STATISTICAL ANALYSIS PLAN
VERSION 4.0

PROTOCOL CP-MGAH22-04

A PHASE 3, RANDOMIZED STUDY OF MARGETUXIMAB PLUS CHEMOTHERAPY VS. TRASTUZUMAB PLUS CHEMOTHERAPY IN THE TREATMENT OF PATIENTS WITH HER2+ METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR ANTI-HER2 THERAPIES AND REQUIRE SYSTEMIC TREATMENT

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
ADaM	Analysis Dataset Model
AE	Adverse event
AESI	Adverse event of special interest
CBR	Clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
CDST	CRO DSMC Support Team
CR	Complete response
CRO	Clinical Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
E-R	Exposure-response
ER	Estrogen receptor
HR	Hazard ratio
HRQoL	Health related quality of life
IHC	immunohistochemistry
IRE	Immediately reportable events
ISH	in situ hybridization
ITT	Intent-to-treat
IxRS	Interactive Response System
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute

NFBSI	Network-Functional Assessment of Cancer Therapy – Breast Cancer Symptom Index
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PT	Preferred Term
PR	Partial response
PgR	Progesterone receptor
RE	Response-Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAS	Statistical Analysis System
SD	Stable disease
SD	Standard deviation
SOC	System Organ Class
SDTM	Study Data Tabulation Model
TEAE	Treatment emergent adverse event
T-DM1	Ado-trastuzumab emtansine
TLF	Table, listing and figure

1 INTRODUCTION

This document describes the details of the statistical analyses, data summaries, and data conventions to be used for study CP-MGAH22-04. This Phase 3 study was designed to compare the efficacy and safety of the margetuximab plus chemotherapy to trastuzumab plus chemotherapy in patients with HER2+ metastatic breast cancer who have received at least two prior lines of anti-HER2 directed therapies in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three, lines of therapy overall in the metastatic setting. Analyses and summaries are described to allow for statistically meaningful conclusions to be drawn from this study.

CP-MGAH22-04 also includes a sub-study cohort to evaluate the safety and tolerability of sequential reductions in margetuximab infusion duration from 120 minutes in Cycle 1 to 30 minutes in Cycle 2 and beyond. Patients who participate in the infusion sub-study will not be randomized and will be enrolled to receive either monotherapy margetuximab or margetuximab in combination with protocol-specified physician's choice of chemotherapy. Patients must have received at least 4 prior lines of therapy for metastatic disease to be eligible for the infusion sub-study, therefore the patient population will not overlap with the randomized portion of CP-MGAH22-04.

1.1 Data Cutoffs

This randomized study includes two primary endpoints, progression-free survival (PFS) and overall survival (OS) that are anticipated to be assessed at different time points. Two assessments for PFS will be made: 1) PFS will be assessed for futility when approximately 100 PFS events have occurred and 2) the primary PFS analysis will take place when approximately 257 PFS events have occurred or after all planned patients (N=530) have been randomized, whichever occurs later.

The first interim OS analysis will occur at the time of the primary PFS analysis. A second interim analysis for OS will be performed when 70% of the target OS events have occurred if this has not yet occurred at the time of the primary PFS analysis.

A data cutoff date corresponding to the PFS analyses (futility and final) and interim OS analyses will be established and the data domains required for each analysis will be locked and datasets extracted. All visit dates up to this date will be included. Partial dates will follow the rules described in **Section 6.1.2**. Durations for end dates that have not occurred will be censored.

The final analysis for OS will be conducted when approximately 385 deaths have occurred. A final database lock will occur at this time.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy, as measured by PFS assessed by independent review and OS, of margetuximab plus chemotherapy compared to trastuzumab plus chemotherapy in patients with advanced HER2-positive breast cancer who have received at least two prior lines of anti-HER2 directed therapies in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three, lines of therapy overall in the metastatic setting. In either case, patients must have received prior treatment with pertuzumab in the (neo)adjuvant or metastatic setting.

Infusion Sub-Study: The primary objective of the infusion sub-study is to determine the safety and tolerability of margetuximab administered at a reduced infusion time in Cycle 2 and beyond. The incidence of Grade 3 or greater infusion-related reactions (IRRs) by the end of Cycle 2 is the primary outcome measure.

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate PFS, as assessed by the study investigators, of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
- To evaluate by independent review, the objective response rate (ORR) of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.

Infusion sub-study: Incidence of all Grade infusion-related reactions in all sub-study patients is the secondary outcome measure.

2.3 Tertiary Objectives

The tertiary objectives are:

- To evaluate the health-related quality of life (HRQoL), as assessed using the Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI-16) and EQ-5D-5L, associated with margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
- To characterize the safety profile of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
- To evaluate the clinical benefit rate (CBR) of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients. Both independently assessed and investigator assessed CBR will be evaluated.

- To evaluate ORR, as assessed by study investigators, of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
- To evaluate the duration of response (DOR) of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients. Both independently assessed and investigator assessed DOR will be evaluated.
- To characterize the population pharmacokinetics and exposure-response (E-R) relationships of margetuximab in these patients.
- To evaluate the anti-drug antibodies (ADA) directed against margetuximab and its effects on pharmacokinetics (PK), efficacy, and safety in these patients.

2.4 Exploratory Objective(s)

To evaluate the effect of allelic variation in CD16A, CD32A, and CD32B on the efficacy of margetuximab in all patients receiving study treatments.

3 STUDY DESIGN AND PLAN

3.1 Overall Study Design and Plan

This is a randomized, Phase 3, open-label, comparator-controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy, for the treatment of patients with advanced HER2+ breast cancer who have received at least two prior lines of anti-HER2 directed therapies in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three, lines of therapy overall 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. The selected chemotherapy must be allowed for use per local regulations. Upon meeting entry criteria, patients enrolled in the study will be randomized 1:1 to receive either margetuximab or trastuzumab to be administered in combination with the chosen chemotherapy. Patients will be treated until disease progression, death, withdrawal of consent, or request by the treating physician to discontinue treatment. Following completion of (or discontinuation from) treatment, patients will be followed for survival.

Randomization will be stratified by backbone chemotherapy regimen, number of metastatic sites, and number of lines of therapy in the metastatic setting. Patients will receive either margetuximab or trastuzumab on Day 1 of a 3-week cycle. Chemotherapy will be given prior to margetuximab or trastuzumab on days when both study drug and chemotherapy are administered.

Tumor evaluations will be performed according to the schedules outlined in the latest version of the protocol. Disease response will be determined both locally and by central review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patient treatment decisions will be based on local (investigator) reviews of available assessments. Central radiological and medical review will be conducted by BioClinica and will be blinded to the study treatment (margetuximab or trastuzumab). Results of central review will be used for the primary endpoint of PFS.

