembrolizumab and margetuximab
    - For elevations in total bilirubin > 5 × ULN, permanently discontinue pembrolizumab and margetuximab and initiate IV steroids and,

        - If no response to corticosteroid therapy within 3 to 5 days is observed, consider adding immune suppression therapy with mycophenolate. Do not use infliximab in these cases because of a potential for autoimmune hepatitis **(40)**.
        - Monitor liver function testing at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
- Grade 4 elevations
    - Discontinue pembrolizumab and margetuximab
    - Treat as for Grade 3 elevation

6.5.2.3 Pneumonitis

Management guidelines for patients experiencing pneumonitis, are as follows:

- Grade 1 pneumonitis
    - No specific therapy required; close monitoring of lung function and imaging
- Grade 2 pneumonitis
    - Hold pembrolizumab and margetuximab. Begin corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent, per day divided twice daily
        - Taper over 4 weeks as clinically indicated
    - Resume pembrolizumab and margetuximab administration at next scheduled dose if pneumonitis resolves to ≤ Grade 1 within 3 days with or without treatment.
    - Permanently discontinue pembrolizumab and margetuximab for recurrent Grade 2 pneumonitis.
- Grade 3 and 4 pneumonitis
    - Permanently discontinue pembrolizumab and margetuximab.
    - Hospitalize
    - Initiation of maximal supportive care including IV corticosteroids, suggest methylprednisolone at 2-4 mg/kg/day divided twice daily. Higher doses may be used in consultation with the Sponsor's medical monitor
    - If no response to corticosteroid therapy is observed within 3-5 days, consider adding immune suppression therapy (i.e., infliximab, etc.)

6.5.2.4 Dermatologic Toxicity

Management guidelines for patients experiencing dermatologic toxicity are as follows:

- Grade 1 or 2 skin reactions
    - Symptomatic treatment with low-dose topical corticosteroids (betamethasone 0.1% or hydrocortisone 1%) or antihistamines (diphenhydramine).
    - Persistent (7-14 days) Grade 1 or 2 rash should be managed with higher dose topical corticosteroids and/or oral prednisone (1-2 mg/kg/day) if there is not improvement with initial topical therapies or the rash is associated with other dermal toxicities such as pruritus.
- Grade 3 skin reactions
    - Hold pembrolizumab and margetuximab. Initiate oral corticosteroids (oral prednisone 1-2 mg/kg/day)
    - Pembrolizumab and margetuximab combination administration may be restarted at the next scheduled dosing if symptoms resolve to ≤ Grade 2 within 14 days.
    - Grade 3 skin toxicity that does not resolve to ≤ Grade 2 within 14 days of initiation of oral corticosteroids requires permanent discontinuation of study drugs.
- Grade 4 skin reactions
    - Discontinue pembrolizumab and margetuximab.
    - Initiate oral corticosteroids (oral prednisone 1-2 mg/kg/day)
    - Consideration should be given to start IV corticosteroids (methylprednisolone 1-2 mg/kg/day) for Grade 4 dermatologic toxicities with tapering on resolution to < Grade 2 over 30 days.

6.5.2.5 Nephritis/Renal Failure

Management guidelines for patients experiencing nephritis are as follows:

- Grade 1 nephritis
    - No specific therapy required; close monitoring of renal function
- Grade 2 nephritis
    - Hold pembrolizumab and margetuximab
    - Consider nephrology consultation and renal biopsy to confirm interstitial nephritis.
    - Begin corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent, per day divided twice daily
        - Taper over 4 weeks as clinically indicated
    - Resume pembrolizumab and margetuximab administration at next scheduled dose if:

        - Nephritis resolves to ≤ Grade 1 within 14 days with or without treatment

- Grade 3 and 4 nephritis
    - Permanently discontinue pembrolizumab and margetuximab
    - Consider hospitalization, nephrology consultation, and renal biopsy to confirm interstitial nephritis
    - Begin corticosteroids: 2 to 4 mg/kg of oral or IV prednisone or equivalent, per day divided twice daily
        - Taper over 4 weeks as clinically indicated

6.5.2.6 Immune-Mediated Hypophysitis

Management guidelines for patients experiencing hypophysitis are as follows:

- Grade 2 or 3 hypophysitis documented on MRI
    - Hold pembrolizumab and margetuximab
    - Consult endocrinologist
    - Consider hospitalization
    - Begin short course of high dose IV corticosteroids: e.g., methylprednisolone 2-4 mg/kg IV (or equivalent) divided twice daily
    - Initiate hormonal replacement as indicated
    - Pembrolizumab and margetuximab combination treatment may be resumed as allowed by protocol when
        - Endocrinopathy is controlled with appropriate replacement therapy
        - Corticosteroid dose reduced to ≤ 10 mg prednisone or equivalent per day
    - Repeat brain MRI as clinically indicated
- Grade 4 hypophysitis
    - Permanently discontinue pembrolizumab and margetuximab.

6.5.2.7 Thyroid Toxicity

Thyroid disorders can occur at any time during treatment with pembrolizumab. Monitor patients for changes in thyroid function per protocol and as indicated based on clinical evaluation and for clinical signs and symptoms of thyroid disorders. Isolated hypothyroidism may generally be managed with replacement therapy without treatment interruption and without corticosteroids, and a suggested treatment guideline for hyperthyroidism is described below:

- Grade 1 hyperthyroidism
  - No specific therapy required
- Grade 2 hyperthyroidism
  - Hold pembrolizumab and margetuximab
  - Consider starting oral corticosteroid therapy
  - Resume pembrolizumab and margetuximab if corticosteroid dose is reduced to ≤ 10 mg prednisone or equivalent per day and stable on hormone replacement therapy (if necessary).
- Grade 3 or 4 hyperthyroidism
  - Hold pembrolizumab and margetuximab
  - Consider hospitalization and consulting endocrinologist
    - Begin IV corticosteroids such as methylprednisolone 2-4 mg/kg IV (or equivalent) divided twice daily
  - Initiate hormonal replacement as necessary
  - May consider restarting pembrolizumab and margetuximab with complete resolution or stable on hormone replacement therapy within 14 days

6.5.2.8 Type 1 Diabetes Mellitus

The following guidelines should be followed for diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

- For **T1DM** or **Grade 3-4** Hyperglycemia
- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

6.5.2.9 Other Immune-Related AEs

- Intolerable/persistent Grade 2
  - Hold pembrolizumab and margetuximab
  - Based on the type and severity of AE, administer corticosteroids
  - Ensure adequate evaluation to confirm etiology and/or exclude other causes

- Grade 3
  - Hold or discontinue pembrolizumab and margetuximab based on the type of event
    - Discontinuation is required for AEs such as, but not limited to, Guillain-Barré Syndrome and encephalitis
    - Recurrence of the same Grade 3 toxicity requires discontinuation
- Grade 4
  - Permanently discontinue

6.5.3 Cardiotoxicities of Specific Interest

6.5.3.1 Decreased Left Ventricular Ejection Fraction

Left ventricular ejection fraction (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.

Specifically, for events of decreased cardiac function, patients will be discontinued from further treatment if either of the following criteria are met:

- ≥ 15% absolute decrease in LVEF from pre-treatment values, or
- LVEF below institutional normal limits (or 50% if no limits are available) and ≥ 10% absolute decrease in LVEF from pretreatment values

6.5.3.2 Myocarditis

- Grade 1 or 2 myocarditis
  - Hold pembrolizumab and margetuximab
  - Based on severity, administer corticosteroids
  - Ensure adequate evaluation to confirm etiology and/or exclude other causes
- Grade 3 or 4 myocarditis
  - Permanently discontinue pembrolizumab and margetuximab
  - Based on severity, administer corticosteroids
  - Ensure adequate evaluation to confirm etiology and/or exclude other causes

6.6 Method of Assigning Patients to Treatment Groups

Patients will be assigned sequentially to the dose escalation cohorts and cohort expansion portions of the study.

6.7 Blinding

This is an open-label study and no blinding will be employed.

6.8 Concomitant Therapy

Margetuximab and pembrolizumab are the only anti-cancer drugs to be administered routinely in this study. No concomitant anti-cancer therapy will be given with exception of adjuvant hormonal therapy for treatment of patients with breast or prostate cancer. All concomitant medications and blood products administered during the patient's participation in the study until the post treatment follow-up visit must be recorded in the source document and on the electronic Case Report Form (eCRF). All changes in infusions, including interruptions and their duration as well as reductions in rate and duration must be recorded.

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

- Any other anti-neoplastic therapies including but not limited to chemotherapy or other small molecules, biologics, or radiotherapy are not allowed. For patients who require palliative radiotherapy (i.e., cumulative dose less than 3000 rads, limited field of distribution) for reasons other than disease progression, therapy with margetuximab and/or pembrolizumab may be interrupted for up to 4 weeks. Palliative radiotherapy may not be given concurrently with either margetuximab or pembrolizumab. Treatment with palliative therapy should be initiated at least 24 hours after receiving either margetuximab or pembrolizumab, and re-initiation of margetuximab or pembrolizumab can begin seven (7) days after the completion of palliative radiotherapy if there were no complications associated with the radiotherapy. Palliative radiotherapy fields also should not overlap tumor lesions that have previously been designated as target lesions. In the event that this is medically necessary for palliative purposes, the patient may continue on study, but will no longer be evaluable for objective response from the time palliative radiotherapy is initiated.
- Patients may not receive other investigational drugs during the period of study participation.

- Because margetuximab has the capacity to induce ADCC and pembrolizumab has 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 in excess of 10 mg daily of prednisone or equivalent is prohibited other than for the management of drug-related adverse experiences. Steroids or other immune suppression therapy may be employed in the treatment of suspected margetuximab or pembrolizumab-associated immune-inflammatory or autoimmune AEs in consultation with the Sponsor. Note: inhaled steroids are allowed for management of asthma.
- The use of other immuno-suppressive agents is prohibited, unless they are being used to treat an adverse event.
- Use of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor or other growth factors is prohibited.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial 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. Flu - Mist®) are live attenuated vaccines, and are not allowed.

Patients may receive the following concurrent therapy:

- 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 and should be documented on the concomitant medication form. IV fluids used for symptomatic treatment/hydration should also be documented on the medication form.
- Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitors is allowed.
- All patients should use highly effective methods of contraception during treatment and for a period of 7 months after discontinuation of treatment. Highly effective birth control includes hormonal contraceptives, intrauterine device or system, vasectomy, or tubal ligation. If a highly effective method is not achievable, then a “double barrier” method is an effective alternative in which the male partner must use a condom with spermicide and the female partner must use a diaphragm or cervical cap concurrently.

6.9 Restrictions

6.9.1 Prior Therapy

Prior therapy restrictions are described in the inclusion/exclusion criteria specified in **Section 5**.

