CLINICAL TRIAL PROTOCOL: CP-MGAH22-04
PROTOCOL AMENDMENT 4

Study Title:	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
Study Number:	CP-MGAH22-04
Study Phase:	3
Product Name:	Margetuximab
IND Number:	
EudraCT Number:	2015-000380-13
Indication:	Metastatic or Locally Advanced HER2-positive Breast Cancer
Coordinating Principal Investigator:	TBD
Sponsor:	MacroGenics, Inc. 9704 Medical Center Drive Rockville, MD 20850 USA 301-251-5172
Sponsor's Medical Monitor:	Refer to Study Contact List

Confidentiality Statement

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Study Number:	CP-MGAH22-04

This clinical study protocol has been approved by the Sponsor:

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

Vice-President, Clinical Research
MacroGenics, Inc.

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

Senior Director, Biostatistics
MacroGenics, Inc.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

21CFR	United States Code of Federal Regulations, Title 21
β-hCG	Beta human chorionic gonadotropin
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)
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
BID	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
°C	Degrees Celsius
C_{max}	Maximum serum concentration
C_{trough}	Trough serum concentration
Ca	Calcium
CAP	College of American Pathologists
CBC	Complete blood count
CBR	Clinical benefit rate
CDR	Complementarity-determining region
Ch4D5	Chimeric 4D5

CHF	Congestive heart failure
Cl	Chloride
CI	Confidence interval
CL	Plasma clearance
CR	Complete response
CRO	Contract research organization
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DBP	Diastolic blood pressure
DoR	Duration of Response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
E-R	Exposure-response
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
FcγR	Fc gamma receptor
FISH	Fluorescence in situ hybridization
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical Practice
HC	Heavy chain
hCG	Human chorionic gonadotropin
Hct	Hematocrit

HEENT	Head, eyes, ears, nose, and throat
HER2+	Human epithelial growth factor receptor 2 positive
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-related quality of life
HR	Hazard ratio
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
Ig	Immunoglobulin
IND	Investigational New Drug
IRB	Institutional Review Board
IRE	Immediately Reportable Event
ISH	In-situ hybridization
IUD	Intrauterine device
IV	Intravenous
IxRS	Interactive Response System
K	Potassium
Kg	Kilogram
LC	Light chain
LDH	Lactate dehydrogenase
LVEF	Left ventricle ejection fraction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter

mm	Millimeter
msec	Millisecond
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
Na	Sodium
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NFBSI-16	Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index - 16
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PE	Physical examination
PES	Polyethersulfone
PFS	Progression free survival
PI	Principal Investigator
PK	Pharmacokinetic
PPK	Population pharmacokinetics
PO	By oral administration
PR	Partial response
PgR	Progesterone receptor
PRO	Patient reported outcome
PT	Prothrombin time
PVC	Polyvinyl chloride
Q3W	Every 3 weeks
QW	Every week

RANKL	Receptor activator of nuclear factor kappa B ligand
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Stable disease
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
T_{half}	Terminal half-life
T_{max}	Time to maximum serum concentration
T-DM1	Ado-trastuzumab emtansine
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
V_{ss}	Volume of distribution at steady state
WBC	White blood cell

1 SYNOPSIS

Sponsor: MacroGenics, Inc.	**IND Number:**
Name of Finished Product: Margetuximab	
Study Title: 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	
Study Number: CP-MGAH22-04	
Investigator(s)/Centers: This study will be executed at approximately 200 centers in approximately 25 countries.	
Study Phase: 3	
Primary Objectives The primary objective of this study is to evaluate the efficacy, as measured by progression-free survival (PFS) assessed by independent review and overall survival (OS), of margetuximab plus chemotherapy compared with trastuzumab plus chemotherapy in patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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. **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 outcome measure.	
Secondary Objectives • To evaluate PFS, as assessed by 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:** To evaluate the incidence of all Grade infusion-related reactions in all sub-study patients.	
Tertiary Objectives • To evaluate 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. • 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. • To characterize the population pharmacokinetics (PPK) and exposure-response (E-R) relationships of margetuximab in these patients. • To evaluate anti-drug antibodies (ADA) directed against margetuximab and its effects on pharmacokinetics (PK), efficacy, and safety in these patients.	

Exploratory Objective

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

Rationale

Therapy directed against HER2, either via a monoclonal antibody or derivatives or by small molecule inhibition, has shown efficacy in patients with advanced breast cancer. To date, no HER2-targeted agents have been approved in the United States (US) to specifically treat patients after two prior lines of treatment, although both lapatinib and trastuzumab are often used in this setting. The purpose of this study is to evaluate the activity of margetuximab in combination with standard of care chemotherapies in the setting of patients with metastatic HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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. Because common practice is to treat these patients with an anti-HER2 agent in combination with chemotherapy, it is unethical to compare the effect of margetuximab with placebo, and therefore an active comparator was chosen. Trastuzumab is commonly used in this setting, and the comparison will directly evaluate whether enhanced antibody dependent cell-mediated cytotoxicity (ADCC) produces superior clinical efficacy. Although not approved in this setting, trastuzumab is an acceptable comparator because continued treatment with trastuzumab after failure while on trastuzumab has demonstrated clinical benefit. In addition, trastuzumab has a generally favorable toxicity profile compared with lapatinib, and is commonly used in clinical practice **(4, 15)**.

The decision to allow physician's choice of chemotherapy from among a selected list is based on the well-described finding **(7)** that, in the treatment of advanced breast cancer, sequential single agent chemotherapies are superior to combination therapy, and that, other than eribulin – which showed a modest survival benefit - no one agent has been clearly shown to be superior to another in the salvage setting. Common practice is to choose a therapy based on individual patient needs and combine that with trastuzumab. Rather than dictate the therapy, investigators will choose the patient's combination chemotherapy from a predetermined list, allowing for a tailored approach to each individual patient's status (also similar to the control arm in the eribulin pivotal study **(6)**. To minimize bias, the selected chemotherapy will be chosen and documented prior to patient randomization.

Infusion Sub-Study: This protocol will include a sub-study that reduces infusion time from 120 to 30 minutes. Reduced infusion times will decrease the burden on patients receiving margetuximab.

Study Design

Overview

This is a Phase 3, randomized, 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 2 prior lines of anti-HER2 directed therapy 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 all 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.

The study will include a non-randomized sub-study cohort of approximately 78 subjects with HER2+ metastatic breast cancer to receive either single agent margetuximab or margetuximab in combination with the Investigator's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). This infusion sub-study will enroll patients meeting all criteria for the randomized study with the exception of the requirements for prior therapy; the infusion sub-study will require patients to have received at least 4 prior lines of therapy for metastatic breast cancer, as well as prior trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1).

Treatment Groups

Patients in the randomized portion of the study, will receive either margetuximab or trastuzumab in combination with the preselected chemotherapy of the investigator's choice. Patient randomization will be stratified by number of metastatic sites (≤2, >2), number of lines of therapy in the metastatic setting (≤2, >2), and choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).

Patients in the Infusion Sub-Study will receive margetuximab alone or in combination with protocol-specified physician choice chemotherapy.

Study Population

This study will enroll patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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.

The infusion sub-study will enroll a similar patient population with the exception of requiring at least 4 prior lines of therapy (including trastuzumab, pertuzumab and T-DM1) for metastatic HER2+ breast cancer, so that there is no direct overlap with the primary study population for the randomized component of this trial.

Inclusion/Exclusion Criteria

Inclusion Criteria

To be included in this study, patients must:

General

1. Be able 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 and completion of HRQoL assessments.
2. Be ≥ 18 years old. Patients may be male or female.
3. Have histologically proven, metastatic or locally advanced, relapsed/refractory HER2+ (3+ by IHC or ISH-amplified as per American Society of Clinical Oncology [ASCO] and the College of American Pathologists [CAP] Guidelines) breast cancer based on the most recently available tumor biopsy collected from the patient. HER2 status must be documented from a reference laboratory that conforms to standards set for accreditation by CAP or an equivalent accreditation authority. Confirmatory IHC testing is not required for study entry. Tumors may be estrogen receptor (ER)/progesterone receptor (PgR) positive or negative.
4. Have received at least 2 prior lines of anti-HER2 directed therapy 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. In either case, patients must have received prior treatment with pertuzumab in the (neo)adjuvant or metastatic setting. Prior radiotherapy, hormonal therapies, and other anti-HER2 therapies are allowed.
5. Have received treatment with at least one, and no more than three, lines of therapy overall in the metastatic setting. Hormonal therapies will not be considered when determining the number of previous lines of therapy in the metastatic setting. Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 6 months of the completion of therapy will be considered a line of treatment for metastatic disease. Eligible patients must have progressed on or following, the most recent line of therapy. Dose interruptions, delays, pauses during previous therapy, or changes in therapy to manage toxicity will not constitute a new line of therapy provided disease progression did not occur.
6. 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).
7. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**Appendix 4**).
8. Have life expectancy ≥ 12 weeks.
9. Have either measurable or non-measurable disease as per RECIST 1.1 criteria and documented by CT and/or MRI.

Laboratory Features

10. Have acceptable laboratory parameters as follows:
    a. Platelet count ≥ 100 × 10^3/μL without having received a transfusion or growth factor support within 4 weeks prior to randomization.
    b. Hemoglobin ≥ 9.0 g/dL without having received a transfusion or growth factor support within 4 weeks prior to randomization.
    c. Absolute neutrophil count ≥ 1.5 × 10^3/μL in the absence of any growth factor support given within 4 weeks prior to randomization.
    d. Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) ≤ 3.0 × the upper limit of normal (ULN), except patients with liver metastases, who may enroll with ALT/AST ≤ 5.0 × ULN.
    e. Total bilirubin ≤ 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within laboratory normal limits.
    f. Creatinine < 1.5 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.

Reproductive Features

11. Female patients of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a negative result from a serum pregnancy test performed within 14 days of randomization and a negative serum or urine pregnancy test on the day of first study treatment prior to the initiation of study treatment.