A Data Safety Monitoring Committee (DSMC) will monitor safety throughout the randomized portion of the trial and perform interim analyses for PFS and OS at prespecified time points. The DSMC will perform a futility analysis after 100 PFS events have occurred, and will perform two interim analyses of OS: one at the time of the primary assessment of PFS and a second when 70% of the OS events have occurred. The role and function of the DSMC are described more fully in the DSMC Charter.

The primary PFS analysis will occur when approximately 257 PFS events have occurred or after all patients have been randomized, whichever occurs last. The final OS analysis will be conducted when 385 deaths have been reported.

3.1.1 Infusion Sub-Study

CP-MGAH22-04 will include a non-randomized sub-study cohort of about 78 patients to evaluate safety and tolerability of margetuximab infusion duration reduction from 120 minutes in Cycle 1 to 30 minutes in Cycle 2 and beyond. The sub-study will start with a run-in group, in which about 9 patients will receive a 120-minute margetuximab infusion (as a single agent, or in combination with protocol-specified chemotherapy) in Cycle 1, in order to have 6 patients receive 60-minute infusions in Cycle 2 and beyond (Stage A1). If no stopping rules are met, an additional cohort of about 9 patients will be enrolled to receive a 120-minute margetuximab infusion in Cycle 1, in order to have 6 patients receive a 30-minute infusions at Cycle 2 and beyond (Stage A2). Patients enrolled into Stage A1 and A2 will be assigned to receive the reduced infusions until 6 patients have received reduced infusion times. Any extra patients beyond 6 in run-in groups A1 or A2 will continue 120-minute infusions until the Stage B regimen is confirmed. In the absence of Grade 3 or higher IRRs, patients in Stage A may reduce infusion duration to the Stage B regimen.

Safety events observed in Stage A1 and A2 will be used to inform infusion reduction schemes for a subsequent group of about 60 patients enrolled to Stage B, who will receive margetuximab over a 120-minute infusion in Cycle 1, followed by either a 60-minute or 30-minute infusion in Cycles 2 and beyond. Details of the study design and stopping rules can be found in Section 6.7.1 and Figure 1 of the latest version of protocol (**CP-MGAH22-04 Protocol Amend 3**, dated 26 January 2018).

3.2 Statistical Hypotheses

The primary endpoints of centrally-assessed PFS and OS will be compared between groups and tested in sequential order. PFS will be tested first. If PFS is statistically significant, only then will OS be tested. Both hypotheses will be evaluated at $\alpha = 0.05$.

The null hypothesis for each endpoint is that the two treatment arms are the same. The alternative hypothesis is that the survival distributions of both PFS and OS are different.

The null and alternative hypotheses to be tested for PFS:

H_o: $PFS_T = PFS_M$,

H_1: $PFS_T \neq PFS_M$

AND

The null and alternative hypotheses to be tested for OS:

H_o: $OS_T = OS_M$,

H_1: $OS_T \neq OS_M$

For the above hypotheses: T = trastuzumab plus chemotherapy, M = margetuximab plus chemotherapy. Rejecting either the PFS null hypothesis or both the PFS and OS null

hypotheses will be considered sufficient for achieving the study's primary objective. If the PFS null is not rejected, based on the hierarchical approach, OS cannot be tested.

3.3 Randomization and Sample Size Justification

3.3.1 Randomization and Blinding

Approximately 530 patients will be randomized 1:1 to either margetuximab plus chemotherapy or trastuzumab plus chemotherapy via an Interactive Response System (IxRS) within 3 days of Study Day 1 (Cycle 1 Day 1).

Central randomization will be used. Blocked randomization will be used to achieve treatment balance within each stratum.

The stratification factors are:

- Choice of backbone chemotherapy
  - Capecitabine
  - Eribulin
  - Gemcitabine
  - Vinorelbine
- Number of metastatic sites
  - ≤2
  - >2
- Number of lines of prior therapy in the metastatic setting
  - ≤2
  - >2

This is an open-label Sponsor-blinded study. Patients and investigators will not be blinded to treatment assignment. However, clinical data with respect to treatment assignment will remain blinded to the Sponsor and certain contract research organization (CRO) staff unless unblinding is required for operational aspects of the study. Specifically, all Sponsor and CRO staff directly involved in the conduct of data analyses will remain blinded. Unblinding will occur at the time of the final PFS analysis.

Infusion sub-study: The sub-study will be single arm and unblinded. Patients who participate in the infusion sub-study will be enrolled to receive either monotherapy margetuximab or margetuximab in combination with protocol-specified physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).

3.3.2 Sample Size Justification

This study has two primary endpoints. The first primary endpoint is centrally-assessed PFS and the second primary endpoint is OS. These two endpoints will be assessed in a sequential order with PFS being assessed first. OS will only be assessed if a statistically significant difference is obtained in PFS.

It is estimated that the median PFS for patients treated with trastuzumab plus chemotherapy is approximately 4 months. To detect a 2 month improvement in median PFS from 4 months to 6 months (HR=0.67) in patients treated with margetuximab plus chemotherapy, assuming that PFS is exponentially distributed, a total of 257 PFS events are required to provide 90% power at a 2-sided α=0.05. The analysis of the primary PFS endpoint will occur when about 257 events have occurred or after all patients have randomized, whichever occurs later. The sample size for this study is calculated to ensure 80% power for the analysis of OS. The median OS for patients treated with trastuzumab plus chemotherapy is estimated to be 12 months. This study is designed to detect an increase to a median survival of 16 months in patients treated with margetuximab plus chemotherapy (HR=0.75). Assuming that OS is exponentially distributed with median OS time of 12 months for trastuzumab plus chemotherapy arm and 16 months for margetuximab plus chemotherapy arm, 2 interim analyses are performed as described in **Section 6.1.1**, and a Lan-DeMets alpha spending function using an O'Brien-Fleming stopping boundary is used, approximately 385 deaths will be required to provide 80% power to achieve statistical significance at overall type I error of 2-sided alpha=0.05. It is anticipated that approximately 530 patients will be accrued to achieve this number of events.

The planned sample size for the infusion sub-study is approximately 78 patients, including about 18 patients for Stage A and 60 patients for Stage B. A target sample size of 60 patients for Stage B of the infusion sub-study is intended to provide confirmation of accelerated infusion tolerability.

Total trial enrollment, including randomized and infusion sub-study cohorts, is expected to be approximately 608.

4 STUDY POPULATIONS

4.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population represents all randomized patients. Patients will be analyzed according to the treatment assigned at randomization. This population will be used to summarize baseline data and for the assessment of PFS, OS, and HRQoL.

4.2 Response Evaluable Population

The Response-Evaluable (RE) population represents all patients who are randomized and have measurable disease at baseline. This population will be used for ORR and CBR.