6.9.2 Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study, although it is recommended that, to the extent possible, patients have a fluid intake of ≥ 2 liters on days associated with PK sampling, and that electrocardiograms will be obtained pre-meal.

6.9.3 Patient Activity Restrictions

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

6.10 Treatment Compliance

Margetuximab and pembrolizumab will be administered by healthcare professionals under the supervision of the investigators. Records of margetuximab and pembrolizumab 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 investigational site visits and at the completion of the study.

6.11 Packaging and Labeling

6.11.1 Pembrolizumab

Pembrolizumab will be provided by MacroGenics in the commercial packaging, with an auxiliary label indicating for clinical trial use only.

Pembrolizumab is supplied as follows:

- KEYTRUDA® (pembrolizumab) for injection (lyophilized powder): carton containing one 50 mg single-use vial (NDC 0006-3029-02), or as solution for infusion in one 100 mg single use vial.

Please see the Pharmacy Manual for detailed information about the packaging and labeling of pembrolizumab.

6.11.2 Margetuximab

Margetuximab will be supplied in 250 mg/10 mL (25 mg/mL) single-use vials. Margetuximab will be labelled according to local regulatory health authority requirements. Please see the Pharmacy Manual for detailed information about the packaging of margetuximab.

Normal saline in 250-mL (or other) IV bags will be obtained from the institution's usual commercial supplier for the dilution of margetuximab solution for IV administration.

6.12 Storage and Accountability

Pembrolizumab and margetuximab should be stored as outlined below. To ensure compliance with recommended storage conditions, temperature logs will be maintained. The refrigerator must have a digital min/max thermometer or continuous recording device. Vials should be stored in an appropriate locked room accessible only to the pharmacy personnel or a duly designated person.

See Pharmacy Manual for details.

6.12.1 Pembrolizumab

Pembrolizumab is marketed as KEYTRUDA® by Merck & Co., Inc, Whitehouse Station, NJ 08889.

Pembrolizumab must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and must not be frozen. Keep pembrolizumab in the original carton to protect from light during storage. Do not shake pembrolizumab vials. Refer to the Pharmacy Manual for details of storage conditions.

6.12.2 Margetuximab

Vials containing margetuximab must be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and must not be frozen. Keep margetuximab in the original carton to protect from light during storage. Do not shake margetuximab vials. Refer to the Pharmacy Manual for additional details.

6.12.3 Accounting for the Materials

Accurate accounting of all study medication 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 for inspection by the study monitors. Additional details regarding storage, handling, and accountability can be found in the Pharmacy Manual.

6.13 Investigational Product Disposition at End of Study

Upon completion or termination of the study, all unopened vials of study medication must be returned to MacroGenics or its representative, unless the site has received written authorization from MacroGenics to destroy study drug at the site. All drug returns to MacroGenics or its representative 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 are documented and maintained and copies provided to the Sponsor.

7 STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. Time and Events Schedule (**Appendix 1** and **Appendix 2**) details the schedule of assessments by study day.

Note: On days where multiple procedures are required at the same time point, the PK sample should be collected first.

7.1 Informed Consent

The investigator is responsible for ensuring that the patient or his/her legal representative provides informed consent prior to performing any study related assessments, evaluations, or procedures. Informed consent for this study must be provided by signing an Institutional Review Board (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. Informed consent will be obtained prior to any study screening procedures being performed.

7.2 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 medical conditions (e.g., hospitalizations, surgeries, prior cancer history) should be collected. During the screening period (prior to first dose of pembrolizumab or margetuximab), any untoward event that occurs should be recorded as medical history and not as an AE, unless it is due to a protocol-related procedure. Thereafter (i.e., after the time of study drug administration), any untoward event should be collected as an AE.

7.3 Prior and Concomitant Medications

All concomitant medications and blood products administered during the patient's participation in the study until the End of Treatment (EOT) Visit (or 28 days after the last dose of study drug, whichever occurs later) must be recorded in the source document and on the electronic case report form (eCRF). To the extent possible, patients who receive anti-cancer agents, either approved or experimental, after removal from study therapy should have this information recorded in the eCRF, including the name of the agent and the duration of exposure.

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

7.4 Physical Examination

The investigator will perform physical examination of all patients. Physical examination will include height (baseline only), weight, and examination of skin, HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, and neurologic system as specified in **Appendix 1** and **Appendix 2**. Interval physical exams (symptom-directed) noting any changes from baseline will be recorded after the initial exam.

Weight will be measured during screening, Day 1, and then before each dose of pembrolizumab and/or margetuximab.

Any abnormalities found during the physical exams prior to dosing should be reported on the medical history form. Any abnormalities found during physical exams after first dose should be recorded as AEs.

7.5 Vital Signs

Vital signs include temperature, pulse, blood pressure, and respiratory rate and will be obtained during each treatment cycle as follows:

- In relation to pembrolizumab infusions on Days 1: Vital signs will be taken immediately before the pembrolizumab infusion (up to 5 minutes before the infusion [pre-dose]); at 15 minutes after the start of infusion; at 30 minutes (end of infusion), and at 1 hour after infusion completion if the margetuximab dose has not already commenced.
- In relation to margetuximab infusions on Days 1: Vital signs will be taken immediately before margetuximab infusion (up to 5 minutes before the infusion [pre-dose]), at 60 minutes after start of infusion, at 120 minutes (end of infusion), and at 1 hour after the completion of infusion.
- NOTE: For subsequent cycles after Cycle 1: The 1-hour post-infusion vital signs measurements for both infusions may be deferred if continued monitoring is not clinically indicated.

7.6 Clinical Laboratory Tests

Blood and urine samples will be collected at the times specified in **Appendix 1** and **Appendix 2**. Hematology, chemistry, pregnancy, urinalysis, coagulation time, and endocrine evaluation tests will be performed locally. Safety labs should be performed and reviewed before study drug administration.

Please consult the Laboratory Manual for specific directions on collection and processing samples.

7.6.1 Laboratory Parameters

Clinical laboratory tests to be performed locally will include the following:

Table 4 Clinical Laboratory Tests

Pregnancy test: Urine or serum Human chorionic gonadotropin (hCG) **Hematology:** Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential counts **Serum Chemistry:** Albumin (ALB) Alkaline phosphatase (ALK-P) Alanine aminotransferase (ALT; SGPT) Amylase Aspartate aminotransferase (AST; SGOT) Bicarbonate Blood urea nitrogen (BUN) Calcium (Ca) Chloride (Cl) Creatinine Glucose Lipase Magnesium Phosphorus Potassium (K) Sodium (Na) Total protein Uric acid Bilirubin (Total and Direct)	**Coagulation**: Prothrombin time (PT) International normalized ratio (INR) Activated Partial Thromboplastin Time (APTT) **Endocrine tests:** Free thyroxine (T4) Thyroid-stimulating hormone (TSH) **Urinalysis**: Bilirubin Color Glucose Ketones Nitrite Occult blood pH Protein Specific gravity

Other tests (PK, anti-drug antibody [ADA], cytokines, determination of leukocyte subsets, evaluation of T cell activation status, expression of markers of T cells, determination of T cell infiltration, tumor PD-L1 expression, characterization of HER2 expression, ctDNA, and Fc genotype) will be carried out at Sponsor-specified central laboratories (refer to the Laboratory Manual).

7.6.2 Sample Collection, Storage, and Shipping

Clinical laboratory testing described in **Section 7.6.1** will be performed locally. Details on local and central laboratory specimen collection, storage, and shipping will be provided in the Laboratory Manual.

7.7 Tumor Biopsy Specimens

7.7.1 Samples for HER2 and PD-L1 Testing

A pathologic specimen or unstained slides (sectioned within 3 months of study entry) are requested whenever possible for central HER2 and PD-L1 testing. Samples can be from the patient's original biopsy or resection or be obtained from subsequent samples or contemporaneous biopsy. Samples can be from either primary or metastatic tissue although the latest biopsy is preferred. The results of central HER2 and PD-L1 testing will be used in efficacy analyses and not for eligibility. Eligibility will be determined by HER2 testing of patient's pathologic specimen at the local institution. Details of sample acquisition requirements are provided in the Laboratory Manual.

7.7.1.1 Archival Tumor Biopsy Specimens

Patients enrolled on this study will be required to have an identified archival tumor specimen.

Paraffin-embedded block or 12 unstained slides will be used for the determination of PD-L1 and HER2 expression within tumor specimens using an IHC staining assay or by in-situ hybridization (for HER2). If a tumor biopsy is performed at baseline with resulting sample adequate to make 12 slides, the archived sample requirement will be waived, but it is still strongly encouraged to obtain the archived sample so that comparisons in PD-L1 staining can be made between archived and fresh tissue.

7.7.1.2 Mandatory Baseline Tumor Biopsy and Optional Fresh Paired Tumor Biopsy Specimens

For Part B: At least 20 out of the 60 patients (approximately 10 from each region [North America and Asia]) enrolled in the Cohort Expansion Phase (Part B) under the Original Protocol or Protocol Amendment 1 must be willing to provide consent for baseline and on treatment biopsy samples to be done within 7 days prior to dosing on Cycle 1 Day 1 and on Cycle 2 Day 1, respectively. All patients who consent for the biopsy must have one lesion that in the judgment of the investigator can support pre- and on-treatment biopsies. An attempt to obtain a tumor biopsy of a locally accessible lesion pre- and on-treatment (Cycle 1 Day 1 and Cycle 2 Day 1) will be required for at least 20 of the 60 patients. Tumor lesions used for biopsy should be lesions that are felt to be accessible with acceptable clinical risk in the judgment of the investigator and should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in longest diameter. Lesions to be biopsied should not have been previously irradiated, unless the lesion has grown in size beginning at least 14 days

since the last radiation dose. Note that multiple lesions may be used to obtain the biopsy sample.

Lesions to be biopsied should be of sufficient size to enable acquisition of at least 2 tumor biopsy cores using a 16-gauge biopsy needle. Exceptions to the gauge of the needle may be considered after consultation with the Sponsor's Medical Monitor. Two additional biopsy cores may be obtained to ensure adequate sampling for analysis, if this can be performed with acceptable clinical risk in the judgment of the investigator. Punch biopsies or excisional biopsies are allowed if these can be performed with acceptable clinical risk in the judgment of the investigator. Immediate confirmation of the adequacy of the biopsy specimen and the presence of malignant cells in the tumor biopsy is strongly encouraged.

Additional instructions for the acquisition, processing and storage of tumor biopsy specimens will be provided in the Lab Manual. The paired tumor biopsy specimens will be obtained to enable investigation of the pharmacodynamic effects of the combination of margetuximab and pembrolizumab within the local tumor microenvironment. Studies to be performed will include assessment of local T cell infiltration and the expression of tumor apoptosis markers. KEYNOTE-012 study suggested that PD-L1 status may be relevant to pembrolizumab efficacy **(4)**.