    Further, female patients of childbearing potential must agree to use highly effective contraceptive measures from the time of informed consent through 7 months after the last dose of study drug (either margetuximab or trastuzumab). Highly effective methods of contraception include:

    - Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
        - Oral
        - Intravaginal
        - Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation
        - Oral
        - Injectable
        - Implantable
        - Intrauterine device (IUD)
        - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence

12. Male patients should also have their partners who are women of childbearing potential use a highly effective method of contraception (as shown above) from the time of informed consent through 7 months after last dose of study drug (either margetuximab or trastuzumab).

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Patients with known, untreated brain metastasis.
    - Patients with signs or symptoms of brain metastasis must have a CT or MRI performed within 4 weeks prior to randomization to specifically exclude the presence of radiographically detectable brain metastases.
    - Patients with known, treated brain metastases must have a baseline CT or MRI within 4 weeks of randomization and are eligible provided all therapy for the metastases concluded at least 4 weeks prior to randomization, or, if continued steroid therapy is indicated following therapy, they have been

on a stable dose of steroids (≤ 10 mg/day of prednisone or equivalent) for at least 4 weeks prior to randomization with no symptoms.

2. History of uncontrolled seizures within 6 months of randomization.
3. History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation.
4. Treatment with any local or systemic anti-neoplastic therapy (including hormonal therapies for breast cancer) or any investigational therapy within 2 weeks prior to randomization. Bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors are allowed provided treatment starts prior to randomization.
5. Treatment with corticosteroids (i.e., > 10 mg prednisone per day or equivalent) or other immune suppressive drugs within 2 weeks prior to randomization. Steroids for topical use, inhalational use, nasal spray, or ophthalmic solution are allowed.
6. History of clinically significant cardiovascular disease including but not limited to:
   a. Myocardial infarction or unstable angina within 6 months prior to randomization.
   b. Stroke or transient ischemic attack within 6 months prior to randomization.
   c. Clinically significant cardiac arrhythmias.
   d. Uncontrolled (persistent) hypertension defined as systolic blood pressure (SBP) >180 mmHg or diastolic blood pressure (DBP) >100 mmHg.
   e. Congestive heart failure (New York Heart Association [NYHA] class II-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.
7. Clinically significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation.
8. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to randomization.
9. Known positive testing for human immunodeficiency virus or acquired immune deficiency syndrome.
10. Active 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).
11. Second primary malignancy that has not been in remission for at least 2 years from the anticipated start of study treatment. Exceptions of treated malignancies that do not require a 2-year remission include: non-melanoma skin cancer; cervical carcinoma in situ; squamous intraepithelial lesion; localized prostate cancer (Gleason score < 6); resected melanoma in situ or ductal carcinoma in situ. Patients with second primary breast cancers within 2 years are eligible provided that both primary tumors were HER2+ (3+ by IHC or ISH amplified).
12. History of trauma or major surgery within 4 weeks prior to randomization.
13. 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.
14. Known hypersensitivity to recombinant proteins, polysorbate 80, benzyl alcohol, or any excipient contained in the drug formulation for margetuximab, trastuzumab or other study treatments. Previous infusion reactions to trastuzumab or other monoclonal antibodies will not preclude enrollment provided no contraindication to trastuzumab therapy remains.
15. Any condition that would be a contraindication to receiving trastuzumab as described in the approved local label or a condition that would prevent treatment with the physician's choice of chemotherapy.
16. Vaccination with any live virus vaccine within 4 weeks prior to randomization. Inactivated annual influenza vaccination is allowed at any time.
17. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
18. Active or history of alcohol or other substance abuse within 1 year prior to randomization.
19. Pregnant or breast feeding.
20. Prior participation in a margetuximab clinical study.

21. Any investigative site personnel directly affiliated with this study.
22. Employees of MacroGenics, Inc.
23. Prisoners or other individuals who are involuntarily detained.
24. Any issue or condition that in the opinion of the investigator would contraindicate the patient's participation in the study or confound the results of the study.

Entry Criteria for the Infusion Sub-Study:

1. Patients will meet all entry criteria for the randomized portion of the study with the exception of inclusion criteria #4 and #5.
2. Patients must have received at least 4 prior lines of therapy for metastatic disease. Hormonal therapies will not be considered when determining the number of previous lines of therapy in the metastatic setting. Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 6 months of the completion of therapy will be considered a line of treatment for metastatic disease. Eligible patients must have progressed on or following the most recent line of therapy. Dose interruptions, delays, pauses during previous therapy, or changes in therapy to manage toxicity will not constitute a new line of therapy provided disease progression did not occur.
3. Patients must have received prior trastuzumab, pertuzumab, and T-DM1.

Study Drugs, Dose, and Mode of Administration

Prior to randomization, investigators will choose one of four systemic chemotherapies commonly used in the salvage setting for advanced breast cancer (capecitabine, eribulin, gemcitabine, or vinorelbine) to be administered in combination with the study drug (margetuximab or trastuzumab). The chemotherapy selected must be allowed for use per local regulations (see **Section 6.1.2** for additional information). Chemotherapy will be started on Day 1 of each cycle and administered according to best practices and the starting dose, schedule, and mode of administration described in the following table. Chemotherapy may be discontinued, and antibody therapy continued, after 6 cycles if patients have a response of stable disease or better.

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[a]			
Capecitabine	1000 mg/m^2 BID	BID for 14 days in a 21-day cycle	Oral
Eribulin[b]	1.4 mg/m^2	Day 1 and 8 of a 21-day cycle	IV
Gemcitabine	1000 mg/m^2	Day 1 and 8 of a 21-day cycle	IV
Vinorelbine	25-30 mg/m^2	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

a. The chemotherapy selected must be allowed for use per local regulations (see **Section 6.1.2**). Chemotherapies must be used at the protocol-indicated starting doses, schedule, and route of administration, however dose adjustments to improve tolerability and manage toxicities are permitted.
b. Dose of eribulin noted here is based on use as eribulin mesylate; if free base eribulin is used, equivalent dose of 1.23 mg/m^2 is permitted.

Doses may be modified as recommended in the appropriate local labels and as described in **Section 6**.

Duration of Treatment and Study Duration

Patients will be treated with margetuximab or trastuzumab, both in combination with chemotherapy, in 3-week (21-day) cycles. Patients will be evaluated every 2 cycles (at 6-week intervals) for radiologic and clinical disease progression using RECIST 1.1. Treatment decisions will be made locally based on investigator interpretation of available studies, but central review assessments of radiologic scans will be used for the primary endpoint of PFS. Study treatment will continue until evidence of disease progression, unacceptable toxicity, withdrawal of consent, physician recommendation to discontinue therapy, or death. The anticipated median PFS for the trastuzumab arm is approximately 4 months. The anticipated median PFS for the margetuximab arm is approximately 6 months. There is no requirement to discontinue treatment after a prescribed number of cycles. There is no crossover in this study.

Approximately 530 patients, randomized 1:1 to margetuximab or trastuzumab, will be enrolled in this study. Following discontinuation of study treatment, patients will be followed for survival. The study will continue until there have been approximately 385 survival events, at which point the final survival analysis will take place. It is anticipated that accrual will take 24 months and that total follow up will take an additional 16 months, for a total study duration of approximately 40 months.

Infusion Sub-Study

About 9 patients will receive a 120-minute margetuximab infusion in Cycle 1, in order to have 6 patients receive a 60-minute infusion in Cycle 2 and beyond (Stage A1). Any extra patients beyond 6 in run-in groups A1 or A2 will continue 120-minute infusions until the Stage B regimen is confirmed. 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 infusion 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. 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 A 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. In the absence of Grade 3 or higher IRRs, ongoing patients in Stage A may reduce infusion duration once the Stage B duration is determined.

Post-progression margetuximab may be considered on a case-by-case basis within the infusion substudy only, with agreement of the Sponsor.

Details of the study design and stopping rules can be found in **Section 6.7.1**.

Treatment Schedule (Procedure)

See Schedule of Events (**Appendix 1**)

Criteria for Evaluation

Safety Assessments

- Safety assessment will be based on the evaluation of AEs from the time of initiation of any study therapy through the End of Treatment visit (or 28 days after the last dose of study drug, whichever occurs later) and will be determined based on signs, symptoms, physical examination findings and/or laboratory test results from enrolled patients as appropriate.
- All AEs (related to the protocol or not) will be collected from the time the patient receives the first dose of any study medication.
- AEs reported between the time the patient signed the informed consent and the administration of the first dose of any study medication will be captured as concurrent medical history unless due to a protocol-related procedure.
- AE and SAE recording will continue until the End of Treatment visit is performed (or 28 days after the last dose of study drug, whichever is later).
- 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 disease progression only, without any other SAE) will be documented as an anti-tumor activity outcome and not as an SAE. If an SAE occurs in a patient and it is unclear whether the event is related to progressive disease, the SAE should be reported.

Efficacy Assessments

Tumor assessments will be obtained at Screening using CT and/or MRI scans at time intervals as specified in **Appendix 1** (Schedule of Events). Assessment of skin lesions may be made by photography with a reference ruler or by caliper measurement as described in RECIST 1.1. Treatment will continue until disease progression, withdrawal from the study, or death. At each on-treatment tumor assessment time point, radiologic assessment of tumor status will be made using RECIST 1.1 criteria. Investigators will assess tumor response(s) for determination of suitability for continued therapy and the secondary endpoint of Investigator-Assessed PFS. All patients who have complete response (CR), partial response (PR), stable disease (SD), or non-evaluable as their local radiological assessment are eligible for further therapy. Non-radiological evidence of disease progression should be clearly documented in the electronic case report form (eCRF). With Protocol Amendment 4, central review of radiographic images is discontinued, but investigator-assessed PFS and ORR will continue to be measured.

All patients will have a bone scan performed at baseline and then as clinically indicated during the study for the assessment of bone metastasis. Patients with a history of treated brain metastasis who are otherwise eligible must have a baseline brain CT or MRI within 4 weeks prior to randomization.