4.3 Safety Population

The Safety population represents patients who are randomized and receive any amount of study treatment. Patients will be analyzed according to the actual treatment received rather than the treatment group to which they were randomized. This population will be used for safety, PK, pharmacodynamics, and immunogenicity analyses.

Infusion sub-study: The safety population for the infusion sub-study represents patients who are enrolled in the infusion sub-study and receive any amount of study treatment. This population will be used for all analyses for patients enrolled and treated in the infusion sub-study described in **Section 6** below.

5 ENDPOINTS AND COVARIATES

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoints

The primary endpoints are independently-assessed PFS and OS. PFS is defined as the time from the date of randomization to date of first documented progression or date of death from any cause, whichever occurs first. For patients who are not known to have died or progressed at the time of data cut-off for PFS analysis, the PFS will be censored at the last tumor assessment. The documented progression is determined by radiographic assessment using RECIST v1.1. PFS will be calculated as:

PFS (months) = round ((date of progression or date of death or date of last tumor assessment – date of randomization+1) / (365.25/12), .01)

The following table describes the censoring rules for the primary PFS analysis.

Table 1 Censoring Rules for Primary PFS Analysis

Situation	Date	Outcome
No baseline tumor assessments	Randomization date	Censored
Death prior to 1st scheduled tumor assessment	Date of death	Progressed
No post-baseline tumor assessments in absence of death prior to first scheduled tumor assessment	Randomization date	Censored
Documented disease progression	Date of disease progression	Progressed
Initiation of alternative anti-cancer treatments in absence of PD	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

The OS time is defined as the time from date of randomization 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 were last known to be alive. OS will be calculated as:

OS (months) = round ((date of last known alive or death date – date of randomization+1) / (365.25/12), .01)

Since the endpoints are evaluated in a hierarchical manner, both endpoints will be assessed using a 2-sided $\alpha = 0.05$.

5.1.2 Secondary Efficacy Endpoints

Two secondary endpoints are defined and will be assessed using a 2-sided $\alpha = 0.05$.

To control the type 1 error rate at 0.05 for these 2 secondary endpoints, Hochberg's step-up method will be used. P-values will be assessed in descending order. If the least significant p-value<0.05, both hypotheses are rejected. Otherwise, this endpoint is retained and the second p-value is tested at p<0.025. If a p-value<0.025 (0.05/2) is obtained, this hypothesis is rejected. Otherwise, both hypotheses are retained.

5.1.2.1 Investigator-Assessed Progression-Free Survival

Investigator-assessed PFS will be defined in the same manner as independently-assessed PFS. The only difference is that disease progression will be determined by the investigator instead of by independent assessment via central radiographic review.

5.1.2.2 Independent Review-Assessed Objective Response Rate

Tumor measurements will be assessed using RECIST 1.1 criteria based on independent radiological review. A responder is a patient with baseline measurable disease who achieves a complete response (CR) or partial response (PR) that is confirmed at least 28 days after the initial documentation of an objective response. Patients who have baseline measurable disease but no post-baseline radiographic assessment will be considered as non-responders. Response rate will be calculated as:

ORR = # patients with confirmed response (CR or PR) / # patients in the RE population

5.1.3 Tertiary Efficacy Endpoints

A number of tertiary endpoints will be assessed. No adjustment for multiplicity will be used for these endpoints.

5.1.3.1 Duration of Response

DoR will be based on both independent review and investigator assessed responses (CR or PR). It is defined as time from initial response to date of 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 last tumor assessment.

DoR will be calculated as:

DoR(months) = round ((progression date or death date or date of last tumor assessment – date of initial response+1) / (365.25/12),0.01)

5.1.3.2 Investigator-Assessed ORR

Investigator assessed ORR is calculated the same as in **Section 5.1.2.2**. The only difference is that the response is determined by study investigators.

5.1.3.3 Clinical Benefit Rate

The CBR is defined as the number of patients in the RE population who achieve a best response of CR, PR, or stable disease (SD) of duration >6 months. It will be evaluated based on both independent review assessed and investigator assessed responses.

CBR will be calculated as:

CBR = # patients with best response CR, PR, SD >6 months / # patients in RE population

5.1.3.4 NFBSI-16 and EQ-5D-5L HRQoL Surveys

Quality of life data will be collected from direct reports from patients on the randomized portion of CP-MGAH22-04 using the NFBSI-16 and EQ-5D-5L questionnaires. The primary analysis of NFBSI-16 will be based on the total score with secondary analyses of the subscales that add to the total. Analysis of EQ-5D-5L will be based on both the EQ-5D utility index and the EQ-5D VAS score.

These data will be collected according to the schedules outlined in the latest version of the protocol.

To help reduce missing data, intensive training of the sites, central monitoring of the timely completion of the questionnaires, and regular communication with the sites will be performed.

5.1.3.5 Population Pharmacokinetics and Exposure-Response Relationships

Serum concentrations of margetuximab will be collected according to the schedules outlined in the latest version of the protocol. Single and multiple dose PK parameters for margetuximab (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.

5.1.3.6 Anti-Drug Antibodies

ADA samples will be collected according to the schedules outlined in the latest version of the protocol. Samples will be classified as negative or positive and summarized as such.

5.1.4 Exploratory Endpoints

Associations between efficacy endpoints (response, PFS and OS) and respective alleles coding for CD16A (VV, FF, and VF), CD32A (HH, RR, HR), and CD32B (II, TT, and IT) may be explored. Specifically, logistic regression model for response, and Cox proportional

hazards model for PFS and OS, respectively, may be applied with treatment, each protein, and their interactions being included as covariates. In particular, for protein CD16A, the alleles coding will be grouped as VV vs (VF and FF) in the models to assess the treatment effect difference in VV vs (VF and FF).

In addition, the impact of subsequent use of T-DM1 (after discontinuing from SOPHIA treatment) on the efficacy endpoint OS will be evaluated by time-dependent Cox model.

5.2 Safety Endpoints

5.2.1 Adverse Events

Safety and tolerability will be assessed from time of study drug initiation through the End of Treatment visit (or 28 days after the last dose of study drug, whichever occurs later). Safety will be evaluated primarily by summarizing adverse events (AEs), immediately reportable events (IREs), adverse events of special interest (AESIs), and serious adverse events (SAEs). Adverse events will be summarized by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA v18.0 or higher). Events will be summarized by severity (using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 or later) and relationship to study drug (as assessed by the investigator). Patients will be counted only once for each preferred term, once for each system organ class or AESI and by the highest event severity, regardless of how many events the subject experienced.

These events will be recorded by the Investigators in the electronic case report forms (eCRFs). Verbatim terms will be coded to lower-level terms in the MedDRA coding dictionary.