For Part C: Patients will not be required to have pre- and on-treatment biopsies.

7.8 Cardiac Evaluations

7.8.1 12-Lead Electrocardiograms

Twelve-lead electrocardiograms (ECGs, in triplicate, approximately 1 minute apart) will be obtained according to the Time and Events (**Appendix 1** and **Appendix 2**) in order to evaluate the potential cardiac effects of margetuximab or prior anti-HER2 treatment, including QT interval prolongation. There are no requirements for fasting and no restrictions for fluid and food intake by the patients during the study, although it is recommended that, to the extent possible, ECGs be obtained pre-meal. However, this may not be possible because of infusion times and clinic logistics.

To account for intrinsic variability, all ECGs should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). Central interpretation of ECGs will be used for data analysis purposes.

If a PK sample collection coincides with measurement of ECGs, the PK sample should be collected first, and ECG measurements taken after the patient has rested for approximately 5 – 10 minutes. The planned and actual times of the ECG assessments will be recorded on the eCRFs.

Dose Escalation Phase (Part A)

- Cycle 1:
  - Pembrolizumab infusion on Day 1: ECGs will be obtained immediately before the pembrolizumab infusion (up to 3 minutes before the infusion [pre-dose]) and at 30 minutes (end of infusion).
  - Margetuximab infusion on Day 1 (intensive PK day): ECGs will be taken at 120 minutes (end of infusion) and at 24 hours after the completion of infusion.
- Cycles 2 through 5:
  - Pembrolizumab infusions on Day 1 of each cycle: ECG will be obtained immediately prior to the first pembrolizumab infusion (up to 3 minutes before the infusion [pre-dose]).
  - Margetuximab infusions on Day 1 of each cycle (except Cycle 3): ECG will be obtained immediately prior to the first margetuximab infusion (up to 3 minutes before the infusion [pre-dose])
  - Margetuximab infusion on Day 1 of Cycle 3 (intensive PK day): ECGs will be taken immediately before margetuximab infusion (up to 3 minutes before the infusion [pre-dose]), at 120 minutes (end of infusion), and at 24 hours after infusion completion.
- End of Treatment Visit:
  - ECGs will be taken at no specific time point during End of Treatment Visit.

Cohort Expansion Phase (Parts B – C):

- Cycles 1, 3, 5 and 7 only
  - Pembrolizumab infusions on Day 1 of Cycles 1, 3, 5, and 7: ECG will be obtained immediately prior to the first pembrolizumab infusion (up to 3 minutes before the infusion [pre-dose]) and at 30 minutes (end of infusion).
  - Margetuximab infusions on Day 1 of Cycles 1, 3, 5, and 7: ECG will be obtained at 120 minutes (end of infusion).
- End of Treatment Visit:
  - ECGs will be taken at no specific time point during End of Treatment Visit.

7.8.2 Multigated Acquisition Ventriculography Scanning and Echocardiography

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** and **Appendix 2**). 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.

7.9 Safety Assessments

7.9.1 Criteria for Evaluation

All AEs and SAEs, regardless of causality, will be reported from the time a signed and dated ICF (see **Section 7.1**) is obtained through 28 days following the last dose of study drug or the End of Treatment Visit or until the start of a subsequent systemic anticancer therapy (whichever occurs first). After the completion of the 28 day-period or start of a subsequent systemic anticancer therapy, only treatment-related AEs will be reported.

- Protocol-related AEs and SAEs will be collected from the time the patient has consented to study participation.
- AEs reported after the informed consent document is signed and prior to treatment with study drug should be captured as medical history; however, if the Investigator believes the AE may have been caused by a protocol procedure it will be reported to the Sponsor or its designee and/or entered on the eCRF. SAEs considered related to study drug should be reported at any time, even after the patient's final visit.
- Progression of the underlying neoplasm resulting in hospitalization or death (e.g., patient hospitalized for or dies from PD only, without any other SAE) will be documented as an antitumor activity outcome and not as an SAE, unless considered as drug-related by the investigator. If an SAE occurs in a patient and it is unclear whether the event is related to PD, the SAE should be reported.
- The reporting of laboratory/vital signs abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:
    - Any criterion for an SAE is fulfilled
    - The laboratory/vital signs abnormality causes the patient to discontinue from the study treatment
    - The laboratory/vital signs abnormality causes the patient to interrupt the study treatment

- The laboratory/vital signs abnormality requires intervention
- The laboratory/vital signs are deemed clinically significant, based on medical judgement.

7.9.2 Adverse Event: Definitions

7.9.2.1 Adverse Event

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug-related by the investigator.

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event will also be considered to be any untoward effect of a study-related procedure, which is conducted after signed informed consent and prior to study drug administration.

All adverse events will be recorded from the time the consent form is signed through 28 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in **Section 7.9.6** - Notification to the Sponsor of Events Requiring Immediate Reporting.

7.9.2.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is a 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 (i.e., the relationship cannot be ruled out).

7.9.2.3 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 could be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it.

7.9.2.4 Treatment Emergent Adverse Event

An event that is temporally associated with administration of study product is defined as a treatment-emergent adverse event (TEAE). Events meeting this definition will be those

occurring during or after administration of the first dose of study drug. Events that existed before the first administration of study product and then increased in severity during or after the first administration of study product will also be considered treatment emergent. Such events will be captured on the eCRF as new events, with the onset date as the date of the increase in severity.

7.9.2.5 Serious Adverse Events

A SAE is any adverse event that results in any of the following outcomes:

- Death
- Life-threatening (immediate risk of death)
- Inpatient hospitalization 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 that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

7.9.2.6 Immediately Reportable Event

Immediately reportable events (IREs) are events that must be reported immediately to MacroGenics Product Safety within 24 hours of being identified. IREs include but are not limited to:

- SAEs
- AEs leading to permanent discontinuation of study drug in an individual patient.
- All pregnancies and exposure during breastfeeding, from the time of treatment through 7 months following cessation of study treatment. All pregnant and/or lactating female partners of a male patient must be requested to complete a Pregnant Partner Consent Form so that pregnant partner, fetal, and/or newborn information can be collected. Upon confirmation of serum pregnancy testing, the patient will be followed for the outcome of pregnancy. All live newborns will be followed six months after the birth, and all necessary information will be collected to assess the effects of study drug on the newborn. If necessary, the follow-up period will be extended for the newborn.

- Adverse events of special interest (AESI) considered immediately reportable events as described in **Section 7.9.3** and below:
  - ≥ Grade 3 Infusion-related reactions or CRS (see also **Section 6.5.1**)
  - irAE (see also **Section 6.5.2**)
  - Cardiotoxicity (see also **Section 6.5.3**)
- Administration of a dose significantly greater (+ 20%) than the planned dose of either margetuximab or pembrolizumab resulting in an event of clinical consequence.
- Any suspected transmission of an infectious agent via study drug (margetuximab or pembrolizumab).
- Withdrawal of the patient from study drug administration for any reason other than disease progression.
- Abnormal liver enzymes that meet the criteria for potential Hy's law, which is defined as AST and/or ALT that is greater than 3 × ULN and total bilirubin that is greater than 2 × ULN without any alternate etiology.

In those cases, in which the IRE is considered related to study drug and the event is of sufficient clinical concern to warrant study drug discontinuation, 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 withdraws consent or is withdrawn from the study by the investigator). At any time after completion of the study, if an investigator becomes aware of a SAE that is suspected related to study drug, the investigator should report the event to MacroGenics Product Safety immediately.

A physician's assessment of the event is expected to be completed in conjunction with reporting an IRE to MacroGenics Product Safety.

7.9.3 Adverse Events of Special Interest

AESI will include the following:

- All Infusion reactions including cytokine release syndrome. (Grade 3 or greater will be reported as IREs)
- Immune-related AEs of Grade 3 or greater suggestive of an autoimmune process, including but not limited to: pneumonitis, colitis, autoimmune hepatitis, arthritis, glomerulonephritis, myocarditis and cardiomyopathy, hypophysitis, thyroiditis, myositis, uveitis, neurotoxicity, or other autoimmune endocrinopathies, pericarditis, or myocarditis
- Left ventricular dysfunction requiring delay or cessation of margetuximab
- Administration of an overdose, as defined in **Section 7.9.5.2** of either margetuximab or pembrolizumab resulting in an event of clinical consequence.

7.9.4 Performing Adverse Event Assessments

Medical evaluation and classification of the adverse event must be performed by the investigator who is qualified to review AE information. The determination of seriousness, severity and causality must be made according to the following criteria:

Assessment of Seriousness: Event *seriousness* will be determined according to the definition of an SAE in **Section 7.9.2**. Seriousness serves as a guide for defining regulatory reporting obligations for AEs.

Assessment of Severity: Event *severity* will be assigned according to the investigator's assessment using the CTCAE Version 4.03 (for described events and syndromes). For events not contained in CTCAE, the investigator may assign severity according to the following scale:

- Grade 1 = Mild
- Grade 2 = Moderate AE
- Grade 3 = Severe AE
- Grade 4 = Life-threatening or disabling AE
- Grade 5 = Death related to AE

Any event or laboratory value judged as Grade 4 severity should be separately evaluated to determine whether it also meets the serious criterion of "immediately life threatening" (see **Section 7.9.2.5**).

Note: Severity is not synonymous with seriousness. The term "severe" is often used to describe the intensity (severity) of a specific event. The event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

Assessment of Causality: The investigator is required to provide an assessment of causality or relationship of AEs to the study drug based on 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified, and 3) biological plausibility. Causality must be assessed separately for each drug. The causality assessment categories that will be used for this study are described below.

Causality assessments that are considered **not related** to study drug:

None: The event is related to an etiology other than the study drug (the alternative etiology should be documented in the patient's medical record).

Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.

If an SAE is considered "unlikely" or "unrelated" to study drug, the investigator should offer his/her clinical opinion as to what factor(s), agent(s), or process(es) were the likely causative mechanism for the event.

Causality assessments that are 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, 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; a plausible mechanism for the event to be related to the study drug and causes other than the study drug has been ruled out and/or the event re-appeared on re-exposure to the study drug.

Assessment of Expectedness: As part of the regulatory reporting requirements, the Sponsor must perform an assessment of expectedness (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product) for AEs. Adverse reactions will be considered unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information (e.g., the Adverse Drug Reaction section of the investigator's brochure [IB]) for the study product.

7.9.5 Reporting of Adverse Events to the Sponsor

Throughout the study, the investigator must document all AEs on the eCRF in a timely manner. Adverse events will be collected and followed from the time the patient provides informed consent for the study (see **Section 7.1**) until 28 days following the last dose of study drug or the End of Treatment Visit or until the start of a subsequent systemic anticancer therapy (whichever occurs first). After the completion of the 28 day-period or start of a subsequent systemic anticancer therapy, only treatment-related AEs will be reported. If a patient experiences an AE after the informed consent document is signed and prior to treatment with study drug, it should be captured as medical history; however, if the investigator believes the AE may have been caused by a protocol-related procedure it will be recorded as an AE and entered onto the eCRF.