When applicable, digital images of skin lesions will be obtained on the same schedule for radiographic evaluations.

Patients who are discontinued from study treatment in the absence of progression will be followed up every 3 months for tumor evaluations. Upon disease progression, all patients will be followed up every 3 months for survival status until death, withdrawal of informed consent, lost to follow up, or the end of study

Pharmacokinetic Assessments

With Protocol Amendment 4, PK sample collection will be discontinued for patients who are still receiving study treatment.

Immunogenicity Assessments

With Protocol Amendment 4, collection of samples for anti-drug antibody (ADA) assay will be decreased in frequency from once every 6 weeks (every 2 treatment cycles) to once every 12 weeks (every 4 treatment cycles), consistent with radiographic evaluation. ADA samples will continue to be collected at end of treatment and during follow-up.

The generation of ADA directed against margetuximab will be assayed using ELISA. Samples positive for ADA will be evaluated for neutralizing activity.

Analysis Populations:

Three analysis populations are defined:

- **Intent-to-Treat Population** – all patients randomized. Patients will be analyzed according to the treatment (margetuximab or trastuzumab) assigned during randomization. This population will be used to summarize baseline data and evaluate PFS, OS, and HRQoL.
- **Response Evaluable Population** – all patients who are randomized who have measurable disease at baseline. This population will be used to evaluate ORR and CBR.
- **Safety Population** – all patients who are randomized and receive any amount of any 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 (PD), and immunogenicity analyses.

Statistical Methods:

Sample Size Determination

There are 2 primary endpoints in this study. The first primary endpoint is centrally determined PFS and the second primary endpoint is OS. These two endpoints will be assessed in a hierarchical manner 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 and chemotherapy is 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, a total of 257 PFS events are required to provide 90% power at a 2-sided alpha=0.05. The analysis of the primary PFS endpoint will occur when about 257 events have occurred or when all patients have been randomized, whichever occurs later.

The sample size 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 OS of 16 months in patients treated with margetuximab plus chemotherapy (hazard ratio [HR]=0.75). To detect a 4-month improvement in OS from 12 months to 16 months, a total of 385 events are required to provide 80% power at a 2-sided alpha=0.05. It is anticipated that about 530 patients will be accrued to achieve this number of events. Patients will be enrolled over 24 months, and estimated to remain on study for an average of 16 months, for a total anticipated study duration of approximately 40 months.

The sample size of approximately 78 patients is planned for the infusion sub-study, consisting of 18 patients for Stage A and about 60 patients for Stage B. The sample size of 60 patients for Stage B of the infusion sub-study is derived to provide adequate assessment of the primary safety endpoint.

Efficacy Analyses

Definition of Efficacy Endpoints

Progression-free survival – defined as the time from randomization date to the date of first documented disease progression or death from any cause, whichever occurs first. For patients who are not known to be dead or progressed at time of data cut-off for PFS analysis, the PFS will be censored at the last tumor assessment.

Overall survival – defined as the time from 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 are last known to be alive.

Objective response rate – the proportion of patients in the response evaluable population achieving a best response of CR or PR when such responses are confirmed at least 28 days after initial observation of response. Patients who have baseline measurable disease but no post-baseline radiographic assessment will be considered as non-responders.

Duration of response – defined as the time from initial response to date of first documented disease 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.

Clinical benefit rate - the proportion of patients in the response evaluable population achieving a best response of CR, PR, or SD of duration >6 months.

HRQoL – Patients will be administered the EQ-5D-5L and NFBSI-16 quality of life questionnaires at baseline, Day 1 of each odd cycle, and at study completion. Change from baseline on global scores will be assessed. Patients in the infusion sub-study will not complete quality of life and healthcare usage assessments.

Analysis of Primary Efficacy Endpoints

The primary analysis for PFS will be conducted when about 257 PFS events have occurred. Analysis of OS will be conducted at the time of PFS analysis and subsequently when 70% of the OS events and a final OS analysis when about 385 survival events have occurred.

For both PFS and OS, Kaplan-Meier methods will be used to generate survival curves and estimate the median OS and PFS along with corresponding 95% confidence intervals (CIs) for each treatment group. A log-rank test stratified by protocol defined stratification factors will be used to compare both time-to-event endpoints between the two treatment groups. In addition, the hazard ratios and 95% CIs for PFS and OS will be assessed using stratified Cox proportional hazards models with treatment as the only covariate.

Analysis of Secondary Endpoints

The secondary endpoints of investigator-assessed PFS and independent review assessed ORR will be assessed using the Hochberg step-up procedure for multiplicity adjustment. P-values will be assessed in descending order. If the least significant p-value<0.05, then 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.

Investigator-assessed PFS will be analyzed using the same methods as described above for the primary endpoint of PFS.

Independent review assessed ORR will be compared between groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors.

Analysis of Tertiary Endpoints

No multiplicity adjustment will be used for tertiary endpoints.

Duration of response, where response is assessed by study investigators and by independent review, respectively, will be analyzed using Kaplan-Meier methods and compared between two treatment groups using a stratified log-rank test.

Investigator assessed ORR will also be compared between two treatment groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors.

Clinical benefit where response is assessed by study investigators and by independent review, respectively, will also be compared between two treatment groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors.

Change in tumor size over time will be summarized and the best percentage change from baseline will be presented by waterfall plots. Change calculations will be based on target lesions only.

Direct reports from patients will be obtained using the NFBSI-16 and EQ-5D-5L Questionnaires **(10, 16)**. Responses Data will be collected at baseline, Day 1 of each Odd cycle, and at the End of Treatment visit. The primary patient-reported outcome (PRO) endpoint for analysis will be the NFBSI-16 total score, with secondary analysis of the subscales that add to the total (disease related symptoms, treatment side effects, and function/well-being. Analyses using mixed model repeated measures using the baseline score and protocol defined stratification factors are planned as covariates. Subscale scores will be tabulated and summarized for additional analyses. Data from the EQ-5D-5L scale will be summarized by study visit. To minimize missing data, sites will be instructed and patients educated on the importance of recording the direct patient experience in order to appreciate the positive and negative aspects of treating advanced breast cancer, and they will specifically be trained on best practices for patient enrollment, adherence to endpoint data collection requirements, and methods to ensure complete data capture and management. Every effort will be made to collect survey data at all defined visits including at early withdrawal. Reasons for missing data will be summarized.

Pharmacokinetic Analysis: Serum concentrations of margetuximab will be summarized by study visits using descriptive statistics and graphed over time. Any population PK modeling will be performed by an external vendor. An analysis plan will be created prior to analysis.

Summary statistics will be tabulated for serum PK parameters by margetuximab dose. Geometric means and percent coefficients of variation will be reported for C_{max}, AUC_{tau}, AUC_{inf}, and C_{trough}; arithmetic means and standard deviations will be reported for T_{half}, CL, and V_{ss}; and medians, minimum, and maximum will be reported for T_{max}.

Exposure-Response Analyses: E-R analyses will be conducted separately using key efficacy and safety parameters of interest. An analysis plan will be created prior to analysis.

Immunogenicity Analysis: The proportion of patients who are negative for ADA at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and those patients who have positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized. Neutralizing activity will be determined for samples with positive ADA. The effects of ADA on key PK, efficacy, and safety parameters will be investigated.

Safety Analyses: AEs 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.

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

In cases where an abnormality resulted in a repeat laboratory test, the repeat value will be used for the summaries. A list of repeated labs including original values and repeat values will be included.

Graphs of mean values over time may also be generated.

Electrocardiograms (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. LVEF will be evaluated by echocardiogram or MUGA and changes from baseline summarized.

Infusion Sub-Study: Summary statistics will be calculated to describe incidence of infusion-related reactions by grade and by cycle for margetuximab given as monotherapy or in combination with chemotherapy.

2 BACKGROUND INFORMATION

2.1 HER2+ Metastatic Breast Cancer Current Therapy

Among women, invasive adenocarcinoma of the breast is the most common non-dermatological cancer and the second leading cause of death in the United States (US). While early detection and treatment have reduced the death rate associated with breast cancer, for women diagnosed with metastatic breast cancer (MBC) in the US, the overall prognosis remains poor, with an estimated 40,300 deaths due to this disease in 2014 **(23)**. In the European Union (EU), mortality associated with breast cancer was estimated to affect 92,000 individuals in 2012 **(15)**. Metastatic breast cancer can be identified either as the initial presentation of the disease, or after recurrence following previous treatment for local disease. Prior to the era of targeted therapies, patients with HER2+ tumors had more aggressive tumors that foretold a shorter survival. The introduction of trastuzumab into clinical practice in 1998 and subsequent therapeutic developments dramatically altered the natural history of HER2+ MBC **(14)**. Direct targeting of the HER2 oncoprotein lengthened survival in patients with HER2+ MBC to the point that now patients with HER2+ disease have a much more favorable prognosis than prior to the introduction of trastuzumab.