Only treatment-emergent adverse events (TEAEs) will be summarized in tables. Events that occur prior to first dose will not be included in these summaries (unless the event worsens post first dose) but will be included in patient listings. In addition, events related to tumor progression/worsening of underlying disease (including those with a fatal outcome) will be collected as efficacy endpoints, and not documented as AEs/SAEs. A TEAE is defined as any event that is newly occurring after the first administration of study drug or an event that existed at the time of first study drug administration but increased in severity after study drug administration. An ongoing TEAE that changes in severity (increases or decreases) will be captured as a new event.

The AESIs will include:

- All infusion-related reactions; only Grade 3 or greater will be reported as Immediate Reportable Events.
- Left ventricular dysfunction requiring delay or cessation of margetuximab or trastuzumab administration.

Infusion sub-study: AEs, IREs, AESIs, and SAEs will be summarized as described above. In particular, the safety and tolerability of reduced margetuximab infusion times will be assessed based on:

- Incidence of Grade 3 or greater IRRs by the end of Cycle 2 in Stage B patients who received a Cycle 2 dose at a lowered infusion rate (primary outcome measure).
- Overall incidence of all Grade IRRs in all sub-study patients (secondary outcome measure).

5.2.2 Laboratory Evaluations

Standard safety laboratory parameters collected via a central 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. If a value is considered as an abnormal change from baseline and of clinical significance, it is considered as an AE. **Table 2** identifies the routine laboratory tests that will be performed.

Table 2 Laboratory Parameters

Pregnancy test • Blood serum human chorionic gonadotropin (hCG) **Hematology:** • Hematocrit (Hct) • Hemoglobin (Hgb) • 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) • Aspartate aminotransferase (AST; SGOT) • Amylase • Bicarbonate • Blood urea nitrogen (BUN) • Total Bilirubin (direct and indirect) • Calcium (Ca) • Chloride (Cl) • Creatinine • Glucose • Magnesium • Lactate dehydrogenase (LDH) • Lipase • Phosphorus • Potassium (K) • Sodium (Na) • Total protein	**Coagulation:** • Prothrombin time (PT) • Activated partial thromboplastin time (aPTT) **Urinalysis:** • Bilirubin • Glucose • Ketones • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen • Leukocytes

5.2.3 Cardiac Evaluations

Twelve-lead surface electrocardiograms (ECGs) will be obtained according to the schedules outlined in the latest version of the protocol.

ECGs will be obtained in triplicate. Means from these 3 replicates will be used for analysis. The following continuous endpoints will be summarized:

- Heart rate
- QT interval
- QTcB (Bazett's correction) = QT /√ RR
- QTcF (Fridericia's correction) = QT / RR^ (1/3)

These derived values will be provided in the data from the central ECG vendor. While both QTcB and QTcF are expected to be available, analysis will be based on QTcF.

MUGA scanning or echocardiogram will be obtained according to the Appendix 1 Schedule of Events in the latest version of protocol**.** Only left ventricular ejection fraction (LVEF) data will be collected and evaluated.

Abnormalities will be reported as AEs and summarized as such.

5.2.4 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.

5.2.5 Vital Signs

Vital sign assessments will be performed according to the schedules outlined in the latest version of the protocol. Abnormalities such as drops in blood pressure and high temperatures that are measured at any time will be graded according to criteria in the CTCAE.

5.2.6 Pharmacokinetic and Immunogenicity Evaluations

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

5.2.7 Covariates and Stratification Factors

As stated in **Section 3.3.1**, randomization will be stratified by backbone chemotherapy, number of metastatic sites, and number of lines of therapy in the metastatic setting. If a

patient is mistakenly randomized into an incorrect stratum, then that patient will nonetheless be analyzed as a part of that stratum.

These 3 factors will be the stratification factors used for the stratified analyses described in **Section 6.3.1**.

Data will be pooled across regions and centers.

Patients who participate in the infusion sub-study will not be stratified nor randomized.

6 STATISTICAL METHODOLOGY

6.1 General Considerations

All statistical inferences will be based on two-sided tests.

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 (SD), median, minimum, and maximum.

Unless otherwise noted, continuous variable summaries will be summarized with one more significant digit than the original values. P-values will be reported in 0.XXXX format where XXXX represent the value rounded to four decimal places. Any p-value <0.0001 will be presented as <0.0001.

If needed, data will be provided in data listings sorted by treatment, patient ID and study visit. Summary tables will be by treatment group (margetuximab plus chemotherapy, trastuzumab plus chemotherapy).

Study Day 1 is defined as the first day of study drug administration. A 3-day window is allowed between randomization and dosing. If randomization and dosing do occur on separate days, randomization day will be defined as: Study Day -2, -1, 0. In all cases, endpoints that are time related (OS, PFS) will be determined from time of randomization.

Unless otherwise noted, baseline values will be defined as the most recent value collected prior to the first dose of study drug.

Data summaries and tabulations will be conducted using SAS® software Version 9.3 or higher. Note that the tables, listings and figures (TLFs) listed in each section below are not meant to be exhaustive. Rather they represent current overview of which data will be presented in TLFs. To avoid an unnecessary SAP amendment, a separate document will be used to capture all these TLFs and their modifications, if any, as well as any additional TLFs as appropriate.

All analyses described in subsequent sections are intended for the randomized portion of the study. Analyses that also apply to the infusion sub-study will be specified in applicable sections.

6.1.1 Interim Analyses

A charter will be prepared and signed off by DSMC members prior to study start. They will be supported by the CRO DSMC Support Team (CDST) who will be unblinded as needed and will not interact unnecessarily with study team members who are blinded to the trial.

When approximately 100 of the planned PFS events have occurred, a futility analysis will be performed. Futility will be assessed using conditional power conducted both under the initial study design and under the current trend of the data. The hazard ratio (HR) used in the

calculation will be derived from stratified Cox proportional hazards model. The CDST biostatistician supporting the DSMC will provide these calculations.

The DSMC may consider recommending termination of the study if conditional power is low, such as <20%. However, the DSMC will use the conditional power assessment, safety evaluations, and study conduct considerations (e.g., recruitment, design assumptions, protocol adherence/deviations, dropout rate, data quality, etc.) in their evaluation.

The DSMC will also perform a maximum of three efficacy evaluations for the OS endpoint. The first evaluation will be at the time of the PFS assessment endpoint, the second will occur when approximately 70% of the OS events have occurred if the OS endpoint has not been reached at the time of the PFS assessment and lastly if not reached at the second interim, at the time of study completion when approximately 385 OS events have occurred. The Lan-DeMets alpha spending function using an O'Brien-Fleming stopping boundary will be used to control overall type I error at 2-sided 0.05. The efficacy boundaries based on this method will depend on the actual observed number of OS events at each analysis and hence will be calculated and provided to DSMC once the actual number of OS events is known for each interim analysis. For example, if we observe 139 OS events (as expected per simulation) at the time of observing 257 PFS events for the primary PFS analysis, then the efficacy boundaries at each interim and final analysis are as follows (ADDPlan v6, with O'Brien-Fleming type alpha spending function and Schoenfeld formula for sample size calculation).