To identify the occurrence of any new medical complaints or worsening of previous complaints, non-leading questioning should be posed to the patient.

Events related to disease progression/worsening of underlying disease (including those with a fatal outcome) will be collected as efficacy endpoints, and not documented as AEs/SAEs. These events may not qualify for expedited reporting to regulatory agencies if consistent with expected rates of progression for the underlying disease. However, if an AE/SAE occurs in a patient and it is unclear if the event is due to progressive disease, the AE/SAE should be reported.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer that occurs to any patient from the time the consent is signed through 90 days following cessation of treatment, or 28 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor.

After 28 days following the last dose of study drug administration, if an Investigator becomes aware of an SAE that s/he suspects is related to study drug, the Investigator should report the event to the Sponsor.

If a patient reports signs and symptoms that represent a single medical syndrome, diagnosis, or concept, the syndrome/diagnosis/concept should be documented (e.g., cough, runny nose, fever = Upper Respiratory Tract Infection) in the eCRF.

The investigator must follow all SAEs until resolution and record the date of resolution. Resolution of an event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Adverse events occurring after the patient completes the trial or after early termination need not be reported unless the event is serious and the investigator believes that the event may have been caused by the study drug or a protocol procedure. All pending pregnancy outcomes will be reported to the Sponsor after completion of the trial. It is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the trial or within 7 months of completing the trial.

7.9.5.1 Changes in Clinical Laboratory Parameters

Safety laboratory assessments will be carried out locally and evaluated by the investigator to ensure patient safety. The investigator is responsible for reviewing the results of all laboratory tests as they become available. Laboratory tests will be graded according to CTCAE v 4.03.

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. Abnormal laboratory findings should be reported as an AE if it meets any of the following criteria: 1) causes the patient to discontinue

from study treatment, 2) causes the patient to interrupt the study treatment, or 3) requires intervention.

Generally, Grade 1 laboratory findings need not be reported as AEs unless clinically significant. The investigator will evaluate laboratory findings of ≥ Grade 2 or higher classification to determine their clinical significance and if an AE has occurred. Consistent with the CTCAE designation of Grade 3 events as severe or medically significant and Grade 4 events as life-threatening, Grade 3 and Grade 4 laboratory findings should be reported as AEs or SAEs, as appropriate. Grade 2 laboratory findings may be reported as AEs if, in the opinion of the investigator, the event exhibits clinical significance. If clinically relevant abnormal laboratory values are associated with clinical symptom(s), or consistent with a diagnosis, the diagnosis should be reported as the AE (e.g., hemoglobin 9 g/dL in an adult female = anemia). If these clinically relevant abnormal laboratory values do not result in a diagnosis, the test result or finding should be reported as the AE assuming that it does not represent a laboratory error. Repeat testing may be indicated. Such laboratory values should generally be recorded as "increased" or "decreased" (e.g., change from baseline hemoglobin of 13 g/dL to 11 g/dL = hemoglobin decreased). Investigators are required to report any abnormal liver enzyme laboratory values meeting the criteria for potential Hy's Law as described in **Section 7.9.2.6** for immediately reportable event).

7.9.5.2 Overdose

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

7.9.5.2.1 Pembrolizumab

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7.9.5.2.2 Margetuximab

In the event of an overdose, the patient should be closely monitored for potential AEs.

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7.9.6 Notification to the Sponsor of Events Requiring Immediate Reporting

IREs, as defined in **Section 7.9.2**, are events that must be reported immediately to MacroGenics Product Safety or designee within 24 hours of being identified via the IRE reporting form.

Throughout the study, the investigator must immediately complete and fax/email the *Immediately Reportable Event (IRE)* Report Form within 24 hours of identifying the event to MacroGenics Product Safety or designee. The IRE Report Form and IRE Report Form Completion Guidelines are found in the Study Procedures Manual. Additionally, the information regarding IREs needs to be entered into the eCRFs as soon as possible, as outlined in your site contract.

In case of patient or patient partner pregnancy, the MacroGenics Pregnancy Exposure Form must also be completed per Study Procedures. The investigator must attempt to follow the pregnancy to term or termination in order to report on outcome and health status of mother and child. The Pregnancy Exposure Form is found in the Study Procedures Manual.

7.9.7 Emergency Unblinding

Not applicable. This is an open-label study.

7.10 Efficacy, Immunogenicity, Pharmacokinetic, and Pharmacodynamic Assessments

7.10.1 Efficacy Assessments

7.10.1.1 Radiologic Evaluation: Treatment of Patients According to Principles of Immune-Related Response Criteria

Tumor assessments will be obtained at screening using CT and/or MRI scans at time intervals as specified in the **Appendix 1** and **Appendix 2** (Time and Events Tables). Radiographic disease assessments will occur every 6 weeks (i.e., following 2 cycles of treatment [specifically prior to Cycles 3, 5, 7, etc.]) for the first 24 weeks and then every 12 weeks thereafter until documented progression, initiation of alternative anti-cancer therapy, lost to follow up, withdrawal of informed consent, death, or end of study. Treatment will continue until patients have completed study therapy and required follow-up, experienced disease progression according to irRC, or have been withdrawn from the study (see **Section 4.4** and **Section 5.3**). At each on-treatment tumor assessment time point, the objective response status will be determined. In the context of the statistical analysis for this trial, objective response determination and the assessment of best overall response (BOR) will be defined using both conventional RECIST 1.1 criteria (**Appendix 7**) as well as an adaptation of these criteria, designated as immune-related response criteria (irRC) (**Appendix 8**). Patient management decisions, however, will be made solely based on the immune-related response criteria.

For patients who demonstrate acceptable tolerability of treatment with pembrolizumab and margetuximab and achieve an objective response assessment of irCR, irPR or irSD, or unconfirmed clinically stable irPD, therapy may be continued (see **Section 4.4** and **Section 5.3**).

For patients who are otherwise clinically stable, but have met conventional criteria for PD, therapy may be continued at the discretion of the investigator pending confirmation of progression at the next scheduled tumor assessment. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression, and that the investigator feels the patient may still derive benefit from continuation of therapy. Treatment of patients according to irRC principles is supported by well-documented evidence that in some patients treated with T cell directed, immune-modulatory agents, their tumors can evolve to an objective response after an initial period characterized by either apparent radiographic growth of target lesions or the development of new target lesions that would otherwise meet the criteria for disease progression using conventional response criteria (**Appendix 7**).

For patients in whom progression is confirmed at the next scheduled tumor assessment, the criteria for immune-related PD (irPD) will have been met, and treatment with margetuximab and pembrolizumab should be discontinued. The patient should be removed from study participation after completion of protocol specified follow-up (see **Section 8.3** and **Appendix 1** and **Appendix 2**). For patients who experience an objective response of immune-related complete response (irCR) or immune-related partial response (irPR), responses will be considered unconfirmed until the response has been documented by a subsequent confirmatory scan obtained no less than 4 weeks after the initial scan demonstrating an objective response.

7.10.1.2 Objective Response and Response Duration

Target and non-target lesions will be designated and evaluated using both conventional RECIST 1.1 criteria (**Appendix 7**) and irRC (**Appendix 8**) as noted above for the purposes of statistical analysis. Objective responses will be categorized as CR, PR, SD, or PD for conventional RECIST 1.1 criteria and irCR, irPR, irSD, and irPD for the immune-related response criteria. Determination of the objective response rate will be calculated based on the proportion of response evaluable patients achieving CR or PR using the respective criteria, when such responses are confirmed by a subsequent scan obtained at least 28 days after the initial documentation of objective response. Response-evaluable patients will include those patients who have measurable disease and have had a baseline tumor assessment and at least 1 on-treatment tumor assessment (see **Appendix 1** and **Appendix 2**). Objective responses that are not subsequently documented with a confirmatory CT or MRI scan (e.g., unconfirmed responses) will not be included as an objective response for the purpose of calculating overall objective response rates. Response duration will be calculated from the time of initial response (CR or PR) documentation (in patients who have a subsequent confirmation of objective response) to the time of progressive disease or death, whichever occurs first.

7.10.1.3 Progression-Free Survival (PFS)

PFS will be calculated as the time from the date of the first dose of study drug until the date of any documented PD or the date of death from any cause, whichever occurs first (**Appendix 5**). A patient's PFS will be censored if at the time of last assessment for progression, the patient remains progression free. PFS will be determined using conventional RECIST 1.1 criteria. In addition, PFS rate at 3 and 6 months will be evaluated.

7.10.1.4 Overall Survival

Overall survival (OS) will be calculated as the time from the first dose of study drug until death due to any cause. A patient's OS will be censored if at the time of last contact, the patient was alive. In addition, OS rate at 1 and 2 years will be evaluated.

7.10.2 Immunogenicity

Blood samples for the immunogenicity assessments (i.e., anti-drug antibody [ADA]) of margetuximab will be collected at the following time points given in the table below.

Table 5 Immunogenicity Blood Sampling Schedule (Parts A, B, and C)

Time Point	Study Day	Treatment Day of Cycle	ADA Sampling Time	ADA Sample Collection for Margetuximab
Cycle 1	1	1	0 (Predose) [a]	X
Cycle 2	22	1	0 (Predose) [b]	X
Odd Cycles (3, 5, 7, 9, 11, etc.)	43, 85, 127, etc.	1	0 (Predose) [b]	X
End of Treatment Visit or 28 days after last dose of study drug [c]	NA	NA	NA [d]	X

a Predose ADA sample will be collected prior to margetuximab infusion.
b Predose sample collected prior to margetuximab infusion; the start of infusion is designated as time = 0.
c Whichever time point occurs later.
d Not applicable; however, ADA sample will be collected simultaneously with PK sample.
NOTE: Actual start and end of infusion times and ADA sample collection times will be recorded on the eCRFs. The above ADA sample collection should be followed for all patients enrolled in Dose Escalation and Cohort Expansion.

7.10.3 Pharmacokinetics

Serum concentrations of margetuximab will be monitored using a quantitative sandwich ELISA. Single and multiple dose PK parameters for margetuximab (e.g., C_{max}, T_{max}, AUC_{tau}, AUC_{inf}, C_{trough}, CL, V_{ss}, and T_{half}) will be derived from margetuximab serum concentration versus time data. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Blood samples for margetuximab PK will be collected at the following time points given in the table below. 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 or PK assessment.

