STATISTICAL ANALYSIS PLAN
VERSION 2.0

PROTOCOL CP-MGAH22-05

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

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
GEJ	Gastroesophageal Junction
irCR	immune-related complete response
IRE	Immediately reportable events
irPD	immune-related progressive disease
irPR	immune-related partial response
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irSD	immune-related stable disease
IV	Intravenously
LVEF	Left ventricular ejection fraction
MAD	Maximum administrated dose
MedDRA	Medical dictionary for regulatory activities
MTD	Maximum tolerated dose
MUGA	Multi Gated Acquisition Scan

ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD	pharmacodynamics
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PT	Preferred Term
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease
SOC	System Organ Class
SPP	Statistical programming plan
TEAE	Treatment emergent adverse event
TLF	Table, listing and figure

1 INTRODUCTION

This study is an open-label, dose escalation, Phase 1b/2 study designed to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of margetuximab administered intravenously (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+ gastroesophageal junction (GEJ) or gastric cancer (GC).

This SAP describes in detail the statistical methods to be used for analysis of the primary and secondary efficacy endpoints, the safety endpoints, and the PK parameters to be collected from this study.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

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 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 and immune-related RECIST (irRECIST), in patients that have failed first-line trastuzumab-containing regimens.

2.2 Secondary Objective(s)

Secondary objectives 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 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 STUDY DESIGN AND PLAN

3.1 Overall Study Design and Plan

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.

The study consists of a Dose Escalation Phase 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 to further define the safety and initial efficacy of the combination with the margetuximab dose established in the first phase.

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 24 weeks 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 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 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.

See the Study Evaluation Table of the latest version of the protocol for the full description of study evaluations, including the number and timing of visits and the procedures to be performed at each visit.

3.2 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 (**Table 1**) provides the 2-sided 95% confidence interval (CI) for a number of potential response rates under various sample sizes.

Table 1 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%).

4 ANALYSIS POPULATIONS

Two populations will be used for 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.

5 ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Response Endpoints

- Response by RECIST v1.1: The response by radiographic assessment using RECIST v1.1 is categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The CR and PR are required to be confirmed at least 28 days after the initial observation of such response.
- Immune-related Response by irRECIST: The immune-related response by radiographic assessment using irRECIST is categorized as immune-related complete response (irCR), immune-related partial response (irPR), immune-related stable disease (irSD), and immune-related progressive disease (irPD). The irCR, irPR and irPD are required to be confirmed at least 28 days after the initial observation of such response.

5.1.2 Time to Event Endpoints

- Progression-free survival (PFS): The PFS is defined as the time from the first dose date to the date of first documented progression or death from any cause, whichever occurs first. For patients who are not known to be dead or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the date of the last tumor assessment. The documented progression is determined by radiographic assessment using RECIST v1.1. PFS will be calculated as:

  PFS (months) = (date of event [documented progression or death] or date of censoring – first dose date +1) / (365.25/12)

- Duration of response (DoR): The DoR is defined as the time from the date of initial response to the date of first documented progression or death from any cause, whichever occurs first. DoR will be analyzed for responding patients only. For responding patients who are not known to be dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. The documented progression is determined by radiographic assessment using RECIST v1.1. DoR will be calculated as:

  DoR(months) = (date of event [documented progression or death] or date of censoring – date of initial response+1) / (365.25/12)

DoR may also be determined by irRECIST.

- Overall survival (OS): The OS is defined as the time from the first dose date to the date of death from any cause. For patients who are not known to be dead at the time of data cut-off for OS analysis, the OS will be censored at the time they are last known to be alive. OS will be calculated as:

OS (months) = (date of death or last known alive – first dose date +1) / (365.25/12)]

5.2 Safety Endpoints

5.2.1 Adverse Events

Safety will primarily be addressed by evaluations of adverse events (AEs). An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject, occurring as part of a research study, which does not necessarily have to have a causal relationship with use of a medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease whether or not considered related to the medicinal product.

AEs will be captured starting with signing of the informed consent form through 28 days following cessation of treatment. Only treatment-related serious AEs will be captured afterwards. These events will be recorded by the Investigators in the eCRFs. Verbatim terms will be coded to lower-level terms using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

Only treatment-emergent adverse events (TEAEs) will be summarized as safety endpoints. A TEAE is defined as any event that is newly occurring on or after the administration of study drug or an event that existed before but increased in severity on or after study drug administration. For each TEAE, a new AE is recorded whenever the toxicity/severity changes. AEs that occurred before and did not worsen on or after study drug administration are considered non-treatment emergent AEs and will only be summarized as medical history.

5.2.2 Laboratory Evaluations

Standard safety laboratory parameters collected via a local laboratory will be summarized and graded according to CTCAE Version 4.03. Lab values falling outside of a clinically accepted reference range or values that differ significantly from previous values will be evaluated for clinical significance. Abnormal laboratory findings should be considered 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.