Table 3 Example of Efficacy Boundaries at Planned Interim and Final Analyses

Analysis	Timing of Analysis	Observed number (% of information fraction) of OS Events at Each Analysis	Efficacy Boundary in Terms of Two-Sided Significance Level
First Interim	Time of Primary PFS Analysis	139 (36%)	0.0004
Second Interim	70% of Overall OS Events	270 (70%)	0.0146
Final	100% of Overall OS Events	385 (100%)	0.0454

In addition, the DSMC will meet regularly to evaluate patient safety and study conduct for the randomized cohorts only. The first such meeting will occur within approximately 90 days after the first subject is randomized. Subsequent meetings are described in DSMC section of the latest version of the protocol. As a result of these meetings, the DSMC has the authority to request additional data and recommend modifications to the study. The DSMC will not provide unblinded data to the study team, but may provide aggregate data summaries as needed for decision making.

6.1.2 Missing Data

Every effort will be made to minimize the amount of missing data. However, there will be some patients who are either lost to follow-up, withdraw consent from the study, miss certain visits, or have other such causes of missing data. Where dates are missing or only partial dates are available, the following rules will be used:

- Missing month, day and year present – if the year part of the date is the same as the dosing year, impute the 1st month of dosing, otherwise June will be imputed.
- Missing day, month and year present – if the year and month are the same as dosing year and month, impute the 1st day of dosing, otherwise impute 15.
- Missing day and month, year present – day and month imputed as June 30.
- Missing year is not allowed and no imputation of missing year will be used.

For prior and concomitant medication: If the end date is missing or partial, the date will be compared as far as possible with the date of first administration of study medication. The medication will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) that it was stopped prior to the first administration of study medication.

For Adverse Events: If the AE onset date is missing or partial, the date will be compared as far as possible with the date of first administration of study medication. AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) that the AE started prior to the first administration of study medication.

6.2 Standard Summaries and Analyses

Patient disposition, demographics, baseline characteristics, cancer history, medical history, concomitant medications, study drug exposure, and protocol deviation/violation data will be summarized using descriptive statistics.

6.2.1 Demographics, Baseline Characteristics, and Cancer History

Demographic and baseline characteristics including height, weight, body surface area (BSA), age, gender, cancer history, including HER2 testing (immunohistochemistry [IHC] and/or in situ hybridization [ISH] results), Fc receptor polymorphisms, prior chemotherapies, surgeries, and radiation received will be summarized. Patients will be excluded from the summaries of an individual parameter if data are missing. No statistical comparisons are planned as randomization should help to balance these parameters between the two treatment groups.

Table 4 Demographics

Summary	Population
Listing and Summary of Patient Disposition	All patients screened
Number of Patients Screened, Randomized and Treated by Country/Site	All patients screened
Listing and Summary of Protocol Deviations	ITT
Listing and Summary of Patient Demographics	ITT
Listing and Summary of HER2 Expression by CRF and External Laboratory	ITT
Listing and Summary of History of Breast Cancer	ITT
Listing and Summary of Estrogen Receptor (ER)/Progesterone Receptor (PgR) Status	ITT
Listing and Summary of Cancer Disease History Other than Breast Cancer	ITT
Listing and Summary of Prior Systemic/Hormonal Therapy, Radiotherapy, Surgery for Breast Cancer	ITT
Listing and Summary of Prior Systemic Therapy, Radiation, Surgery for Cancer Other than Breast Cancer	ITT
Listing and Summary of Other (Non cancer) Prior Treatments	ITT
Summary of Disease Assessment – Target Lesions at Screening	ITT
Summary of Disease Assessment – Non-Target Lesions at Screening	ITT
Listing and Summary of Medical History	ITT
Listing and Summary of Stratification Factors	ITT

Infusion sub-study: Above summaries and listings, if applicable, will also be performed for patients enrolled and treated in infusion sub-study.

6.2.2 Study Drug Exposure

Summaries using descriptive statistics will be provided for drug exposure for margetuximab plus chemotherapy or trastuzumab plus chemotherapy. Exposure will be summarized to assess the use of each chemotherapy (capecitabine, eribulin, gemcitabine, vinorelbine) in the presence and absence of margetuximab or trastuzumab.

Table 5 Summary of Drug Exposure

Summary	Population
Listing of Drug Exposure for Margetuximab	Safety
Listing of Drug Exposure for Trastuzumab	Safety
Listing of Drug Exposure for Backbone Chemotherapy	Safety
Listing and Summary of Patient Withdrawals from Dosing due to Margetuximab or Trastuzumab	Safety
Listing and Summary of Patient Withdrawals due to Dosing from Backbone Chemotherapy	Safety
Summary of Number of Cycles of Study Drug - Margetuximab and Trastuzumab	Safety
Summary of Number of Cycles of Backbone Chemotherapy Received	Safety
Summary of Total Dose of Study Drug Received – Margetuximab and Trastuzumab	Safety
Summary of Total Dose Received - Backbone Chemotherapy	Safety
Summary of Number of Margetuximab and Trastuzumab Infusions Interrupted or Prematurely Terminated	Safety
Summary of Dose Intensity for Margetuximab and Trastuzumab	Safety
Summary of Dose Intensity for Backbone Chemotherapy	Safety
Summary of Number of Backbone Chemotherapies Infusions Interrupted or Prematurely Terminated	Safety
Summary of Dose Schedule Modifications for Toxicity by Reason - Margetuximab and Trastuzumab	Safety
Summary of Dose Discontinuations by Reason - Margetuximab and Trastuzumab	Safety
Summary of Dose Modifications for Toxicity by Reason – Backbone Chemotherapy	Safety
Summary of Dose Discontinuations by Reason – Backbone Chemotherapy	Safety

Infusion sub-study: Above summaries for drug exposure for margetuximab as well as backbone chemotherapies will be also performed for patients enrolled and treated in infusion sub-study.

6.3 Efficacy Endpoint Analyses

6.3.1 Primary Endpoint Analyses

6.3.1.1 Progression Free Survival and Overall Survival – Primary Analyses

The same analysis methodology will be used to assess PFS and OS. Survival curves for the two treatment groups will be generated using the Kaplan –Meier method. The groups will be compared using a stratified log-rank test, stratified by backbone chemotherapy, number of metastatic sites, and number of lines of prior therapy in the metastatic setting. The stratified log rank test will be carried out with the PROC LIFETEST procedure in SAS® with the

Breslow method for handling ties. The following pooling strategy will be employed to handle a potential issue of small strata (defined as < 5 events):

- If there are no small strata, then the stratified log rank test will be performed stratified by the original 3 stratification factors.
- In the case of small strata, one or more stratification factors will be removed, in the order of the number of metastatic sites, the number of lines of prior therapy, and backbone chemotherapy based on clinical importance, until there are no strata with fewer than 5 events under the remaining stratification factors. Then the stratified log rank test will be performed stratified by the remaining stratification factors.
- If the procedure for removing stratification factors in the case of small strata results in the removal of all 3 stratification factors, then the unstratified log-rank test will be performed.