Table 6 Pharmacokinetics Blood Sampling Schedule for Margetuximab

Tumor Assessment Cycle	Treatment Day of Cycle	Pembrolizumab /Margetuximab Dose Number [a, b]	PK Sampling Time After the end of Infusion (hr)	PK Sample Collection for Margetuximab	
				Dose Escalation	Cohort Expansion
Initial (1st)	1	1	0 (Predose) [c]	X	X
			EOI [d]	X	X
			5 [g]	X	X
	2		24 [g]	X	NA
	8		NA [h]	X	NA
2nd	1	2	0 (Predose) [e]	X	X
			EOI [d]	X	X
3rd	1	3	0 (Predose) [e]	X	X
			EOI [d]	X	X
	2		24 [g]	X	NA
5th & 7th Cycle	1		0 (Predose) [e]	X	X
			EOI [d]	X	X
EOTV	NA [f]	EOTV (28 days after the last dose of study drug)	NA [f]	X	X

a Pembrolizumab dose and margetuximab dose administered as 0.5 hour (30 min) and 2-hour (120 min) infusions, respectively.

b Margetuximab may be administered the day following pembrolizumab administration for safety reasons or scheduling purposes.

c Predose PK sample on Study Day 1 (Treatment Day 1 of Initial [1st] Cycle) will be collected prior to margetuximab infusion; ADA sample for this time point will be collected prior to margetuximab infusion.

d EOI= end of margetuximab infusion; sample will be collected within 5 min to the end of infusion.

e All other predose PK samples will be collected prior to margetuximab infusion simultaneously with ADA sample.

f Not applicable as this is for the end of treatment visit (EOTV); however, PK sample will be collected simultaneously with ADA sample.

g These times are noted from margetuximab end of infusion. If there are delays in margetuximab infusion, these time points will be at 5, and 24 hours post end of margetuximab infusion, respectively.

h No specific time point is mandated for expansion Cycle 1 Day 8 PK blood draw. But time of draw should be noted on the CRF.

NOTE: Actual start and end of infusion times and PK sample collection times will be recorded on the CRFs.

7.10.4 Pharmacodynamics/Biomarkers

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

Tests to be performed may include the following:

- Determination of Fc receptor genotypes for *CD16A, CD32A* and *CD32B*

- Characterization of alterations in serum cytokine levels to include, but not limited to, IL-2, IL-6, IL-10, IFN-γ, and TNF-α
- Enumeration of lymphocyte subsets, NK cells and other activation markers and activation status over time via multi-parameter flow cytometry; evaluation of the T-reg population over time
- Determination of the potentiation of HER2 specific adaptive humoral and cellular immune responses: Plasma samples analyzed by ELISA to measure endogenous anti-HER2 IgG levels; PBMC samples analyzed by ELISpot to measure HER2-specific T-cell activity
- Determination of PD-L1 expression will be explored via IHC staining of archival tumor biopsy specimens (unless fresh tumor sample submitted and used to determine PD-L1 expression and no archived sample obtained)

Limited to Cohort Expansion Phase (Parts B-C) only (unless otherwise noted):

- Determination of mutational burden (Guradant 360 assay), as well as mismatch repair status by microsatellite instability (from pathology reports, when available).
- Determination of PD-L1 tumor cell membranous expression and T cell infiltration (including but not limited to CD4+ and CD8+ T cells) into the tumor bed via IHC staining of paired pre- and on-treatment tumor biopsy specimens.
- Part B only: Determination of HER2 tumor cell membranous expression via IHC staining of pre-treatment and on-treatment tumor biopsy specimens.
- Determination of gene expression signatures in tissues (i.e., by nanostring technology), which may be indicative of immunotherapy responses associated with the agents on trial.

7.11 Other Study Procedures

7.11.1 Central Laboratory Evaluations

MacroGenics or its designee will provide blood sampling supplies such as polypropylene transport tubes, labels, and log sheets. Serum tubes should be labeled with the patient's number, date, and time of sampling. The investigator will maintain a log with the same data.

Specimens must be appropriately prepared, divided if appropriate, frozen, and shipped (while often retaining certain replicate samples at the site) according to the instructions in the Laboratory Manual.

7.11.2 Sample Retention and Further Testing

Samples acquired for protocol specified assays will be retained for study purposes (analysis/re-analysis) up to 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. If patients consent to the use of their study samples for non-study research purposes, these samples may also be used for exploratory testing (including assay development/ optimization) and may be retained up to 15 years from the end of study.

7.12 Appropriateness of Measurements

Routine laboratory evaluations including hematology, chemistry, coagulation, and urinalysis will be carried out in local institutional laboratories. Additional local safety laboratory assessments may be used to supplement the protocol-prescribed assessments and may be used to elucidate certain AEs.

Serum concentrations of margetuximab will be monitored using an ELISA based assay. Standard bridging ELISAs will be carried out in the Sponsor's designated central laboratory to characterize the immunogenicity of margetuximab. Analysis of PK data will be carried out using industry standard software. Population PK modeling may be performed and an appropriate model and model parameters may be described.

7.12.1 Rationale for Use of Immune Response Criteria

Patients will be managed according to irRC principles. This approach allows for limited treatment of patients beyond the initial radiographic documentation of disease progression, assuming that patients are tolerating therapy adequately, that patients remain otherwise clinically stable despite this initial radiographic evidence of disease progression and that the investigator considers that the patient may still derive benefit from continuation of therapy. Treatment of patients according to irRC principles is supported by well-documented evidence that in some patients treated with T cell directed, immune-modulatory agents, their tumors can evolve to an objective response after an initial period characterized by either growth of target lesions or the development of new target lesions that would otherwise meet the criteria for disease progression using conventional response criteria (**Appendix 8**). Further details regarding the application of this approach are described in **Section 7.10.1**.

8 STUDY ACTIVITIES

A table of study activities including screening, on-study and end-of study visits is presented in **Appendix 1** and **Appendix 2**, Time and Events Tables.

Blood volumes required for various laboratory tests are shown in **Appendix 3** (Dose Escalation Phase [Part A]) and **Appendix 4** (Cohort Expansion Phase [Parts B–C]).

8.1 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. Only those patients who meet all inclusion/exclusion criteria specified in **Section 5** will be entered into this study.

8.2 Registration

Each patient must be registered with MacroGenics prior to enrollment. The following information should be provided during registration:

- Date of birth
- Date of signed informed consent
- Planned date of first pembrolizumab and margetuximab administration
- Eligibility confirmation documents

The instructions for the registration process are provided in the Study Manual.

8.3 End of Treatment Visit

A list of evaluations to be performed for the End of Treatment visit is provided in **Appendix 1** and **Appendix 2**. Criteria for triggering the End of Treatment visit are specified in **Section 5.3**. The End of Treatment Visit should be performed after the patient has met off-treatment criteria and End of Study should be noted after patient has been followed for at least 28 days after the last dose of study drug depending on ability to follow the patient and duration and severity of ongoing AEs. It is recognized that certain patients (such as those experiencing progression of disease) may be cared for in facilities other than the participating investigational site, may proceed to receive other cancer therapy, and/or may elect not to return to the investigational site. Therefore, this visit is considered optional, but should be carried out whenever possible.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

This Phase 1b/2a study is primarily observational and, thus, the majority of the statistical summaries will be descriptive. Summary statistics will consist of absolute and relative frequencies of each category of discrete variables and of means, standard deviations, medians, minimums and maximums for continuous variables.

Safety and efficacy summaries will be provided for each dose level cohort during dose escalation and for all dose level cohorts combined, as well as for expansion part. Response rates may be calculated for specific disease sub-groups, if appropriate.

Baseline will be considered the closest value obtained prior to first dose. Data that are reported as missing will be treated as missing in all data summaries. Incomplete dates will be imputed and defined in the Statistical Analysis Plan. In descriptive summaries for safety, observations that are spurious (extreme relative to the majority of the data) will not be altered or removed from the summary.

9.2 Determination of Sample Size

The number of patients enrolled in the Dose Escalation Phase (Part A) cannot be precisely determined in advance and could range up to 12 patients based on 3+3 design applied to 2 dose levels. This patient number does not take into account patient replacement for non-evaluable patients.

The Cohort Expansion Phases of the trial will enroll up to 85 patients.

The first expansion cohort (Part B) includes 30 patients in North America and 30 patients in Asia with relapsed/refractory unresectable locally advanced or metastatic HER2+ GEJ or GC.

Part C will enroll up to 25 patients in North American and/or Asia with relapsed/refractory unresectable locally advanced or metastatic HER2+ (IHC 3+) gene amplification GC.

The sample size for each part in the Cohort Expansion Phase is primarily based on providing preliminary estimation of responses. The following table provides the 2-sided 95% confidence interval (CI) for a number of potential response rates under various sample sizes.

Table 7 Response Rates and 95% Confidence Intervals

Sample Size	Number of Responses	Response Rate (%)	95% Confidence Interval (%)
30	1	3.3	0 – 17
30	5	16.7	5.6 – 34.7
30	10	33.3	17.3 – 52.8
30	15	50.0	31.3- 68.7
30	20	66.7	47.2 – 82.7
25	1	4	0 – 20.4
25	3	12	2.5 – 31.2
25	6	24	9.4 – 45.1
25	9	36	18.0 – 57.5

After 15 patients were enrolled in each region in Part B and after each patient had at least one post-baseline tumor assessment, a futility rule was applied and enrollment in that region was continued. The enrollment could have been stopped if there was no more than one response. One response out of 15 patients will have greater than 80% confidence to rule out the response rate of 20% or higher (the upper limit of one-sided 80% CI for response rate < 20%).

9.2.1 Analysis Populations

Two populations will be used for data analysis, the **Safety Population** and **the Response Evaluable Population**, as defined below:

- **Safety Population**: All patients who received at least one dose of either margetuximab or pembrolizumab. This population will be used for safety analysis and for analysis of PFS and OS. Patients who receive at least one dose of margetuximab will be included in PK, PD, and immunogenicity analyses.
- **Response Evaluable Population:** All patients who have baseline measurable disease and received one dose of either margetuximab or pembrolizumab. This population will be used for analysis of ORR.

Patients who withdraw before receiving all protocol-specified treatment before completion of the DLT evaluation period for a reason unrelated to drug toxicity will be considered to have inadequate data to support dose escalation. In this case, replacement patients may be enrolled at the same dose level and schedule as necessary to complete the cohort.

9.3 Demographics and Baseline Characteristics

Patient disposition, demographics, baseline characteristics, disease history, medical history, concomitant medications, and study drug exposure data will be summarized using descriptive statistics.

9.4 Safety Endpoint(s)

9.4.1 Adverse Events

Adverse events will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Only treatment-emergent AEs, as defined in **Section 7.9.2**, 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.