5.2.3 Physical Examinations

Physical examinations will be performed according to the schedules outlined in the latest version of the protocols. Abnormalities that were not present prior to dosing will be captured and summarized as adverse event data. Those present prior to dosing will be included as medical history.

5.2.4 Vital Signs

Vital sign assessments will be performed according to the schedules outlined in the latest version of the protocol. Abnormalities will be captured as AEs only if it meets SAE criteria, cause discontinuation or interruption of study treatment, requires intervention, or deemed clinically significant based on medical judgement.

5.2.5 Cardiac Evaluations

5.2.5.1 12-Lead Electrocardiograms

Twelve-lead electrocardiograms (ECGs, in triplicate, approximately 1 minute apart) will be obtained according to the to the schedules outlined in the latest version of the protocol in order to evaluate the potential cardiac effects of margetuximab or prior anti-HER2 treatment, including QT interval prolongation.

5.2.5.2 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 schedules outlined in the latest version of the protocol. 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.

5.3 Pharmacokinetic, Pharmacodynamic, and Immunological Parameter Endpoints

PK samples and ADA samples will be collected according to the schedules outlined in the latest version of the protocol.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

This Phase 1b/2 study is primarily observational and, thus, the majority of the statistical summaries will be descriptive. Safety and efficacy summaries will be provided for each dose level cohort and for all dose level cohorts combined. Response rates will be calculated for the response evaluable population.

Unless otherwise specified, the following general considerations are applied in data analyses:

- The baseline value is defined as the latest value prior to the start of study drugs.
- Categorical data will be summarized by the number and percent of patients falling within each category.
- Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum.
- Time-to-event endpoints will be summarized by the number and percent of the event, median time and corresponding 95% confidence interval (CI), and event free rate and corresponding 95% CI at the specified time points of interest.
- All data summaries and tabulations will be conducted using SAS® software Version 9.3 or higher.

6.2 Missing Data

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 Programming Plan (SPP). 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.

6.3 Patient Disposition and Baseline Characteristics

6.3.1 Patient Disposition

For patient disposition, the number and percentage of patients who reach various study milestones are summarized: All screened patients are broken down by screen failures (with reasons if collected) and enrolled. Then the category of enrolled is broken down by never treated (with reasons if collected) and treated. The category of treated will further be broken down by treatment ongoing and treatment discontinuation (with reasons for discontinuation, which also include protocol-defined treatment completion, if any). The end of study status for all enrolled patients will also be included. Duration of study, defined as from the date of first dose to the date of withdraw of consent, lost to follow up, death, or the last contact date, will be summarized.

6.3.2 Patient Demographics and Baseline Characteristics

Patient demographics, baseline disease characteristics, disease history, medical history and other collected baseline data will be summarized using descriptive statistics.

6.4 Study Drug Exposures and Concomitant Medications

Study drug exposure and concomitant medications will be summarized by descriptive statistics.

For each study drug (margetuximab and pembrolimumab), the summary of study drug exposure will include descriptive statistics as well as frequency counts for the number of doses received, the total dose administrated as well as the total dose intended, and the dose intensity which is calculated as percentage of total dose administrated divided by total dose intended during the period that study drug was administrated. Duration of study treatment exposure will also be summarized.

The summary of concomitant medications will include the number and percentage of patients who receive any concomitant medications as well as each concomitant medication by drug class.

6.5 Protocol Deviations

Major protocol deviations will be identified prior to database lock for final analysis and will be listed and summarized.

6.6 Efficacy Endpoint Analyses

6.6.1 Analyses of Response Endpoints

The objective response rate (ORR) is estimated as the proportion of patients in the response evaluable population achieving a CR or PR per RECIST v1.1. A two-sided 95% exact binomial CI for ORR will be calculated. In addition, the ORR per irRECIST and its 95% CI will also be calculated.

6.6.2 Analyses of Time to Event Endpoints

6.6.2.1 PFS

The Kaplan-Meier method will be applied to estimate PFS curve, median PFS time, and PFS rates at 3 and 6 months. The method of Brookmeyer and Crowley **(1)** will be used to construct 95% CI for median PFS. The 95% CIs for PFS rate at 3 and 6 months will be calculated by normal approximation after log(-log) transformation.

For primary PFS analysis, the following table describes the censoring rules.

Table 2 Censoring Rules for Primary PFS Analysis

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

A sensitivity analyses for PFS will be performed to assess the robustness of above primary PFS analysis. For this sensitivity analysis, the censoring rules are the same as in **Table 2** except that documented progression or death will be considered as an event, regardless when it occurs during the study.

6.6.2.2 DoR

The Kaplan-Meier method will be applied to estimate DoR curve, median DoR time, and DoR rates at 3 and 6 months. The same censoring rules as in **Table 2** will be applied. The method of Brookmeyer and Crowley **(1)** will be used to construct 95% CI for median DoR. The 95% CIs for DoR rate at 3 and 6 months will be calculated by normal approximation after log(-log) transformation. These analyses will also be repeated for DoR based on irRECIST.