Median PFS and median OS will be estimated using Kaplan-Meier method. The hazard ratio for PFS and OS and their 95% CIs will be determined from the stratified Cox proportional hazards model with treatment as the only covariate, ties handled by Breslow method, and the above pooling strategy applied.

In order to assess the comparability of follow-up time between the two treatment groups, the amount of follow-up in each treatment group will be summarized by the mean number of follow-up months as well as the number of patients followed by month of follow-up.

Table 6 Primary Endpoint Summaries

Summary	**Population**
Patient Listing of PFS and OS	ITT
Summary of Follow-up Time for PFS and OS	ITT
Summary of Stratified PFS	ITT
Kaplan-Meier Curves for PFS	ITT
Summary of Stratified OS	ITT
Kaplan-Meier Curves for OS	ITT
Summary of Stratified Cox Proportional Hazards Model for PFS	ITT
Summary of Stratified Cox Proportional Hazards Model for OS	ITT
Kaplan-Meier Curves for PFS at the Futility Assessment	ITT (1st 100 events)
Summary of Conditional Power for PFS at the Futility Assessment	ITT (1st 100 events)

6.3.1.2 Sensitivity Analyses for Progression Free Survival and Overall Survival

Since these analyses are exploratory, no multiplicity correction will be used.

6.3.1.2.1 Sensitivity Analyses for PFS

1. Unstratified log-rank test as well as the hazard ratio and its 95% CI based on unstratified Cox model for PFS analysis with the censoring rules as in **Table 1** will be performed.
2. The PFS analyses described in **Section 6.3.1.1** will be repeated with the censoring rules defined in **Table 1**, except that the documented progression or death will be considered a PFS event regardless when it occurs during the study.
3. The PFS analyses described in **Section 6.3.1.1** will be repeated with the censoring rules defined in **Table 1**, except that clinical progression in absence of documented tumor progression will be considered a PFS event. The clinical progression is a progression based on criteria other than radiographic assessment using RECIST v1.1, such as symptom deteriorations or cytology.
4. The PFS analyses described in **Section 6.3.1.1** will be repeated with the censoring rules defined in **Table 1**, with additional censoring at last tumor assessment prior to treatment discontinuation for patients who discontinued study treatment due to reasons other than documented PD or death.

6.3.1.2.2 Sensitivity Analyses for OS

Unstratified log-rank test as well as the hazard ratio estimation and its 95% CI based on unstratified Cox model will be performed for OS analysis.

6.3.1.2.3 Subgroup Analyses of PFS and OS

Cox regression including the single covariate of treatment effect will also be used to assess the consistency of the treatment effect for a number of subgroups as described below. The hazard ratio and 95% confidence interval will be computed and displayed in two forest plots, one for PFS and the other for OS.

The following subgroups for both PFS and OS will be examined:

- Backbone chemotherapy (capecitabine, gemcitabine, eribulin, vinorelbine)
- Number of metastatic sites (1-2, >2)
- Number of lines of prior therapy in the metastatic setting (≤2, >2)
- Prior use of T-DM1 (yes, no)
- Region (North America, Europe, Other)

- HER2 status (3+ or ISH amplified, Other)
- Age (≤60, >60)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0, 1)
- Race (White, Black, Asian, Other)
- CD16A (FF, FV, VV)
- CD32A (HH, HR, RR)
- CD32B (II, IT, TT)
- Estrogen receptor (ER) and progesterone receptor (PgR) status (ER+ and/or PgR+, ER-and PgR-, Unknown)

6.3.2 Secondary and Selected Tertiary Endpoint Analyses

6.3.2.1 Investigator-Assessed PFS

The analyses described in **Section 6.3.1.1** and **Section 6.3.1.2.1** will be performed for investigator assessed PFS. The concordance/discordance of progression by investigator compared to independent review will be summarized.

Infusion sub-study: Investigator assessed PFS and OS will also be analyzed for patients enrolled and treated in the infusion sub-study.

6.3.2.2 Objective Response Rate, Duration of Response, and Clinical Benefit Rate

ORR and CBR, assessed by both independent review and by investigators, will be assessed using the best overall response achieved during the study. This response must be confirmed at least 28 days after initial response to be considered a confirmed objective response for the purpose of calculation of ORR. The two treatment groups will be compared using a Mantel-Haenszel Chi-Square test stratified by backbone chemotherapy, number of metastatic sites, and number of lines of therapy in the metastatic setting. The same pooling strategy as described in **Section 6.3.1.1** will be applied to handle a potential issue of small strata (defined as <5 patients).

Change from baseline in tumor size over time will be summarized as well as presented by spider plots. The best percentage change from baseline will be presented by waterfall plots. Change calculations will be based on target lesions measured by independent review as well as by investigators.

DOR curves, assessed by independent review and by investigators, respectively, for the two treatment groups will be generated using the Kaplan –Meier method. The groups will be compared using a stratified log-rank test.

Table 7 ORR, DOR, and CBR Summaries

Summary	Population
Listing of Investigator Assessed Responses and Independently Assessed Responses	**RE**
Summary of Independently Assessed Stratified ORR	RE
Summary of Investigator Assessed Stratified ORR	RE
Summary of Independently Assessed Stratified CBR	RE
Summary of Investigator Assessed Stratified CBR	RE
Summary of Investigator Assessed Stratified DOR	Responders
Summary of Independently Assessed Stratified DOR	Responders
Kaplan Meier Curves for Independently Assessed DOR	Responders
Kaplan Meier Curves for Investigator Assessed DOR	Responders
Summary of Independently Assessed Responses Compared with Investigator Assessed Responses	RE
Spider Plots and Summary of Change in Independently Assessed Tumor Size Over Time	Patients with baseline and post-baseline target lesion measurements
Spider Plots and Summary of Change in Investigator Assessed Tumor Size Over Time	Patients with baseline and post-baseline target lesion measurements
Waterfall Plot of Best Percentage Change from Baseline in Independently Assessed Tumor Size	Patients with baseline and post-baseline target lesion measurements
Waterfall Plot of Best Percentage Change from Baseline in Investigator Assessed Tumor Size	Patients with baseline and post-baseline target lesion measurements
Listing of Tumor Assessments by Investigators and by Independent Review	RE

Infusion sub-study: Analyses of ORR, CBR, change from baseline in tumor size over time, and DoR based on investigator assessed data will also be performed for patients enrolled and treated in the infusion sub-study.