The following tables of adverse event data will be created to summarize the number and percent of patients who experience at least one event of each of the following types:

- Any TEAEs
- Treatment related TEAEs
- TEAEs with CTCAE Grade severity Grade ≥ 3
- Treatment related TEAEs by CTCAE Grade severity Grade ≥ 3
- TEAEs related to each individual study drug
- Any SAEs (this may be a listing if there are few events)
- Treatment related SAEs
- SAEs related to each individual study drug
- Fatal AEs (this may be a listing if there are few events)
- AESIs
- IREs
- TEAEs that result in study discontinuation
- TEAEs which lead to interruption of each individual study drug
- TEAEs that lead to withdrawal of each individual study drug

All of these tables will display the number and percent of patients that experience the given event and will display events by MedDRA System Organ Class (SOC) and Preferred Term. Events will be displayed alphabetically for SOC and Preferred Term. 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 AE types.

9.4.2 Laboratory Values

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

A list of repeated labs including original values and repeat values will be included.

Graphs of mean values over time may also be generated.

9.4.3 Other Safety Endpoints

ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Vital signs will be summarized with descriptive statistics at each visit and time point where they are collected.

9.5 Efficacy Endpoints

Response will be categorized as CR, PR, SD, or PD and evaluated using RECIST 1.1 criteria (**Appendix 7**) and as irCR, irPR, irSD, or irPD using the irRC (**Appendix 8**). The ORR will be the proportion of patients in the response evaluable population achieving CR or PR when such responses are confirmed at least 28 days after the initial observation of an objective response. A two-sided 95% exact binomial confidence interval will be calculated around the ORR for each expansion region and also by tumor type.

Response duration will be calculated for responders as the time from initial response (CR or PR) to the time of PD or death. Kaplan-Meier methods will be used to estimate response duration over time and the median response duration. Responders who complete the study without documented PD will be censored at the date of their last tumor assessment.

PFS will be calculated as the time from the initial infusion of pembrolizumab or margetuximab until documented disease progression or death from any cause. Patients with no PFS event (no disease progression or death from any cause) will be censored at the date of their last tumor assessment. In addition, PFS rates will be calculated at 3 and 6-month time points from the first dose of study drug. Kaplan-Meier methods will be used to estimate PFS over time and the median duration of PFS. The method of Brookmeyer and Crowley **(9)** will be used to construct 95% CIs around PFS estimates of the median and other quartiles for each expansion region and also by tumor type.

Incomplete and missing data can complicate interpretation of PFS. **Appendix 5** describes the handling of these data for the PFS analysis.

Overall survival is defined as the time from the initial infusion of pembrolizumab or margetuximab to death from any cause. Patients who are alive at last contact will be censored at the date that the patient was last known to be alive. Kaplan-Meier methods will be used to estimate the overall survival function. In addition, OS rate will be calculated at 1 year and 2-year time points from the first dose of study drug.

9.6 Other Assessments or Analyses

Pharmacokinetic Analysis: Summary statistics will be tabulated for PK parameters by margetuximab dose. Geometric means and percent coefficients of variation will be reported for C_{max}, AUC_{tau}, and C_{trough}; arithmetic means and standard deviations will be reported for terminal half-life (T_{half}), CL, and V_{ss}; and medians, minimum, and maximum will be reported for T_{max}. Separate scatter plots of C_{max} and AUC will be provided versus dose to assess dose dependency. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Immunogenicity Analysis: The proportion of patients who are negative for margetuximab ADA at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and those who have positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized.

Pharmacodynamic Analysis: Summary statistics for pharmacodynamics parameters such as, but not limited to, those listed under section, "Pharmacodynamics/Biomarkers/Tumor Biopsy" (**Section 7.10.4**) and corresponding changes from baseline, will be summarized and/or may also be presented graphically as will possible associations between changes in pharmacodynamics measures of interest and margetuximab dose and exposure may be explored.

10 QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. MacroGenics, Inc. 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.

10.1 Monitoring, Auditing and Inspections

To ensure the safety of participants 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 (refer to **Section 11.5** for additional information on source documents).

MacroGenics, Inc. 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 a sample 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 will be raised for any datum that is unclear or is contradictory with the source documents. The investigator and 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.).

10.2 Data Collection and Management

An electronic data capture system will be used in this trial. Other data assessments, such as central laboratory assays, immunochemistry, and ECG data, will be managed by central vendors for transfer to MacroGenics, Inc. or representative for use in the study analysis database.

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 will not be submitted to the Sponsor (e.g., the signed informed consent document; patient initials) 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 electronic case report forms (eCRFs) using 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. 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 patient 's 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. Sites resolve the queries and correct the entered data accordingly. Every change to data is captured in the EDC system audit trail. Adverse events and medical history 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 site will be provided with a compact disk containing the eCRFs for each of their patients.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) 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, IB, 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 unconditional approval of the study protocol and the informed consent forms (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 unconditional 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; written verification that the modification was submitted should be obtained.

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

- The protocol and the investigator's brochure (IB) and any amendments or updates.
- The informed consent form(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 violations or deviations
- Notification when the study has been completed.

- Proof of indemnity/liability insurance.
- Other documents required by the IRB/IEC

11.2 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), the current ICH Guideline for Good Clinical Practice (ICH E6), and all other applicable regulations.

The protocol and the informed consent document will be reviewed and approved by the IRB/IEC of each participating center before study initiation. Serious adverse events, regardless of causality, will be reported to the Sponsor/designee and to the IRB/IEC, if required by local regulations. The investigator will keep the IRB/IEC informed regarding the progress of the study.

11.3 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' representatives 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.

11.4 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, except as necessary for monitoring by the relevant regulatory authorities, the Sponsor of the clinical trial, 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]), on protection of individuals with regard to personal data.

11.5 Case Report Forms and Study Records

Source data in a clinical trial 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 onto CRFs designed to capture all observations and other data pertinent to the clinical investigation. Data should be recorded on source documents and entered onto eCRFs. Electronic CRFs should be filled out completely 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.

11.6 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.

The investigator may be subjected to a field audit by MacroGenics, Inc. (or designee) and/or regulatory inspectors in order to validate the participation of patients in the study and to verify the data reported on the eCRFs on file at MacroGenics, Inc. MacroGenics or representatives should be notified immediately of any audits scheduled by any regulatory authorities. Copies of audit reports, findings and/or correspondence from regulatory authorities for audits conducted on a MacroGenics-sponsored study should be promptly forwarded to MacroGenics or representatives.

11.7 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, Inc. is required to maintain study records for longer periods (e.g., applicable local regulations);

therefore, MacroGenics, Inc or representatives. should be contacted before study records are removed from the control of the investigational site for any reason. The investigator must obtain written permission from MacroGenics, Inc or representatives prior to destruction of study documents.

11.8 Financial Disclosure

The investigator and sub-investigators will be required to disclose any applicable financial arrangement as defined in US or local regulation (i.e. 21 CFR 54). The following information will be collected: 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 margetuximab; and any significant equity interest in MacroGenics, Inc., as defined in 21 CFR 54. Investigators are obliged to update the Sponsor or representatives with any changes in reported information up to 1 year following the end of the study (as defined in **Section 4.7.2**).

In consideration of participation in the study, MacroGenics, Inc. 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.

11.9 Publication and Disclosure Policy

Data collected in this clinical study belong to the study Sponsor which will formulate a policy on the use of study data. This policy will be codified in the Clinical Trial Agreement. This includes authorship issues: scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

11.10 Discontinuation of the Study or Study Sites

11.10.1 Discontinuation of Study Sites

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

11.10.2 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.

11.11 Identification of the Coordinating Principal Investigator

A Coordinating Principal Investigator will be appointed by the Sponsor Medical Monitor prior to the end of the study.

As part of his or her responsibilities, the Coordinating Principal Investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the Coordinating Principal Investigator.

12 REFERENCE LIST

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

1. **Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, and Kelsen DP**, Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J. Natl. Cancer Inst, 1994. 86(14): p. 1086-1091.

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Appendix 1 Time and Events Schedule: Dose Escalation (Part A)

EVALUATION/PROCEDURE [1]	Screening	Cycle 1			Cycle 2	Cycle 3		Cycle 4 & Beyond	End of Treatment Visit	Follow-Up Visit
	Day -28 to 0	Day 1	Day 2	Day 8	Day 1	Day 1	Day 2	Day 1		
STUDY DRUG ADMINISTRATION [2]										
Pembrolizumab		x			x	X		x		
Margetuximab		x			x	X		x		
ELIGIBILITY										
Informed consent [3]	x									
Patient registration		x								
HER2 status testing [3]	x									
Medical history	x									
Review of concomitant medications	x	x	x		x	x	x	x	x	
ECOG performance status	x	x			x	x		x	x	
ECG [4]	x	x	x		x	x	x	x	x	
MUGA or Echocardiography [5]	x					x		x	x	
β-hCG pregnancy test [6]	x									
Archival biopsy specimen	x									

Safety & Pharmacodynamic Evaluation										
Physical examination [7]	x	x			x	x		x	x	
Monitor for Adverse Events		Continuous								
CBC with differential, platelet count [8, 12]	x	x			x	x		x	x	
Chemistry panel [8, 12, 13]	x	x			x	x		x	x	
Free T4 and TSH [8, 12]		x			x	x		x		
PT; aPTT [8, 12]		x			x	x		x		
Urinalysis [8, 12]	x	x			x	x		x	x	
HER2-specific immune responses (PBMC, plasma) [9]		x						x	x	
Flow cytometry: Lymphocyte subsets, NK cells and activation markers [10]		x	x	x	x	x		x	x	
Fc receptor genotyping [11]		x								
Serum Cytokine sampling [14]		x	x							
Vital signs (pulse, respirations, blood pressure, temperature) [15]	x	x			x	x		x	x	
Therapeutic Activity										
Disease assessment by RECIST and irRC: CT/MRI chest, abdomen and pelvis [16]	x					x		x [16]	x	x
CT/MRI brain [16, 17]	x					x		x [16, 17]	x	x
Pharmacokinetics/Immunogenicity										
Margetuximab PK sampling [18]		x	x	x	x	x	x	x	x	
ADA blood sample (anti-margetuximab antibodies) [19]		x			x	x		x	x	

Contacts										
Telephone, Electronic Contact, or office visit										x

1 Visits occur ± 3 days of a scheduled visit, with exception of Cycle 1 Day 1 and unless otherwise noted.

2 Pembrolizumab must be administered first. An effort should be made to begin the margetuximab infusion between 30 minutes to 60 minutes after the completion of the pembrolizumab infusion. It is understood that this window may not always be attainable, but it is the preferred window of time to administer margetuximab. Margetuximab may be administered the next day for safety reasons or scheduling purposes. The start and stop time of each pembrolizumab and margetuximab infusion must be documented.

3 To be obtained before registration (no time constraint).

4 Timing of ECGs in relation to pembrolizumab:

- Cycle 1 - ECGs will be obtained immediately before the pembrolizumab infusion (up to 3 minutes before the infusion [pre-dose]) and at 30 minutes (end of infusion) on Day 1.
- Cycles 2 through 5 - ECG will be obtained immediately prior to the first pembrolizumab infusion (up to 3 minutes before the infusion [pre-dose]) on Day 1 of each cycle.
- ECGs are obtained through Cycle 7 and thereafter not again until the End of Treatment Visit.