In the US and elsewhere, several agents are approved for the treatment of HER2+ breast cancer. For patients who require systemic therapy as part of definitive surgical resection, either neo-adjuvant therapy with trastuzumab - and increasingly - pertuzumab **(13)**, or adjuvant therapy with trastuzumab **(21)**, both in combination with cytotoxic chemotherapy, is the treatment of choice. Treatment at the time of recurrence is determined in part by the length of the original treatment-free interval. Patients whose disease recurs late after adjuvant treatment are often treated with the same or similar anti-HER2 regimen (trastuzumab ± pertuzumab) **(2, 24)**used in the neo-adjuvant or adjuvant setting. Patients whose disease recurs shortly after initial neoadjuvant/adjuvant therapy (within 6 months) will often proceed to a second-line regimen, usually ado-trastuzumab emtansine (T-DM1) monotherapy **(25)** or other anti-HER2 agents in combination with chemotherapy. The progression of therapies for de novo MBC is similar, with trastuzumab (± pertuzumab) used in combination with chemotherapy in first-line **(2)** and T-DM1 monotherapy or other anti-HER2 therapies in combination with chemotherapy used in the second-line. Of note, T-DM1 approved only for use in patients who have previously received trastuzumab, and the benefit of this agent as first-line therapy, either alone or in combination with pertuzumab, has not yet been demonstrated. Trastuzumab is also approved for use as a monotherapy in patients who have received previous chemotherapy **(11)**, although its use is limited in this indication **(14)**. Lapatinib, a small molecule tyrosine kinase inhibitor of both HER1 (EGFR) and HER2, has been approved in the US for use in combination with capecitabine in patients who have previously received an anthracycline, a taxane and trastuzumab **(12)** and additionally in Europe in combination with trastuzumab **(3)**. In theory, this allows for lapatinib use immediately after T-DM1: however, in practice, lapatinib is more often used in a later line of therapy for patients with HER2+ tumors. Given the effectiveness of neoadjuvant, adjuvant, and first-line therapies in HER+ disease, more patients are surviving and suitable for later-line therapy. However, recurrence of disease is common, and additional treatments are needed.

2.2 Rationale for Treatment with HER2-targeting Agents After Prior Receipt of HER2-targeting Agents in MBC Therapy

There is mounting evidence that continued therapy with anti-HER2 antibodies provides additional benefit beyond early therapy. A small study by von Minckwitz et al. **(26)** established early on that continued HER2 blockade provides benefit beyond first-line therapy. In this study, patients who experienced disease progression on trastuzumab and docetaxel were randomized to continue trastuzumab with a different chemotherapy or chemotherapy alone. Despite the small study population, there was a clear demonstration of prolonged progression free survival (PFS) among patients who continued on trastuzumab. T-DM1 was approved based on a prolongation of PFS compared with lapatinib in patients who had previously received trastuzumab **(25)**. In the recently reported trial of T-DM1 in patients who had previously received trastuzumab and lapatinib **(17)**, patients who received T-DM1 had prolonged PFS and overall survival (OS) compared with those who received physicians' choice chemotherapy. Interestingly, in the physicians' choice group, approximately 80% of patients received trastuzumab along with chemotherapy. Patients who demonstrated an objective response to trastuzumab after two prior anti-HER2 therapies in this study had a prolonged response with the median length of response not reached at the time of the data cutoff for publication. Together, these data suggest that patients who have experienced progression during treatment with HER2-targeted agents can still benefit from additional anti-HER2 therapy with the same or different agents, suggesting that the optimal treatment paradigm in later lines remains unsettled.

2.3 Margetuximab Background

Margetuximab **(20)** was derived from 4D5, the murine precursor to the humanized therapeutic antibody, trastuzumab. Chimeric 4D5 (ch4D5) was 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 was 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 Fc receptor, CD16A. In particular, binding to the low-affinity allele of CD16A (CD16A-158F) is enhanced in a proportionally greater fashion than binding to the high-affinity allele (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 with a trastuzumab surrogate against HER2-expressing tumor cell lines in in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) assays and in human tumor xenograft models in human CD16A+ transgenic mice. Since most patients carry the low-affinity allele of CD16A, the enhanced binding properties of margetuximab are expected to confer benefit to the whole patient population and not disproportionately to the high-binding homozygous carriers (V/V genotype). Homozygous high-binding (V/V) carriers make up less than 20% of Caucasian, African American, and Asian populations, and the remainder is composed of low affinity F/F and intermediate affinity F/V carriers.

Based on the greater activity of margetuximab compared with trastuzumab in preclinical animal models with low affinity CD16A+ transgenic mice, and the demonstration of prolonged PFS for patients with metastatic breast cancer treated with trastuzumab in high affinity vs. low affinity carriers **(18)**, it is hypothesized that margetuximab will have superior efficacy compared with trastuzumab when either is used to treat patients with metastatic breast cancer who have received two prior lines of anti-HER2 therapy.

2.3.1 Margetuximab Clinical Experience

Margetuximab is being evaluated for HER2+ metastatic breast cancer in two clinical studies, CP-MGAH22-01 and CP-MGAH22-02.

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 and patients with other carcinomas that overexpress HER2 for whom no standard therapy is available. Two regimens of margetuximab (administered via intravenous [IV] infusion) are being investigated in this study: weekly dosing (0.1 – 6.0 mg/kg) and every 3-week dosing (10.0, 15.0, and 18.0 mg/kg). Patients with stable disease or evidence of disease regression are eligible for continued treatment with margetuximab.

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 immunohistochemistry (IHC) and lack evidence of *HER2* gene amplification by fluorescent in situ hybridization (FISH) or express HER2 at a 1+ level by IHC and have a value of >10.5 by HERmark® testing. The study employs a Simon-two stage optimum design in which an initial cohort of 21 patients will be evaluated. 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 has been amended to evaluate margetuximab at a dose and schedule of 15 mg/kg via IV infusion every 3 weeks for all subsequent patients.

To date, the safety profile of margetuximab in the Phase 1 and 2 studies is generally consistent with that observed for trastuzumab in the same setting. Of note, cardiac toxicity, in

the form of reduction in left-ventricular ejection fraction (LVEF) and/or frank congestive heart failure (CHF), has not been observed to date. No significant decrease (defined as an absolute drop of 15% or to below 50%) in LVEF has been observed in patients receiving margetuximab in the monotherapy studies. Several patients have received multiple cycles of margetuximab in these studies with no apparent cardiotoxicity. Thus, margetuximab appears to be well-tolerated when administered either at a dose of up to 6.0 mg/kg given every week for 3 weeks in a 4-week cycle schedule, or when administered up to a dose of 18.0 mg/kg via every 3-week dosing.

Although not designed as an efficacy study, the Phase 1 study did demonstrate preliminary antitumor activity of margetuximab when used as a monotherapy in the treatment of patients with HER2+ tumors who had experienced multiple treatment failures with previous therapies. In particular, 4 of 21 patients with HER2+ MBC have experienced a partial response (PR) by RECIST criteria. Three of these 4 patients had received prior trastuzumab and lapatinib. No responses have been observed in the Phase 2 study of patients with MBC who express HER2 at the 2+ level by IHC or who have a HERMark® score of ≥10.5.

Detailed clinical data for these ongoing studies are provided in the margetuximab Investigator's Brochure (IB).

2.3.2 Margetuximab Pharmacokinetics and Dose Selection

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 (T_{half}) was estimated at 12.7 days. Interestingly, the individual estimates of clearance (CL) and central volume were slightly lower in patients with breast cancer compared with other tumor types, although the inter-patient variability was greater than the difference observed between groups.

Table 3 Margetuximab Pharmacokinetics at Steady State – 6 mg/kg, 15 mg/kg, 18 mg/kg – CP-MGAH22-01

Parameter (unit)		Margetuximab Dose and Schedule		
		6 mg/kg QW[a] N=19	15 mg/kg Q3W[b] N=6	18 mg/kg Q3W[b] N=6
C_{trough} (µg/mL)	Mean (SD)	73.0 (38.2)	69.9 (42.9)	86.1 (47.9)
	Median (95% CI)	66.9 (20.5 - 169)	61 (15.8 - 180)	77.6 (20.8 - 207)
C_{max} (µg/mL)	Mean (SD)	217 (58.1)	360 (93.9)	429 (103)
	Median (SD)	211 (125 - 355)	345 (222 - 590)	417 (263 - 660)
AUC (µg/mL*h)	Mean (SD)	84700 (30000)	72200 (27200)	87500 (30300)
	Median (95% CI)	80500 (40700 - 15800)	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 3** for margetuximab when dosed at 6.0 mg/kg weekly for 3 of every 4 weeks (n=19), 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 very similar exposure. Serum trough concentrations (C_{trough}) for all three doses are nearly identical, are at or above those reported for trastuzumab in patients with breast cancer **(11)**, and are above that required for inhibition of HER2 signaling as demonstrated for trastuzumab in published reports **(5)**. Similarly, area under the concentration-time curve (AUC) values are also very similar, with the 15.0 mg/kg slightly lower than either 6.0 mg/kg or 18.0 mg/kg. C_{max} differs among the three doses, as would be expected with higher maximal concentrations seen in the 15.0 mg/kg and 18.0 mg/kg doses compared with 6 mg/kg.

At the time of data cutoff (5 January 2015), of the 69 patients treated in ongoing studies CP-MGAH22-01 and CP-MGAH22-02, 48 had been treated at 6.0 mg/kg weekly for 3 of every 4 weeks (n=33), 15.0 mg/kg every 3 weeks (n=9), or 18.0 mg/kg every 3 weeks (n=6). Based on exposure data from CP-MGAH22-01, these patients can be considered as a single cohort of 48 patients that provides clinical experience supporting the selection of the 15.0 mg/kg dose of margetuximab for the current Phase 3 study, despite the different mg/kg doses administered.

There are no obvious differences in the safety profiles of each margetuximab dose evaluated to date suggesting a dose-toxicity relationship. (Details of the number and kind of adverse events [AEs] reported both in aggregate and by dose are available in the IB). In particular, of the 48 patients treated with the best studied margetuximab doses of 6.0 mg/kg, 15.0 mg/kg,

and 18.0 mg/kg to date, no events of congestive heart failure were recorded, and no decreases in LVEF of ≥ 15%, or to < 50% were observed The frequency, type, and severity of AEs observed in these dose groups did not differ from the overall study populations and although the 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}). Given the similarity of margetuximab to trastuzumab, this result is to be expected as no safety differential has been reported between the weekly dose of trastuzumab of 2 mg/kg and the every 3-week dose of 6 mg/kg. In the Phase 1 study of margetuximab, 7 patients have been treated continuously with margetuximab for at least 26 weeks, and of these, 5 patients received doses ≥10.0 mg/kg. No increase in AEs was noted with prolonged exposure, and none of these patients were discontinued from treatment because of toxicity.