6.3.2.3 NFBSI-16 and EQ-5D-5L

The primary HRQoL endpoint for analysis will be the NFBSI-16 total score. Secondary analyses of subscales that add to the total (disease related symptoms, treatment side effects, and function/well-being) will also be summarized.

Change from baseline in NFBSI-16 total score and in EQ-5D-5L utility score will be assessed using mixed model repeated measures analysis (MMRM) with treatment group, the defined stratification factors, time, and treatment group by time interaction as covariates.

Other covariates may be included. Each analysis model will use an unstructured covariance matrix. Least square mean estimates at each time point will be presented.

A Cox proportional hazards model will be used to assess time to symptom progression in NFBSI-16 score. Progression will be defined as a ≥ 5-point decrease from baseline in total NFBSI-16 score. The same covariates will be used as in the MMRM analyses.

Reasons for missed visits will be summarized. Graphical methods will be used to assess the impact of missed visits. Imputation of missing values will be used for the NFBSI-16. If at least half of the items in the scale are answered, any missing items will be assigned the mean value of the completed items.

Table 8 HRQoL Summaries

Summary	Population
Summary of Reasons for missed Visits – NFBSI-16 and EQ-5D-5L	ITT
Summary of NFBSI-16 Mean Scores Overall and by Subscale Across Time	ITT
MMRM Results for NFBSI-16 Total Score	ITT
Summary of Cox Proportional Hazards Model for Time to Symptom Progression	ITT
Kaplan Meier Curves of Time to Symptom Progression	ITT
Graph of NFBSI-16 Mean Total Score Across Time	ITT
Summary of EQ-5D-5L Mean Scores Overall and by Subscale Across Time	ITT
MMRM Results for EQ-5D-5L Total Score	ITT
Graphs of EQ-5D-5L Mean Total Score Across Time	ITT

6.3.3 Exploratory Analyses

The effects of margetuximab on PFS and OS as compared to trastuzumab in each allelic variation of CD16A, CD32A and CD32B will be evaluated by the estimated hazard ratios and 95% CIs as described in **Section 6.3.1.2.3.** The interaction between each genotype and each efficacy endpoint (response, PFS and OS) may be assessed by logistic model for response and Cox model for PFS and OS, respectively.

Infusion sub-study: The analyses of ORR, PFS and OS may be performed in each allelic variation of CD16A, CD32A and CD32B if there are enough data to warrant a meaningful analysis.

In addition, exploratory analyses will be performed to evaluate the impact of the subsequent use of T-DM1 on the effect of margetuximab on OS. Such analyses may include applying a time-dependent Cox model with the treatment as a fixed covariate and the subsequent use of T-DM1 as a time-dependent covariate.

6.3.4 Population Pharmacokinetics, Exposure-Response Relationships, and Anti-Drug Antibodies

Serum concentrations of margetuximab will be summarized by study visit using descriptive statistics and graphed over time. Population PK modeling will be performed by an external vendor. An analysis plan will be created prior to analysis.

Anti-drug antibodies to margetuximab will categorized as positive or negative and summarized using descriptive statistics.

Table 9 Summary of PK and Anti-Drug Antibodies - Margetuximab

Summary	Population
Summary of Serum Concentrations of Margetuximab Over Time	Safety
Graph of Mean Margetuximab Serum Concentrations Over Time	Safety
Summary of Anti-Drug Antibodies to Margetuximab Shift Over Time	Safety

Infusion sub-study: The above described PK and ADA analyses will also be performed for patients enrolled and treated in the infusion sub-study.

6.4 Safety Endpoint Analyses

6.4.1 Adverse Events

A number of summary tables of AE will be displayed. Only TEAEs will be summarized in tables. The safety population will be used for all AE tables. All AE will be incorporated in the listings unless noted otherwise.

All of these summaries, except the overall table, will display the number and percent of patients that experience the given event and will display events by SOC and PT. Events will be displayed in alphabetical order of the SOC and in descending order of overall PT incidence within each SOC. Tables will include events irrespective of attribution unless otherwise indicated.

A table of overall counts without SOC and preferred terms will include the number of patients with:

- Any AE
- Any Drug-Related AE
- Any AE with a CTCAE severity Grade $\geq$3
- Any Drug Related AE with a CTCAE severity grade $\geq$3
- Any Serious AE

- Any Drug Related Serious AE
- Any AE that resulted in study discontinuation
- Any AE that resulted in study drug discontinuation
- Any fatal AE
- Any IRE
- Any AESI

The following tables will be summarized by SOC and PT:

- Number of Patients with AE by highest severity
- Number of Patients with AE by Frequency
- Number of Patients with ≥Grade 3 AE
- Number of Patients with Related AE – overall therapy
- Number of Patients with Related AE by Highest Severity
- Number of Patients with SAE
- Number of Patients with Related SAE
- Number of Patients with AESIs
- Summary of AE with Incidence Rate ≥5%
- Summary of Related AE with Incidence Rate ≥5%
- Summary of AE Leading to Withdrawal of Study Drug
- Summary of AE Leading to Study Discontinuation
- Summary of AE that Result in Interruption or Modification of Dosing Schedule
- Summary of AE that Started During margetuximab or trastuzumab Infusion
- Summary of AE that Started During Backbone Chemotherapy

Table 10 Adverse Event Summaries

Summary	Population
Overall Summary of Adverse Events	Safety
Listing and Summary of Adverse Events	Safety
Listing and Summary of ≥Grade 3 Adverse Events	Safety
Summary of Related Adverse Events	Safety
Summary of ≥Grade 3 Related Adverse Events	Safety
Listing and Summary of Serious Adverse Events	Safety
Summary of Adverse Events with Incidence Rate >5%	Safety
Summary of Related Adverse Events with Incidence Rate >5%	Safety
Summary of Related Serious Adverse Events	Safety
Summary of Adverse Events Attributed to Margetuximab or Trastuzumab	Safety
Summary of Adverse Events Attributed to backbone Chemotherapy	Safety
Summary of IREs	Safety
Summary of Adverse Events Leading to Withdrawal of Study Drug	Safety
Summary of Adverse Events Leading to Discontinuation from the Study	Safety
Summary of Adverse Events that Result in Interruption or Modification of Study Drug	Safety
Summary of Adverse Events that Started During Margetuximab or Trastuzumab Infusion	Safety
Summary of Adverse Events that Started During Backbone Chemotherapy	Safety
Listing and Summary of AESIs – LVEF Dysfunction	Safety
Listing and Summary of AESIs – Infusion Related Reactions	Safety
Listing and Summary of Deaths	Safety
Listing and Summary of Concomitant Medications	Safety
Listing and Summary of Concomitant Surgeries	Safety
Listing and Summary of Concomitant Radiotherapy	Safety
Listing and Summary of Pregnancy Exposure	Safety
Summary of ≥Grade 3 IRR by the End of Cycle 2	Safety
Listing and Summary of All Grade IRR by Cycle	Safety

Infusion sub-study: The above AE analyses will also be performed for patients enrolled and treated in infusion sub-study.