Timing of ECGs in relation to margetuximab:

- Cycle 1 - On Day 1 (intensive PK day) ECGs will be taken at 120 minutes (end of infusion) and at 24 hours after the completion of infusion.
- Cycles 2 through 5 – ECGs will be obtained immediately prior to the first margetuximab infusion (up to 3 minutes before the infusion [pre-dose]) on Day 1 of each cycle. On Day 1 of Cycle 3 (intensive PK day), ECGs will be taken immediately before margetuximab infusion (up to 3 minutes before the infusion [pre-dose]) and at 120 minutes (end of infusion), and at 24 hours after infusion completion.
- End of Treatment at no specific time

5 MUGA or echocardiography to be performed at Screening; Cycle 3 Day 1; Cycle 5 Day 1, and on Day 1 of each 4th cycle thereafter (eg, Cycles 9, 13, 17) while on treatment; and at the End of Treatment visit. Cycle 1 Day 1 MUGA or echo not required if the Screening MUGA scan or echo was performed within 4 weeks of patient randomization. MUGA or echo evaluations may be performed up to 7 days prior to the scheduled study visit.

6 For women of childbearing potential, to be obtained within 72 hours prior to initial dose of pembrolizumab. **For Canadian patients only:** Female patients of childbearing potential must have a negative pregnancy test prior to every cycle of pembrolizumab.

7 Includes height (baseline only) and weight. Note that full physical exams to be done on Screening Day (baseline) and at the EOTV. All other physical exams will be directed physical exams based on patient symptoms, tumor location and as clinically indicated.

8 Sample will be collected prior to pembrolizumab infusion; CBC with differential, platelet count, Chemistry panel, Free T4 and TSH, PT and aPTT, and Urinalysis may occur up to 72 hours in advance of the Day 1 infusion day of each treatment cycle.

9 Blood for HER2-specific immune response to be drawn pre-pembrolizumab infusion on Cycle 1 Day 1; Cycle 4 Day 1; and at End of Treatment Visit. ctDNA testing performed retrospectively for patients who consented to future use testing.

10 Blood for flow cytometry assays to be drawn on Day 1 at pre-pembrolizumab infusion and 5 hours post Margetuximab EOI, on Day 2 and Day 8 for Cycle 1 only; subsequently to be drawn Day1 of each cycle pre-pembrolizumab infusion up to and including Cycle 6, and lastly at End of Treatment Visit.

11 Fc receptor genotyping to be drawn only once on Day 1 of Cycle 1 pre-pembrolizumab infusion.

12 Samples will be analyzed by the local laboratory.

13 Includes ALB, ALK-P, ALT, AST, amylase, bicarbonate, BUN, Ca, Cl, creatinine, glucose, lipase, magnesium, phosphorus, K, Na, total and direct bilirubin, total protein, and uric acid.

14 For cytokine samples: For Dose Escalation: Day 1 sample will be collected pre-pembrolizumab infusion, pre-margetuximab infusion and with the 5 hour after end of margetuximab infusion PK sample, and with the margetuximab PK sample on Day 2. Additional samples should be obtained selectively at additional time points in patients who experience signs and symptoms of cytokine release at the time of the adverse event, with the goal to obtain a cytokine sample immediately at the time of onset of adverse event. Multiple cytokine samples can be drawn for any specific adverse event that is suspected to be due to cytokine release, as clinically indicated; specific date and times of blood draws must be recorded. Separate cytokine samples should be drawn for each adverse event suspected of cytokine release, with specific date and time of draw to be recorded.

15 Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained as follows:

- In relation to pembrolizumab infusions on Days 1: Vital signs will be taken immediately before the pembrolizumab infusion (up to 5 minutes before the infusion [pre-dose]); at 15 minutes after the start of infusion; at 30 minutes (end of infusion), and at 1 hour after infusion if the margetuximab dose has not already commenced.
- In relation to margetuximab infusions on Days 1: Vital signs will be taken immediately before margetuximab infusion (up to 5 minutes before the infusion [pre-dose]), at 60 minutes after start of infusion, at 120 minutes (end of infusion), and at 1 hour after the completion of infusion.
- Note: For subsequent cycles after cycle 1; the 1-hour post-infusion vital signs measurements may be deferred if continuing monitoring is not clinically indicated.

16 Radiographic disease assessments will occur every 6 weeks (i.e., following 2 cycles of treatment) for the first 24 weeks and then every 12 weeks thereafter until documented progression, initiation of alternative anti-cancer therapy, lost to follow up, withdrawal of informed consent, death, or end of study. To be performed within 3 days prior to dosing on Day 1 of every other cycle for the first 24 weeks (specifically prior to Cycles 3, 5, 7 and 9) and then every 4th cycle thereafter (prior to Cycles 13, 17, 21, etc.).

17 Screening brain scans should be performed on all patients who have previous history of CNS metastasis or as clinically indicated. Repeat brains scans will only be performed if the Screening brain scan was positive or as clinically indicated.

18 Pharmacokinetic sampling to be performed according to **Table 6**.

19 See **Table 5** for ADA sample days and times.

Appendix 2 Time and Events Schedule: Cohort Expansion Phase (Parts B – C)

Evaluation/Procedure [1]	Screening Day -28 to 0	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 - 35 Day 1	End of Treatment Visit	Follow-Up Visits
Study Drug Administration [2]							
Pembrolizumab		x	x	x	x		
Margetuximab		X	x	x	x		
Eligibility							
Informed consent [3]	x						
Patient registration		X					
HER2 status testing [3]	x						
Medical history	x						
Review of concomitant medications	x	X	x	x	x	x	
ECOG performance status	x	X	x	x	x	x	
ECG [4]	x	X		x	x	x	
MUGA or Echocardiography [5]	x			x	x	x	
β-hCG pregnancy test [6]	x						
Archival biopsy specimen	x						
Fresh Pre- and On-Treatment Tumor Biopsy [20, Appendix 1]		x [20]	x [20]				

Evaluation/Procedure [1]	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 - 35	End of Treatment Visit	Follow-Up Visits
	Day -28 to 0	Day 1	Day 1	Day 1	Day 1		
Safety & Pharmacodynamic Evaluation							
Physical examination[7]	x	X	x	x	x	x	
Monitor for Adverse Events			Continuous				
CBC with differential, platelet count [8, 12]	x	X	x	x	x	x	
Chemistry panel [8, 12, 13]	x	X	x	x	x	x	
Free T4 and TSH [8, 12]		X	x	x	x		
PT; aPTT [8, 12]		X	x	x	x		
Urinalysis [8, 12]	x	x	x	x	x	x	
HER2-specific immune responses (PBMC, plasma, ctDNA) [9]		x			x	X	
Flow cytometry: Lymphocyte subsets, NK cells and activation markers [10]		x	x	x	x	X	
Fc receptor genotyping [11]		x					
Serum Cytokine sampling [14]		x					
Vital signs (pulse, respirations, blood pressure, temperature)[15]	x	X	x	x	x	X	
Therapeutic Activity							
Disease assessment by RECIST and irRC: CT/MRI chest, abdomen and pelvis [16]	x			x	x [16]	X	x[16]
CT/MRI Brain [16, 17]	x			x	x [16, 17]	X	
Pharmacokinetics/Immunogenicity							
Margetuximab PK sampling [18]		X	x	x	x[18]	X	

Evaluation/Procedure [1]	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 - 35	End of Treatment Visit	Follow-Up Visits
	Day -28 to 0	Day 1	Day 1	Day 1	Day 1		
ADA blood sample (anti-margetuximab antibodies) [19]		X	x	x	x[19]	X	
Contacts							
Telephone, Electronic Contact, or office visit							x

1 Visits occur ± 3 days of scheduled visit, with exception of Cycle 1 Day 1 and unless otherwise noted.

2 Pembrolizumab must be administered first. An effort should be made to begin the margetuximab infusion between 30 minutes to 60 minutes after the completion of the pembrolizumab infusion. It is understood that this window may not always be attainable, but it is the preferred window of time to administer margetuximab. Margetuximab may be administered the next day for safety reasons or scheduling purposes. The start and stop time of each pembrolizumab and margetuximab infusion must be documented.

3 To be obtained before registration (no time constraint).

4 **Timing of ECGs in relation to pembrolizumab:**

Expansion

- Cycles 1, 3, 5, and 7 ECGs will be obtained before pembrolizumab infusion (up to 3 minutes before the infusion [pre-dose] and at 30 minutes (end of infusion) on Day 1
- End of Treatment ECGs will be obtained at no specific time.

Timing of ECGs in relation to margetuximab:

Expansion

- Cycles 1, 3, 5, 7 ECGs will be obtained at 120 minutes (end of infusion) on Day 1 of each cycle.
  End of Treatment ECGs will be obtained at no specific time.

5 MUGA or echocardiography to be performed on Day 1 (or 3 to 4 prior to Day 1) of every other cycle for 6 months; thereafter, these assessments may be performed every 4 cycles.

6 For women of childbearing potential, to be obtained within 72 hours prior to initial dose of pembrolizumab. **For Canadian patients only:** Female patients of childbearing potential must have a negative pregnancy test prior to every cycle of pembrolizumab.

7 Includes height (baseline only) and weight. Note that full physical exams to be done on Screening Day (baseline) and at the EOTV. All other physical exams will be directed physical exams based on patient symptoms, tumor location and as clinically indicated.

8 Sample will be collected prior to pembrolizumab infusion; CBC with differential, platelet count, Chemistry panel, Free T4 and TSH, PT and aPTT, and Urinalysis may occur up to 72 hours in advance of the Day 1 infusion day of each treatment cycle.

9 Blood for HER2-specific immune response to be drawn pre-pembrolizumab infusion on Cycle 1, Day 1; Cycle 4, Day 1; and at End of Treatment Visit.

10 Blood for Flow Cytometry assays to be drawn on Day 1 at pre-pembrolizumab infusion for Cycle 1 to Cycle 6, inclusive, and lastly at End of Treatment Visit.

11 Fc receptor genotyping to be drawn only once on Day 1 of Cycle 1 pre-pembrolizumab infusion.

12 Samples will be analyzed by the local laboratory.

13 Includes ALB, ALK-P, ALT, AST, amylase, bicarbonate, BUN, Ca, Cl, creatinine, glucose, lipase, magnesium, phosphorus, K, Na, total protein, uric acid, total and direct bilirubin.

14 For Cytokine samples: Samples can be obtained selectively at additional time points in patients who experience an adverse even with signs and symptoms of cytokine release, with the goal to obtain a cytokine sample immediately at the time of onset of adverse event. Multiple cytokine samples can be drawn for any specific adverse event that is suspected to be due to cytokine release, as clinically indicated; specific date and times of blood draws must be recorded. Separate cytokine samples should be drawn for each adverse event suspected of cytokine release, with specific date and time of draw to be recorded.