6.6.2.3 OS

The Kaplan-Meier method will be applied to estimate OS curve, median OS time, and OS rates at 1 and 2 years. The method of Brookmeyer and Crowley **(1)** will be used to construct 95% CI for median OS. The 95% CIs for OS rate at 1 and 2 years will be calculated by normal approximation after log(-log) transformation.

6.6.3 Tumor Size Change Over Time

Change in tumor size, measured as the sum of target lesions measurements, from baseline over time will be summarized as well as presented by spider plot. The best percentage change from baseline will be presented by waterfall plot.

6.7 Safety Endpoint Analyses

6.7.1 Treatment Emergent Adverse Events

Only TEAEs will be summarized. The non-treatment emergent AEs are included in medical history summaries. Note that all TEAEs recorded in the eCRFs will be included in the safety analysis, even if they are outside the collection window.

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

- Any TEAEs
- Treatment-related TEAEs
- TEAEs by CTCAE severity Grade ≥ 3
- Treatment-related TEAEs with CTCAE severity Grade ≥ 3
- TEAEs related to each individual study drug
- Any SAEs
- Treatment-related SAEs
- SAEs related to each individual drug
- Fatal AEs
- AESIs
- IREs
- TEAEs that result in study discontinuation
- TEAEs that lead to interruption of each individual drug
- TEAEs that lead to withdrawal of each individual study drug

All of these summaries will display the number and percent of patients who experience the given event and will display events by System/Organ/Class (SOC) and Preferred Term (PT). Events will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC.

In addition, an overall summary table will be generated to display the number and percent of patients who experience at least one event of each of above TEAE types.

6.7.2 Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified labs. Summaries will be grouped by lab panel (hematology, blood chemistry, and urinalysis) and will be displayed by visit for each lab parameter. Graphs of mean values over time may also be generated.

In cases where an abnormality resulted in a repeat lab test, the repeat value will be used for the summaries.

Shift tables will be used to display the percent of patients who have a shift in post-baseline maximum CTCAE grade from baseline for each lab parameter.

6.7.3 Other Safety Endpoints

6.7.3.1 ECG and MUGA Scan

ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. The following categories for QTcF interval and maximum post dose change from baseline QTcF interval (ΔQTcF) will be used in summary and shift tables:

QTcF: ≤ 450 msec, >450 to 480 msec, >480 to 500 msec, and >500 msec

ΔQTcF: ≤ 30 msec, >30 to 60 msec, and >60 msec

MUGA scan or echocardiogram will be presented by change from baseline in LVEF.

6.7.3.2 Physical Exams and Vital Signs

Physical exams and vital signs may be summarized with descriptive statistics at each visit and time point where they are collected. The following categories will be used in shift tables for vital signs.

- Systolic blood pressure (mmHg): <90 (Low), 90-120 (Normal), >120 (High)
- Diastolic blood pressure (mmHg): <60 (Low), 60-80 (Normal), >80 (High)
- Heart rate (Beats/min): <60 (Low), 60-100 (Normal), >100 (High)
- Respiratory Rate (Breaths/min): <12 (Low), 12-18 (Normal), >18 (High)
- Temperature (°F): <97.8 (Low), 97.8-99.1 (Normal), >99.1 (High)

6.8 Pharmacokinetic, Pharmacodynamic, and Immunological Parameter Endpoint 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" of the protocol and corresponding changes from baseline, will be summarized and/or may also be presented graphically as well. Possible associations between changes in pharmacodynamics measures of interest and margetuximab dose and exposure may be explored.

6.9 Futility Analysis

During expansion phase, an futility analysis of ORR will be performed after 15 patients in each region (North America and Asia) have been enrolled and each patient received at least one post baseline tumor assessment. Duration of response for responders as well as tumor size change over time for all 15 patients per region may also be calculated in assisting interim decision making.

6.10 Subgroup Analysis

Efficacy analyses will be performed by race (Asian vs Non-Asian), tumor location (GC vs GEJ), and other demographics and baseline characteristics. The analyses will also be performed by baseline biomarkers such as HER2 IHC status (IHC3+ vs IHC2+), PD-L1 status (PD-L1+ vs PD-L1-), double positive status (HER2 IHC3+ and PD-L1+ vs others), and by alleles coding for CD16A (VV, FF, FV, and FF and FV combined [F Carrier]), respectively.

7 LIST OF TABLES, LISTINGS, AND FIGURES

The list of tables, listings, and figures (TLFs) and associated shells planned for the clinical study report based on the analyses described in this SAP will be provided in a separate statistical programming plan (SPP), which will also include data reporting conventions and programming specifications for the development of these TLFs.

8 REFERENCES

1. **Brookmeyer R, Crowley J.** A Confidence Interval for the Median Survival Time. Biometrics 1982; 38:29-41.