Patients participating in the present study will be randomized to either margetuximab or trastuzumab, both to be administered in combination with a chemotherapy of the investigator's choice to be chosen from a specified list.

The margetuximab dose and schedule selected, 15.0 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 majority of clinical experience with margetuximab has been gained in patients treated at 6.0 mg/kg dosed weekly for 3 of 4 weeks and 15.0 mg/kg and 18.0 mg/kg given every 3 weeks, all of which have similar exposure based on steady-state PK modeling. Similar to the findings with safety, no clear dose-response relationship has been observed for tumor responses between these dose levels, with patients demonstrating responses at multiple dose levels.

Although both trastuzumab and margetuximab have demonstrated anti-tumor activity when given as monotherapy, trastuzumab has greater activity when combined with cytotoxic chemotherapies and is approved for such use. NCCN and European Society for Medical Oncology (ESMO) guidelines recommend the combination of trastuzumab with numerous different chemotherapy regimens, though none are preferred for the treatment of MBC following two prior lines of therapy **(4, 19)**. In HER2- MBC, only eribulin has shown a very modest survival benefit when compared with other commonly used therapies in the metastatic setting **(6)**. Trastuzumab and margetuximab share the same antigen recognition domain, and the preliminary safety profile of margetuximab appears similar to trastuzumab. Trastuzumab has been combined with capecitabine **(22)**, eribulin **(27)**, gemcitabine **(28)**, and vinorelbine **(1)** in the first and later line settings. These agents in combination with trastuzumab have not been compared with each other in a single study in the same setting, so it is not possible to determine if one combination is superior to another, but all have exhibited acceptable safety profiles when used in combination. Because none of these chemotherapy agents has been shown to be superior in the later line setting, it is reasonable to allow a choice of any of the four chemotherapies to be used in combination with trastuzumab or margetuximab. The choice of chemotherapy must be allowed for use per local regulations.

Based on the superior ADCC activity of margetuximab compared with trastuzumab in preclinical in vivo and in vitro models, the preclinical data demonstrating superior antitumor

activity associated with margetuximab, and the observation of clinical responses in patients who have previously received anti-HER2 therapy participating in the ongoing Phase 1 study (see margetuximab IB for detailed data), the combination of margetuximab plus chemotherapy is expected to provide enhanced efficacy and comparable safety over trastuzumab plus chemotherapy in patients with MBC requiring additional therapy after at least two previous anti-HER2 containing regimens.

3 STUDY PURPOSE AND OBJECTIVES

This is a Phase 3, randomized, open-label, comparator-controlled study of margetuximab plus chemotherapy versus trastuzumab plus chemotherapy in patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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.

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy, as measured by progression-free survival (PFS) assessed by independent review and overall survival (OS), of margetuximab plus chemotherapy compared with trastuzumab plus chemotherapy in patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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.

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 outcome measure.

3.2 Secondary Objective

Secondary objectives of this study are:

- To evaluate PFS, as assessed by 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.

3.3 Tertiary Objectives

Tertiary objectives are:

- To evaluate 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.
- 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.
- To characterize the population PK (PPK) and exposure-response (E-R) relationships of margetuximab in these patients.
- To evaluate anti-drug antibodies (ADA) directed against margetuximab and its effects on PK, efficacy, and safety in these patients.

3.4 Exploratory Objective

An exploratory objective of this study is to evaluate the effect of allelic variation in CD16A, CD32A, and CD32B on the efficacy of margetuximab in all patients receiving study treatments.

4 STUDY DESIGN

4.1 Overall Study Design and Plan

4.1.1 Study Design

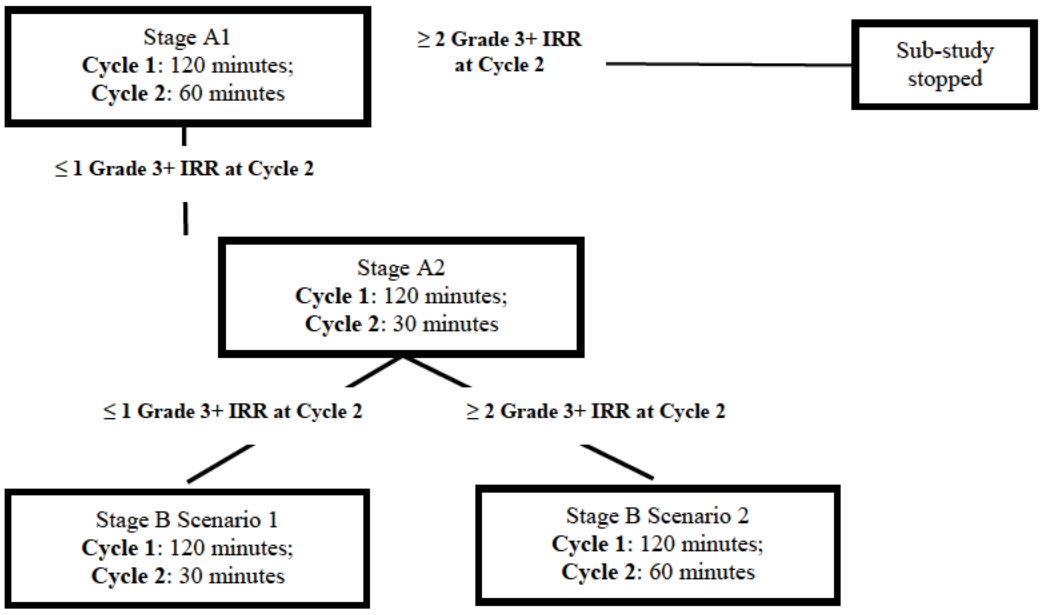
This is a Phase 3, randomized, open-label, comparator-controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy, for the treatment of patients with advanced HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy in the metastatic 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; see **Section 6.1.2** for additional information. Upon meeting all 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.

4.1.1.1 Infusion Sub-Study

The sub-study will start with a run-in group to evaluate the safety and tolerability of reduced infusion times. 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 a 60-minute infusion 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 infusion 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**.

Figure 1: Study Design for Infusion Rate Reduction of Margetuximab



4.1.2 Treatment of Patients

4.1.2.1 Chemotherapy

Patients enrolled in the study will be treated with one of four systemic chemotherapies commonly used in the salvage setting for advanced breast cancer: capecitabine, eribulin, gemcitabine, or vinorelbine (the chemotherapy selected must be allowed for use per local regulations; see **Section 6.1.2** for additional information). Prior to randomization, the treating physician will choose one of these agents to use as the backbone chemotherapy. The choice of chemotherapy may be made based on the investigator's best judgment and the choice of chemotherapy will be documented in the patient electronic case report form (eCRF).

To date, the toxicities observed with margetuximab are similar to those observed with trastuzumab and it is anticipated that combination of either agent with any standard systemic chemotherapy should be acceptable from a safety standpoint. Chemotherapy will be administered according to doses and schedules as described in **Section 6.1** and **Table 4**. Chemotherapy may be discontinued at the investigator's discretion after 6 cycles for patients with a response of at least stable disease and treatment with margetuximab or trastuzumab alone may be continued. Patients who require cessation of chemotherapy because of toxicity related to the chemotherapy should continue on trastuzumab or margetuximab alone provided the patient has not experienced progressive disease. Patients who require reinstitution of a different chemotherapy should have met the rules of treatment discontinuation and, therefore, be discontinued from study treatment. Switching to a different backbone chemotherapy is not permitted on this study following patient randomization.

The backbone chemotherapies to be used during this study are described in **Section 6.1.2**.

4.1.2.2 Study Drugs

Following enrollment and selection of chemotherapy, patients will be randomized 1:1 to receive either margetuximab or trastuzumab. Randomization will be stratified by number of metastatic sites (≤2, >2), number of lines of therapy overall in the metastatic setting (≤2, >2), and choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Patients will receive either margetuximab or trastuzumab on Day 1 of a 3-week cycle. Chemotherapy will be administered according to the schedule of the chosen agent beginning on Day 1 and will be given prior to margetuximab or trastuzumab on days when both study drug and chemotherapy are to be administered.

The study drugs (margetuximab and trastuzumab) to be administered during this study are described in **Section 6.1.1**.

4.1.3 Dose Delays

For patients who experience toxicity due to backbone chemotherapy and the investigator deems it necessary to hold the chemotherapy treatment, treatment with study drug should continue without delay. Chemotherapy treatment should be reinstituted at the next scheduled dose for that chemotherapeutic agent, once toxicity has improved or resolved. Any toxicity that leads to delay in study drug treatment, reinstitution of the study drug at the next scheduled dose of the study drug is recommended. Delays of up to 28 days are allowed, after which patients are discontinued from treatment. For patients who specifically experience a drug-related decrease in cardiac function, guidance on dose delays is provided in **Sections 6.1.1.1.1** and **6.1.1.2.1**.

4.1.4 Disease Assessments

Patients will be evaluated at regular intervals for disease status as described in **Section 7.10.1.1** and **Appendix 1** (Schedule of Events). Computed tomography (CT) and/or magnetic resonance imaging (MRI) scans will be performed prior to treatment (baseline) and every 2 cycles for the first 24 weeks of treatment. Thereafter, beginning with Cycle 9, tumor evaluation will be performed every 4 cycles while on treatment or every 3 months during post-treatment follow-up until documented disease progression, initiation of alternative anti-cancer therapy, lost to follow-up, withdrawal of informed consent, death, or the end of study. Bone scans will be performed on all patients at baseline and then as clinically indicated for the assessment of bone metastasis. Disease response will be determined both locally and by central review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. With Protocol Amendment 4, central review of radiographic images will be discontinued. Investigator-assessed PFS and ORR will continue to be assessed according to the protocol schedule.

Patient treatment decisions will be based on local (investigator) reviews of available assessments. Central reviews will be blinded to study treatment (margetuximab or trastuzumab) and will be used only for the primary endpoint analysis of PFS.