15 Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained as follows:

- In relation to pembrolizumab infusions on Days 1: Vital signs will be taken immediately before the pembrolizumab infusion (up to 5 minutes before the infusion [pre-dose]); at 15 minutes after the start of infusion; at 30 minutes (end of infusion), and at 1 hour after infusion if the margetuximab dose has not already commenced.
- In relation to margetuximab infusions on Days 1: Vital signs will be taken immediately before margetuximab infusion (up to 5 minutes before the infusion [pre-dose]), at 60 minutes after start of infusion, at 120 minutes (end of infusion), and at 1 hour after the completion of infusion.
- Note: For subsequent cycles after Cycle 1; the 1-hour post-infusion vital signs measurements may be deferred if continuing monitoring is not clinically indicated.

16 Radiographic disease assessments will occur every 6 weeks (i.e., following 2 cycles of treatment) for the first 24 weeks and then every 12 weeks thereafter until documented progression, initiation of alternative anti-cancer therapy, lost to follow up, withdrawal of informed consent, death, or end of study. To be performed within 3 days prior to dosing on Day 1 of every other cycle for the first 24 weeks (specifically prior to Cycles 3, 5, 7, and 9) and then every 4th cycle (prior to Cycles 13, 17, 21, etc.). Disease assessment will be done at office follow-up visits until end of study if patient agrees.

17 Screening brain scans should be performed on all patients who have previous history of CNS metastasis or as clinically indicated. Repeat brains scans will only be performed if the Screening brain scan was positive or as clinically indicated.

18 Pharmacokinetic sampling to be performed in accordance with **Table 6**; PK should be collected at Cycles 1, 2, 3, 5, 7, and EOT. EOT should be noted "PK tested using aliquot of ADA collection."

19 See **Table 5** for ADA sample days and times; ADA sample should be collected at Cycles 1, 2, 3, 5, 7, 9, 11 and every odd cycle thereafter (including EOT or 28 days after last dose of study drug).

20 Part B: To be performed for at least 20 of 60 patients enrolled in the Cohort Expansion Phase under the Original Protocol or Protocol Amendment 1 within 3 days prior to dosing on Cycle 1 Day 1 and on Cycle 2 Day 1.

Appendix 3 Table of Laboratory Testing Blood Volumes (Dose Escalation Phase – Part A)

Laboratory Specimens	Tube draw vol (mL)	Screening	Cycle 1			Cycle 2	Cycle 3		Cycle 4+	EOTV	Total
		Day -28 to 0	Day 1	Day 2	Day 8	Day 1	Day 1	Day 2	Day 1		
CBC with differential, platelet count	2	2	2			2	2		2	2	12
Chemistry panel	4	4	4			4	4		4	4	24
Free T4 and TSH	X [1]		X [1]			X [1]	X [1]		X [1]		
PT; aPTT	3		3			3	3		3		12
Flow cytometry: Lymphocyte subsets, NK cells and activation markers	5		10	5	5	5	5		5	5	40
Serum Cytokine	3		9 [2]	3							15
Margetuximab PK	3		9 [2]	3	3	6 [2,3]	6 [2]	3	3	3	36
ADA blood sample (anti-margetuximab Antibodies)	3		3			3	3		3	3	15
Fc receptor genotyping	8.5		8.5								8.5
HER2-specific immune response assays	8		24 [3]						24 [3]	24 [3]	72
Total Required (mL)		10	79.5	11	8	27	27	3	48	41	254.5

1 No additional blood needs to be drawn, add the tests in Chemistry panel tests menu.
2 Volumes are combined the multiple time points in that day.
3 8 mL of CPT tube, 3 tubes are needed for each time point.

Appendix 4 Table of Laboratory Testing Blood Volumes (Cohort Expansion Phase – Parts B - C)

Laboratory Specimens	Tube draw vol (mL)	Screening	Cycle 1		Cycle 2	Cycle 3	Cycle 4+	EOTV	Total
		Day -28 to 0	Day 1	Day 2	Day 1	Day 1	Day 1		
CBC with differential, platelet count	2	2	2		2	2	2	2	12
Chemistry panel	4	4	4		4	4	4	4	24
Free T4 and TSH	X [1]		X [1]		X [1]	X [1]	X [1]		
PT; aPTT	3		3		3	3	3		12
Flow cytometry: Lymphocyte subsets, NK cells and activation markers	5		5		5	5	5	5	25
Serum Cytokine	3		X [2]						
Margetuximab PK	3		9 [3]		6 [3]	6 [3]	3	3	27
ADA blood sample (anti-margetuximab Antibodies)	3		3		3	3	3	3	15
Fc receptor genotyping	8.5		8.5						8.5
HER2-specific immune response assays	8		24 [4]				24 [4]	24 [4]	72
Total Required (mL)		6	58.5		23	23	44	41	195.5

1 No additional blood needs to be drawn, add the tests in Chemistry panel tests menu.
2 Unscheduled blood draw.
3 Volumes are combined the multiple time points in that day.
4 8 mL of CPT tube, 3 tubes are needed for each time point.

Appendix 5 Censoring Rules for PFS

Situation	Date	Outcome
No baseline tumor assessments	**Date of first dose**	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	Date of first dose	Censored
Documented disease progression	Date of disease progression	Progressed
Initiation of alternative anti-cancer treatments in absence of progression	Date of last tumor assessment prior to initiation of such treatment	Censored
Death or progression immediately after missing two or more consecutive scheduled tumor assessments	Date of last tumor assessment prior to missed assessments	Censored

Appendix 6 Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work or office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry-on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 7 RECIST 1.1 Guidelines

(Adapted from Eisenhauer 2009 **(23)**

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

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-measureable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measureable, 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.

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-measureable 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 measureable by reproducible imaging techniques.

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 measureable 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.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

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.

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 lesion(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.

TUMOR RESPONSE EVALUATION

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).

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, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 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').

RESPONSE CRITERIA

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

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.

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 case report form. 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'.

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 measureable, 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 (<10mm 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).

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.

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.

EVALUATION OF BEST OVERALL RESPONSE

The best overall response 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 best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

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 measureable disease at baseline.

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 are 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.

Best overall response: all time points

The *best overall response* 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
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 partial response 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 best overall response 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 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.

CONFIRMATION/DURATION OF RESPONSE

Confirmation

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

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.

Duration of stable disease

Stable disease 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 8 Immune-Related RECIST Guidelines

[Adapted from Wolchok 2009 **(82)**]

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

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

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-measureable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measureable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness 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.

Non-measurable

All other lesions, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measureable 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 measureable by reproducible imaging techniques.

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 measureable 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.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

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**.

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 will not be used to assess *objective* tumor response.

TUMOR RESPONSE EVALUATION

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).

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 previously, 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, saggital 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').

RESPONSE CRITERIA

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

Evaluation of target lesions

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

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

Immune-related Progressive Disease (irPD): 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.

Unlike conventional RECIST criteria, the appearance of new measurable lesions does not automatically denote disease progression under immune-related response criteria. Rather the dimensions of new measurable lesions are added to overall sum of tumor diameters for determination of objective response status. Patients will not be considered as having progression unless the new overall sum of diameters has increased by $\geq$ 20% from the smallest sum of tumor diameters achieved while on study.

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

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 irCR, each node must achieve a short axis <10 mm. For irPR, irSD and irPD, 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 case report form. 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'.

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 measureable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

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

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

Immune-Related Progressive Disease (irPD): Unlike conventional RECIST 1.1, new measurable lesions or increases in the size of non-target lesions do not define PD in isolation in the immune-related response criteria. Rather, immune-related PD is established if the sum of diameters is ≥ 20% of the nadir of the sum of diameters for a given patient.

New Lesions

The appearance of new malignant lesions alone does not denote disease progression. Instead, the diameter of new lesions is added to the sum of diameters for target and non-target lesions.

EVALUATION OF BEST OVERALL RESPONSE

The best overall response 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 best overall response assignment will depend on the findings of both target and non-target disease.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. For patients experiencing irCR or irPR, a confirmatory scan obtained no less than 4 weeks after the original scan is required to confirm the objective response. For patients experiencing irPD, but who demonstrate acceptable tolerability of treatment as evaluated by the investigator, a confirmatory scan obtained no less than 4 weeks after the original scan is required for the confirmation of irPD.

Immune-related response determination per irRECIST

Target Lesions	Non-Target Lesions	%Change Tumor Burden	Immune-Related Response Status
CR	CR	-100%	irCR
PR	Any	≤-30%	irPR
PR	Any	≥-30% to <+20%	irSD
PR	Any	≥+20%	irPD
SD	Any	≥-30% to <+20%	irSD
SD	Any	≥+20%	irPD
PD	Any	≥+20%	irPD

No new lesions allowed to achieve irCR status. Otherwise, presence or absence of new measurable or new non-measurable lesions does not affect response status in isolation. New measurable lesions added to cumulative tumor burden to calculate % change tumor burden for the determination of immune-related response status.

Immune-Related Complete Response (irCR): Complete disappearance of all target and non-target lesions and no new lesions. The short axis of all lymph nodes must be ≤ 10 mm.

Immune-Related Partial Response (irPR): The sum of diameters has decreased ≥ 30% from the baseline, but does not meet the criteria for irCR.

Immune-Related Stable Disease (irSD): The patient does not meet criteria for irCR, irPR or irPD.

Immune-Related Progressive Disease (irPD): The sum of diameters for target lesions and new measureable lesions has increased by ≥ 20% from the nadir sum of diameters

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 are 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.

Best overall response: all time points

The *best overall response* is determined once all the data for the patient is known.

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. Absent this subsequent radiographic confirmation, irCR or irPR designations will be considered as unconfirmed responses.

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 irCR 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 1**.

CONFIRMATION/DURATION OF RESPONSE

Confirmation

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

Duration of overall response

The duration of overall response is measure from the time measurement criteria are first met for irCR/irPR (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 irCR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease 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 irPD).

Appendix 9 Principal Investigator's Agreement

Study Title: A Phase 1b/2, Open Label, Dose Escalation Study of Margetuximab in Combination with Pembrolizumab in Patients with Relapsed/Refractory Advanced HER2+ Gastroesophageal Junction or Gastric Cancer

Study Number: CP-MGAH22-05

I have read the protocol described above.

I have fully discussed the objectives of this trial 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 trial 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 trial 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 trial, I will communicate my intention immediately in writing to the Sponsor.

Signed: _____ **Date:** _____

PI Name (printed): _____

PI Affiliation: _____

PI Address: _____

PI Phone Number: _____

CP-MGAH22-05 Protocol Amendment 6 (29-Jun-2020)
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User Task: eSignatories Approval	arch Approval (Intended or Designee) 29-Jun-2020 19:27:29 GMT+0000

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