6.4.2 Laboratory Values

Laboratory values will be based on central lab results. The list and timing of collection of clinical laboratory parameters are summarized in Appendix 1 Schedule of Events in the latest version of the protocol. These parameters will be summarized by mean, median, standard deviation/standard error, and range across time points. In cases where an abnormality

resulted in a repeat lab test, the repeat value will be used for the summaries. A list of repeated labs including original values and repeat values will be included.

Summary tables will be grouped by parameter type: hematology, serum chemistry, urinalysis, and coagulation. Graphs of mean values across study visits will also be generated. Shift tables from baseline toxicity grade to worst obtained toxicity grade value may also be included.

Table 11 Summary of Laboratory Parameters

Summary	Population
Listing and Summary of Laboratory Parameters by Study Visit – Hematology	Safety
Listing and Summary of Laboratory Parameters by Study Visit – Serum Chemistry	Safety
Listing and Summary of Laboratory Parameters by Study Visit – Urinalysis	Safety
Listing and Summary of Laboratory Parameters by Study Visit – Coagulation	Safety
Shift Table for Hematology Parameters	Safety
Shift Table for Coagulation Parameters	Safety
Listing of Patients with Treatment-Emergent Laboratory Toxicities ≥ Grade 3	Safety
Shift Table for Serum Chemistry Parameters	Safety
Listing and Summary of Abnormal Liver Enzymes Meeting Criteria for Hy's Law	Safety
Graphs of Mean Hematology Parameters Over Time	Safety
Graphs of Mean Serum Chemistry Parameters Over Time	Safety
Graphs of Mean Coagulation Parameters Over Time	Safety

Infusion sub-study: The above laboratory parameters analyses will also be performed for patients enrolled and treated in infusion sub-study.

6.4.3 Electrocardiograms, Multi-Gated Acquisition Scans, Physical Examinations, and Vital Signs

Continuous and categorical ECG data collected as described in Appendix 1 Schedule of Events in the latest version of the protocol will be summarized with descriptive statistics in tables by study visit. Abnormalities will also be captured as AEs and therefore summarized in AE tables.

As mentioned in **Section 5.2.4**, newly occurring physical exam abnormalities will be captured as AEs and will therefore be summarized in the AE tables.

Vital signs (**Section 5.2.5**) will be summarized by study visit with descriptive statistics. Shift tables of baseline toxicity grade value to worst toxicity grade on study value may also be included.

Heart Rate, QTcB, and QTcF will be summarized by visit. QTcF data will be assessed using (1) categorical analysis and (2) concentration response analysis.

Categorical Analysis:

Frequency distributions of maximum recorded post dose QTcF interval and maximum post dose change from baseline QTcF interval (ΔQTcF) will be presented:

- QTcF: ≤ 450 msec, >450 to 480 msec, >480 to 500 msec, and >500 msec
- ΔQTcF: ≤ 30 msec, >30 to 60 msec, and >60 msec

Concentration Response Analysis:

Scatter plot of ΔQTcF versus the nearest corresponding serum margetuximab concentration will be presented. The relationship between ΔQTcF versus drug concentration will be assessed using a linear mixed effects model (**1**).

MUGA scanning or echocardiogram will be presented by change from baseline in LVEF. A graph of LVEF change from baseline will also be generated. In addition, time to >15% reduction in LVEF value may be summarized using a Kaplan-Meier approach.

Table 12 Summary of ECG, Vital Signs, and MUGA Results

Summary	Population
Listing and Summary of Vital Signs Over Time	Safety
Listing and Summary QTcF Interval by Study Visit	Safety
Listing and Summary of QTcB Interval by Study Visit	Safety
Listing and Summary of Heart Rate by Study Visit	Safety
Listing and Summary of Categorical Analysis of QTcF	Safety
Scatter Plot of Change in QTcF vs. Margetuximab Serum Concentration	Safety
Mixed Model Assessing the Relationship Between Change in QTcF and Margetuximab Serum Concentrations	Safety
Summary of Change in LVEF by Study Visit	Safety
Graph of Change in LVEF Over Time	Safety
Kaplan-Meier Results for Time to >15% Reduction in LVEF	Safety

Infusion sub-study: Analyses of above variables will also be performed for patients enrolled and treated in infusion sub-study.

6.5 Data Standards

Clinical Data Interchange Standards Consortium (CDISC) standards will be used. The latest version of Study Data Tabulation Model (SDTM) will be used for data tabulations of the eCRF data and the latest version of Analysis Dataset Model (ADaM) will be used for the analysis datasets.

7 DATA HANDLING CONVENTIONS

1. Study Day will represent a label in the study summaries defining the study day in which a subject assessment is to be conducted. Actual date will be used only where required.
2. Treatment cycle – Treatment cycle will be based on actual infusion dates and may differ from the planned cycle.
3. Study Day 1 – defined as the date of first drug administration following randomization. If a partial date exists, it will be imputed as described in **Section 6.1.2**.
4. Completed Study – Any subject returning for their final study day visit regardless of number of doses received or study visits attended. Reasons for non-completion will be described.
5. If there is >1 baseline value for any parameter, baseline will represent the value closest, but prior to, first dose.
6. Weight - If baseline weight is missing, weight from the screening visit will be used.
7. ECG - If baseline ECG is missing, ECG from the screening visit will be used.
8. If a value is defined as alphanumeric and includes > or ≥, for computation purposes the raw value will be increased by one decimal point beyond the precision of the value and adding one. For example, >9.0 will be imputed as 9.01.
9. If a value is defined as alphanumeric and includes < or ≤, for computation purposes the raw value will be increased by one decimal point beyond the precision of the value and subtracting one. For example, ≤9.0 will be imputed as 8.99.
10. Unscheduled visits – in general, unscheduled visits will be listed in patient listings but not included in patient summaries.

Additional data conventions or updates to this plan may be needed as blinded data are reviewed throughout the study. If so, a Data Convention Document or revised SAP will be created and shared with regulatory authorities, as per local requirements, prior to unblinding.

8 REFERENCES

1. **Garnett, C.E., Beasley, Bhattaram, V., Jadhav, P., Madabushi, R., Stockridge, N., Tornoe, C., Wang, Y., Zhu, H., Goburru, J.** Concentration-QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review. Journal of Clinical Pharmacology, V48, p 13-18, 2008.