4.1.5 Rules for Continuation of Study Treatment

Patients who tolerate the combination therapy may continue on study until disease progression or as otherwise determined by the investigator. Patients who are intolerant of the chosen backbone chemotherapy, but do not exhibit signs of disease progression should continue on margetuximab or trastuzumab alone. At the investigator's discretion, patients who have received at least 6 cycles of treatment and who do not exhibit disease progression may have chemotherapy discontinued but remain on trastuzumab or margetuximab alone. Post-progression margetuximab may be considered on a case-by-case basis, with agreement of the Sponsor's medical monitor, for infusion sub-study patients only.

See **Section 5.4.1** for additional criteria requiring withdrawal from study treatment.

4.2 Rationale for Study Design

Therapy directed against HER2, either via a monoclonal antibody or derivatives or by small molecule inhibition has shown efficacy in patients with advanced breast cancer. To date, no HER2-targeted agents have been approved in the US to specifically treat patients after two prior lines of treatment, although both lapatinib and trastuzumab are often used in this setting. The purpose of this study is to evaluate the activity of margetuximab in combination with standard of care chemotherapies in the setting of patients with metastatic HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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. Because common practice is to treat these patients with an anti-HER2 agent in combination with chemotherapy, it is unethical to compare the effect of margetuximab with placebo, and therefore an active comparator was chosen. Trastuzumab is commonly used in this setting, and the comparison will directly evaluate whether a molecule that has been engineered to enhance ADCC produces superior clinical efficacy. Although not approved in this setting, trastuzumab is an acceptable comparator because continued treatment with trastuzumab after failure while on trastuzumab has demonstrated clinical benefit. In addition, trastuzumab has a generally favorable toxicity profile compared with lapatinib, and is commonly used in clinical practice **(4, 19)**.

The decision to allow physician's choice of chemotherapy from among a selected list is based on the well-described finding **(7)** that, in the treatment of advanced breast cancer, sequential single agent chemotherapies are superior to combination therapy, and that, other than eribulin - which showed a modest survival benefit - no one agent has been clearly shown to be superior to another in the salvage setting. Common practice is to choose a therapy based on individual patient needs and combine that with trastuzumab. Rather than dictate the therapy, investigators will choose the patient's combination chemotherapy from a

predetermined list, allowing for a tailored approach to each individual patient's status (also similar to the control arm in the eribulin pivotal study **(6)**). To minimize bias, the selected chemotherapy will be chosen and documented prior to patient randomization.

See **Section 2.2.1**, which details the rationale of modifying eligibility criteria as of Amendment 2 to enroll patients with metastatic HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy 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.

See **Section 2.2.2,** which explains the rationale for the infusion sub-study.

4.3 Study Duration

It is anticipated that this study will take 24 months to enroll at worldwide sites. An additional 16 months will be required to accrue the 385 survival events necessary for determination of the hazard ratio based on pre-study estimates of PFS and OS for margetuximab and trastuzumab, for a total estimated study duration of approximately 40 months. An interim analysis for futility based on PFS will be performed after a total of about 100 PFS events have occurred. The first primary endpoint of PFS will be evaluated after approximately 257 PFS events have occurred or after all patients have been randomized, whichever occurs later.

4.3.1 Patient Accrual

After obtaining informed consent and conducting pre-study eligibility assessments, eligible patients will be enrolled and randomized in a 1:1 fashion to receive either margetuximab or trastuzumab in combination with the pre-determined choice of chemotherapy. Accrual will continue until approximately 530 patients have been enrolled and randomized or 385 survival events have occurred, whichever occurs first.

Infusion Sub-Study: Up to about 78 patients will be accrued to the study in a non-randomized fashion. Accrual will continue until stopping rules are met or the sub-study is complete.

4.3.2 Definition of End of Study

The end of this study is defined as when the last patient visit occurs or one year after the final survival analysis, whichever occurs first. Patients experiencing clinical benefit with margetuximab treatment at the end of the study may be allowed to continue margetuximab treatment supplied by the study Sponsor. Continued treatment with trastuzumab at the end of the study must be sourced by the study investigator/treating physician and will not be the responsibility of the study Sponsor, unless required by local/site regulations.

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 of these criteria to be eligible for study participation; no exceptions to these criteria will be granted by the Sponsor.

5.1 Inclusion Criteria

To be included in this study, patients must:

General

1. Be able 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 and completion of HRQoL assessments.
2. Be ≥ 18 years old. Patients may be male or female.
3. Have histologically proven metastatic or locally advanced relapsed/refractory HER2+ (3+ by IHC or ISH-amplified as per American Society of Clinical Oncology [ASCO] and the College of American Pathologists [CAP] Guidelines) breast cancer based on the most recently available tumor biopsy collected from the patient. HER2 status must be documented from a reference laboratory that conforms to standards set for accreditation by CAP or an equivalent accreditation authority. Confirmatory IHC testing is not required for study entry. Tumors may be estrogen receptor (ER)/progesterone receptor (PgR) positive or negative.
4. Have received at least 2 prior lines of anti-HER2 directed therapy 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. In either case, patients must have received prior treatment with pertuzumab in the (neo)adjuvant or metastatic setting. Prior radiotherapy, hormonal therapies, and other anti-HER2 therapies are allowed.
5. Have received treatment for at least one, and no more than three, lines of therapy overall in the metastatic setting. Hormonal therapies will not be considered when determining the number of previous lines of therapy in the metastatic setting. Prior neo-adjuvant or 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 progressed on or following, the most recent line of therapy. Dose interruptions, delays, pauses during previous therapy, or changes in therapy to manage toxicity will not constitute a new line of therapy provided disease progression did not occur.

6. 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).
7. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**Appendix 4**).
8. Have life expectancy ≥ 12 weeks.
9. Have either measurable or non-measurable disease as per RECIST 1.1 criteria and documented by CT and/or MRI.

Laboratory Features

10. Have acceptable laboratory parameters as follows:
    a. Platelet count ≥ 100 × 10^3/μL without having received a transfusion or growth factor support within 4 weeks prior to randomization.
    b. Hemoglobin ≥ 9.0 g/dL without having received a transfusion or growth factor support within 4 weeks prior to randomization.
    c. Absolute neutrophil count ≥ 1.5 × 10^3/μL in the absence of any growth factor support given within 4 weeks prior to randomization.
    d. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 3.0 × the upper limit of normal (ULN), except patients with liver metastases, who may enroll with ALT/AST ≤ 5.0 × ULN.
    e. Total bilirubin ≤ 1.5 × ULN, except patients with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within laboratory normal limits.
    f. Creatinine < 1.5 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.

Reproductive Features

11. Female patients of childbearing potential (not surgically sterilized and between menarche and 1-year post menopause) must have a negative result from a serum pregnancy test performed within 14 days of randomization and a negative serum or urine pregnancy test on the day of first study treatment prior to the initiation of study treatment.

    Further, female patients of childbearing potential must agree to use highly effective contraceptive measures from the time of informed consent through 7 months after the last dose of study drug (either margetuximab or trastuzumab). Highly effective methods of contraception include:

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

  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

12. Male patients should also have their partners who are women of childbearing potential use a highly effective method of contraception (as shown above) from the time of informed consent through 7 months after last dose of study drug (either margetuximab or trastuzumab).

5.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Patients with known, untreated brain metastasis.
   - Patients with signs or symptoms of brain metastasis must have a CT or MRI performed within 4 weeks prior to randomization to specifically exclude the presence of radiographically detectable brain metastases.
   - Patients with known, treated brain metastases must have a baseline CT or MRI within 4 weeks of randomization and are eligible provided all therapy for the metastases concluded at least 4 weeks prior to randomization, or, if continued steroid therapy is indicated following therapy, they have been on a stable dose of steroids (≤ 10 mg/day of prednisone or equivalent) for at least 4 weeks prior to randomization with no symptoms.
2. History of uncontrolled seizures within 6 months of randomization.
3. History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation.
4. Treatment with any local or systemic anti-neoplastic therapy (including hormonal therapies for breast cancer) or any investigational therapy within 2 weeks prior to randomization. Bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors are allowed provided treatment starts prior to randomization.

5. Treatment with corticosteroids (i.e., > 10 mg prednisone per day or equivalent) or other immune suppressive drugs within 2 weeks prior to randomization. Steroids for topical use, inhalational use, nasal spray, or ophthalmic solution are allowed.
6. History of clinically significant cardiovascular disease including but not limited to:
    a. Myocardial infarction or unstable angina within 6 months prior to randomization.
    b. Stroke or transient ischemic attack within 6 months prior to randomization.
    c. Clinically significant cardiac arrhythmias.
    d. Uncontrolled (persistent) hypertension defined as systolic blood pressure (SBP) >180 mmHg or diastolic blood pressure (DBP) >100 mmHg.
    e. Congestive heart failure (New York Heart Association [NYHA] class II-IV).
    f. Pericarditis or clinically significant pericardial effusion.
    g. Myocarditis.
    h. LVEF < 50% by echocardiogram or multi-gated acquisition (MUGA) scan.
7. Clinically significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation.
8. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to randomization.
9. Known positive testing for human immunodeficiency virus or acquired immune deficiency syndrome.
10. Active 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).
11. Second primary malignancy that has not been in remission for at least 2 years from the anticipated start of study treatment. Exceptions of treated malignancies that do not require a 2-year remission include: non-melanoma skin cancer; cervical carcinoma in situ; squamous intraepithelial lesion; localized prostate cancer (Gleason score < 6); resected melanoma in situ or ductal carcinoma in situ. Patients with second primary breast cancers within 2 years are eligible provided that both primary tumors were HER2+ (3+ by IHC or in-situ hybridization [ISH] amplified).
12. History of trauma or major surgery within 4 weeks prior to randomization.
13. 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.
14. Known hypersensitivity to recombinant proteins, polysorbate 80, benzyl alcohol, or any excipient contained in the drug formulation for margetuximab, trastuzumab or other study treatments. Previous infusion reactions to trastuzumab or other monoclonal antibodies will not preclude enrollment provided no contraindication to trastuzumab therapy remains.

15. Any condition that would be a contraindication to receiving trastuzumab as described in the approved local label or a condition that would prevent treatment with the physician's choice of chemotherapy.
16. Vaccination with any live virus vaccine within 4 weeks prior to randomization. Inactivated annual influenza vaccination is allowed at any time.
17. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
18. Active or history of alcohol or other substance abuse within 1 year prior to randomization.
19. Pregnant or breast feeding.
20. Prior participation in a margetuximab clinical study.
21. Any investigative site personnel directly affiliated with this study.
22. Employees of MacroGenics, Inc.
23. Prisoners or other individuals who are involuntarily detained.
24. Any issue or condition 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 Entry Criteria for the Infusion Sub-Study

1. Patients will meet all entry criteria for the randomized portion of the study with the exception of inclusion criteria #4 and #5.
2. Patients must have received at least 4 prior lines of therapy for metastatic disease. Hormonal therapies will not be considered when determining the number of previous lines of therapy in the metastatic setting. Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 6 months of the completion of therapy will be considered a line of treatment for metastatic disease. Eligible patients must have progressed on or following the most recent line of therapy. Dose interruptions, delays, pauses during previous therapy, or changes in therapy to manage toxicity will not constitute a new line of therapy provided disease progression did not occur.
3. Patients must have received prior trastuzumab, pertuzumab, and T-DM1.

5.4 Withdrawal of Patient from the Study or Study Drug

5.4.1 Guidelines for Permanent Discontinuation

Patients should be permanently withdrawn from all study treatment for any of the following situations. Patients who are withdrawn from the study will not be replaced.

- Following patient enrollment and treatment, a violation of enrollment criteria or other significant protocol violation is discovered of such nature that continued treatment would not be in the best interest of the patient.

- Patient develops an uncontrolled intercurrent illness unrelated to cancer that renders continuing treatment unsafe or regular study visits impossible.
- Patient experiences an AE or serious adverse event (SAE) that necessitates discontinuation of study drug (i.e., margetuximab or trastuzumab).
- The Sponsor or Regulatory Agency terminates the study, or investigator terminates participation in the study.
- The patient requests to be discontinued from the study, i.e., withdraws consent.
- The patient is noncompliant with study drugs, chemotherapy, other study medication, or protocol-required evaluations.
- Patient is withdrawn at investigator's discretion.
- The patient exhibits progression of disease by RECIST 1.1 criteria.
- The patient becomes pregnant during the study. Upon confirmation of the pregnancy, the patient must discontinue treatment with study drug immediately.
- Treatment delay of study drug greater than 28 days (except due to drug-related cardiac toxicity (see **Section 4.1.3**)).
- Patient death

The Sponsor or its designee must be notified within 24 hours of discontinuations meeting criteria for an Immediately Reportable Event (IRE) (**Section 7.9.2.7**) using the procedures outlined in **Section 7.9.7**. For all permanent discontinuations, patients will continue to be followed as appropriate and consistent with protocol guidelines but should receive no further study treatment. All patients should be followed for survival – the only exception would be withdrawal, by the patient, of consent.

5.4.2 Procedures for Patients Lost to Follow-up

Patients will be considered lost to follow-up if no contact can be established despite repeat attempts to contact. Investigators must document all attempts to contact missing patients throughout the study period unless consent for follow-up has been withdrawn. At a minimum, it is expected that sites will send at least two certified letters to a missing patient to attempt to re-establish contact, and patients will not be considered lost to follow-up until this has occurred. If contact with a missing patient is re-established, resumption of study drug administration may be considered and must be discussed with the medical monitor prior to recommencement. If contact is re-established in the Post-Treatment Follow-up phase, evaluations should resume according to the protocol.

6 STUDY TREATMENTS

6.1 Description of Treatment(s)

An overview of study treatments to be administered during this study is presented in **Table 4**. On days when both the study drug and chemotherapy are to be administered, the chemotherapy will be administered first.

Table 4 Overview of Study Treatments

Agent	Starting Dose	Schedule	Mode of Administration
Chemotherapy[a]			
Capecitabine	1000 mg/m^2 BID	BID for 14 days in a 21-day cycle	Oral
Eribulin[b]	1.4 mg/m^2	Day 1 and 8 of a 21-day cycle	IV
Gemcitabine	1000 mg/m^2	Day 1 and 8 of a 21-day cycle	IV
Vinorelbine	25-30 mg/m^2	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

a The chemotherapy selected must be allowed for use per local regulations (see **Section 6.1.2**). Chemotherapies must be used at the protocol-indicated starting doses, schedule, and route of administration, however dose adjustments to improve tolerability and manage toxicities are permitted.

b Dose of eribulin noted here is based on use as eribulin mesylate; if free base eribulin is used, equivalent dose of 1.23 mg/m^2 is permitted.

All changes in study drug infusions, including interruptions and their duration, as well as reductions in rate and duration, must be recorded. Chemotherapies are to be administered at the starting dose, frequency, and route indicated per protocol.

6.1.1 Study Drugs

6.1.1.1 Margetuximab

Margetuximab will be administered on Day 1 of a 3-week cycle at a dose of 15 mg/kg via IV infusion over 120 minutes, unless the patient is enrolled to the infusion sub-study. On days when both chemotherapy and margetuximab are to be administered, the chemotherapy will be administered first.

6.1.1.1.1 Dose Rate or Schedule Modifications for Toxicity

The rate of margetuximab infusion or dose schedule may be modified for infusion-related reactions or cardiac toxicities, respectively, that are determined to be associated with margetuximab based on the following parameters:

- Infusion-related reactions: follow guidelines described in **Section 6.6.2.2**
- Decreased cardiac function – withhold margetuximab for at least 4 weeks if either of the following criteria are met:
  - ≥ 16% 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

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

Margetuximab may be resumed if, within 8 weeks, the LVEF returns to within normal limits and the absolute decrease from baseline is ≤ 15%.

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

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

6.1.1.2 Trastuzumab

Trastuzumab will be administered via IV infusion on Day 1 of a 21-day cycle at a dose of 8 mg/kg for the first dose (over 90 minutes) and 6 mg/kg for all subsequent doses (over 30 to 90 minutes). On days when both chemotherapy and trastuzumab are to be administered, the chemotherapy will be administered first.

Contraindications

In addition to inclusion exclusion criteria incorporated into this protocol, the following are contraindications specific to the administration of trastuzumab:

- Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients.
- Severe dyspnea at rest due to complications of advanced malignancy or requiring supplemental oxygen therapy.

6.1.1.2.1 Dose Modification for Toxicity

Dose reduction

No reductions in the dose of trastuzumab should be made. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.

The trastuzumab package insert should be consulted for any dose modifications or adjustments. Trastuzumab dosing will be modified for infusion reactions and cardiomyopathy.

For infusion reactions, the guidelines described in **Section 6.6.2.2** should be followed.

Trastuzumab should be withheld for at least 4 weeks if a decrease in cardiac function as follows is observed:

- ≥ 16% absolute decrease in LVEF from pre-treatment values, or
- LVEF below institutional normal limits and ≥ 10% absolute decrease in LVEF from pretreatment values

If LVEF has not improved, or declined further, or symptomatic congestive heart failure (CHF) has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

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

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

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

6.1.2 Backbone Chemotherapy

The choice of backbone chemotherapy will be made by the treating physician prior to randomization. The choice of therapy should be made based on the patient's co-morbidities and the physician's best judgment about the most appropriate chemotherapy for a given patient. Chemotherapies must be used at the protocol-indicated starting doses, schedule, and route of administration (see **Table 4**); however, dose adjustments to improve tolerability and manage toxicities are permitted. Allowable chemotherapeutic agents include capecitabine, eribulin, gemcitabine, and vinorelbine (except in Italy where sites can choose from capecitabine and vinorelbine only per local requirements). The chemotherapy selected must be allowed for use per local regulations and will be supplied locally unless an alternate source for the selected agent is needed. Changes in backbone chemotherapy will not be

allowed following patient randomization (see **Section 4.1.2.1**). Substitution of generic equivalents for branded products is acceptable if such products have been approved by local regulatory authorities for use in the treatment of human diseases. Substitution of different doses due to differences in formulation is allowed provided that the amount of active drug substance is equivalent. The use of therapies other than those used to treat or prevent toxicities, either alone or in combination with either of the 4 allowed chemotherapy agents, is not allowed.

Dose modifications for toxicities associated with chemotherapy agents should be managed according to instructions provided within each product's respective package insert.

If used in the infusion sub-study, backbone chemotherapy will be administered according to the same protocol-specified direction for the randomized cohorts.

6.2 Study Drugs and Supplies

6.2.1 Margetuximab

Margetuximab is a sterile, clear-to-slightly-opalescent, colorless-to-pale-yellow or pale-brown, preservative-free solution for IV administration. Margetuximab will be supplied at a protein concentration of 25 mg/mL in a single-use vial containing 250 mg/10 mL. Margetuximab is packaged in US Pharmacopeia (USP) and Ph. Eur. Conforming Type I borosilicate, 10 mL clear glass vials with FluroTec® coated 4432/50 gray butyl rubber serum stoppers and aluminum seals with plastic overseals. 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, pH 6.1. Requests for additional study drug should be made to MacroGenics, Inc., via Interactive Response System (IxRS) at least 2 weeks in advance.

6.2.2 Trastuzumab

Trastuzumab (marketed as HERCEPTIN® by Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990; Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel) is available as follows:

- 440 mg vial is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial trastuzumab and one vial (20 mL) of Bacteriostatic Water for Injection, USP, containing 1.1% benzyl alcohol as a preservative. Though supplied as a multi-use vial, each vial may only be used once.
- 150 mg vial is supplied in a single-dose vial containing 150 mg trastuzumab as a white lyophilized powder for preparation of a concentrated solution for infusion. Each carton contains one vial trastuzumab 150 mg.

6.2.3 Backbone Chemotherapies

Backbone chemotherapies will be provided locally unless an alternate source for the selected agent is needed.

6.3 Drug Preparation and Administration

6.3.1 General Precautions

The calculated dose for chemotherapy and margetuximab or trastuzumab will be administered based on the patient's actual weight at Cycle 1 Day 1 (baseline). Significant (≥ 10%) change in body weight from baseline should prompt recalculation of dose. For body surface area (BSA) determination, a change in weight of ≥10% will prompt recalculation of BSA and dose according to institutional standards.

Backbone chemotherapies and trastuzumab should be prepared and administered according instructions provided within each product's respective package insert.

Infusion or allergic reactions may occur with the infusion of monoclonal antibodies and other protein-based therapeutics. Precautions for anaphylaxis should be observed during margetuximab and trastuzumab 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 6.6.2.2** 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.

6.3.2 Margetuximab Preparation

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinet.

Before administration, parenteral drug products should be inspected visually. Some visible, translucent, proteinaceous, margetuximab particles may be present. However, if foreign particulate matter or discoloration is observed, the drug should not be administered. The desired amount of margetuximab should be withdrawn from the vial(s) and diluted in a 250 mL polyolefin (e.g., polypropylene) or olefin copolymer (e.g., ethylene and propylene copolymer) (hereafter referred to collectively as "olefin polymer/copolymer"), or polyvinyl chloride (PVC) infusion bag containing 0.9% Sodium Chloride Injection, USP at a final concentration of 2.4 to 7.2 mg/mL. The bag should be appropriately labeled and gently inverted to mix the solution. THE BAG MUST NOT BE SHAKEN; excessive agitation may cause aggregate formation. *A low protein binding polyethersulfone (PES) 0.2 micron filtered administration set must always be used for IV administration of margetuximab.*

Since margetuximab does not contain preservatives, once diluted in normal saline, administration should begin immediately after preparation but can be stored at 2° to 8°C for up to 6 hours after preparation.

Margetuximab should not be administered as an IV push or bolus. Margetuximab should not be mixed or diluted with other drugs. Vials are single unit-dose containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate drug disposal procedures.

6.3.3 Study Drug and Chemotherapy Administration

Margetuximab will be administered as a 120-minute (2-hour) IV infusion after chemotherapy administration for patients in the randomized cohorts. Margetuximab may be administered after completion of chemotherapy administration. Two consecutive doses should be a minimum 18 days apart.

For patients randomized to trastuzumab, the first dose will be administered as a 90-minute infusion after chemotherapy administration. For subsequent doses, trastuzumab will be administered as a 30-90-minute IV infusion. Trastuzumab may be administered after completion of chemotherapy administration. Two consecutive doses should be a minimum 18 days apart.

Chemotherapies will be administered as described in **Table 4** and per each individual agent's prescribing information.

The chosen chemotherapy (if administered IV) and randomized study drug must be administered within ± 10 minutes of the indicated infusion duration.

6.3.3.1 Premedications and Prophylaxis for Chemotherapy

Standard premedications for the administration of the cytotoxic chemotherapy will be employed in the study. For chemotherapy, recommendations made in the locally approved label should be followed for each agent.

6.3.3.2 Premedications for Margetuximab

When margetuximab infusions coincide on the same day with cytotoxic chemotherapy administration, the premedications for the chemotherapy should be employed and should be sufficient for prophylaxis of margetuximab infusion reactions as well.

Premedication is not required, but the following recommendations are made regarding premedications for margetuximab administration on those days upon which that administration is not preceded by a chemotherapeutic agent or if no premedication is employed for that chemotherapy. Premedication should be given within 30 minutes of margetuximab administration if it has not previously been administered prior to backbone

chemotherapy. These recommendations should serve as guidelines and may be modified by the Investigator.

Prior to the infusion:

- 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 10 mg IV or equivalent (for patients at high risk)

6.3.3.3 Premedications for Trastuzumab

There are no premedications specified for administration of trastuzumab (See most current Herceptin Prescribing Information). Dose modifications for toxicity are described in **Section 6.1.1.2.1**.

6.3.4 Additional Instructions for Handling

Margetuximab or trastuzumab should not be mixed or diluted with other drugs. Any partially used vials or diluted dosing solutions should be discarded using appropriate drug disposal procedures. Although trastuzumab may be supplied in a multi-use vial, each vial may only be used once during this study.

6.4 Dispensing Study Drug

Under no circumstances is the investigator allowed to release the clinical study drug supplies for use by another physician not named on Form FDA 1572 (or equivalent document) or 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).

6.5 Selection and Timing of Dose for Each Patient

Patients will be randomized 1:1 to receive either margetuximab or trastuzumab, both in combination with chemotherapy preselected by the investigator. Randomization will be stratified by number of metastatic sites (≤ 2, > 2), number of lines of therapy in the metastatic setting (≤2, >2), and choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Study drug (margetuximab or trastuzumab) will be administered after chemotherapy drugs are administered on Day 1 of each 3-week cycle.

6.5.1 Selection and Timing of Infusion Sub-Study Patients

Patients who participate in the infusion sub-study will not be stratified nor randomized. They will be enrolled to receive either monotherapy margetuximab or margetuximab in combination with protocol-specified (**Table 4**) physician choice chemotherapy, at the

discretion of the investigator. Margetuximab will be administered on Day 1 of each 3-week cycle, after the chemotherapy if combination therapy is chosen.

6.6 Potential Adverse Events and Supportive Care Measures

6.6.1 Study Drugs (Margetuximab and Trastuzumab)

Supportive care measures specific to trastuzumab and margetuximab are described below; recommended modifications for toxicity specific to these agents are provided in **Section 6.1.1**.

6.6.2 Infusion Related Reactions

Infusion-related reactions including hypersensitivity/anaphylactic/anaphylactoid reactions may occur. Precautions for the management of these reactions should be observed during margetuximab and trastuzumab administration.

Infusion reactions associated with margetuximab or trastuzumab administration should be managed according to the standard practice of medicine. General guidelines for the management of such reactions are provided in this section.

Patients should be monitored closely for the development of infusion-related reactions during margetuximab or trastuzumab infusion. Medications and supportive measures for the treatment of severe hypersensitivity reactions should be available for immediate use for an infusion reaction 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., hydrocortisone 25-100 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 also 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 whether the cause of the symptoms is related to emerging infection or infusion reaction. As such, 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 6.6.2.2** for guidance regarding the management of infusion reactions.

6.6.2.1 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 is indicated before resuming the original infusion rate, as tolerated by the patient (see **Section 6.6.2.2**);
- 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.

Guidelines regarding premedications for the prevention of infusion reactions are provided in **Section 6.3.3.2**. Investigators are encouraged to intervene early and vigorously in the treatment of infusion reactions and cytokine release syndrome if they occur.

6.6.2.2 Management of Observed Margetuximab or Trastuzumab Infusion Reactions

The following are treatment guidelines (which may be modified as needed by the responsible investigator according to the best practices of medicine) for margetuximab or trastuzumab infusion reactions:

- 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.
- Grade 2:
  - Stop the infusion.
  - Administer diphenhydramine hydrochloride 25-50 mg IV, ibuprofen 400 mg or institutional equivalent orally 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.
- Monitor for worsening condition.
- For patients with Grade 2 infusion reactions despite premedication, corticosteroids (hydrocortisone 100 mg IV or equivalent) should be considered for acute management of the event. Dexamethasone 10 mg IV should be added to the premedication regimen for subsequent dosing of margetuximab or trastuzumab at the discretion of the investigator.

- Grade 3:
  - STOP THE INFUSION AND DISCONNECT THE INFUSION TUBING FROM THE PATIENT.
  - TO AVOID EXACERBATION OF INFUSION REACTION: DO NOT FLUSH THE TUBING – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN.
  - Administer diphenhydramine hydrochloride 25-50 mg IV, hydrocortisone 100 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (i.e. dexamethasone 10 mg IV) may also be considered for acute management.
  - IV fluids, supplemental oxygen and bronchodilators should be considered as appropriate.
  - If symptoms have resolved to baseline within 6 hours, a rechallenge may be considered at the next scheduled dose, with a 50% reduction of infusion rate. In addition, patients should be premedicated for this rechallenge and for any subsequent doses of margetuximab or trastuzumab, per the premedication guidelines in **Section 6.3.3.2** and **Section 6.3.3.3**. Patients who have a Grade 3 infusion reaction that does not resolve within 6 hours despite medical management should not receive further margetuximab or trastuzumab treatment.
  - Patients who experience a second Grade 3 infusion reaction at the time of rechallenge (irrespective of duration), should not receive further margetuximab or trastuzumab.
  - Report as an immediately reportable event (IRE) within 24 hours.
  - Report the event as an 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 – ASPIRATE RESIDUAL DRUG FROM THE PORT LUMEN.
  - Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg 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.
  - Discontinue the patient from further margetuximab or trastuzumab. (Patients may remain on study and continue to receive backbone chemotherapy if otherwise eligible.)
  - Report as an IRE within 24 hours.
  - Report the event as an SAE.
- Grade 5:
  - Report as an IRE within 24 hours.
  - Report the event as an SAE.

The start time and end time of the infusion and all changes in the infusion of margetuximab or trastuzumab, including interruption of the infusion and overall infusion duration, as well as reductions in infusion rate and duration, must be recorded. The start of infusion is "0" time.

6.7 Method of Assigning Patients to Treatment Groups

This is a randomized, comparator-control study comparing margetuximab plus chemotherapy to trastuzumab plus chemotherapy. Patients enrolled in the study will be stratified according to the number of metastatic sites (≤2, >2), number of lines of therapy in the metastatic setting (≤2, >2), and choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).

Patients who meet eligibility criteria for enrollment will be randomized using IxRS within 3 days of Study Day 1 (Cycle 1 Day 1). A central randomization scheme using permuted blocks will be prepared and patients will be randomized 1:1 to margetuximab plus chemotherapy or trastuzumab plus chemotherapy. To minimize bias, chemotherapy will be selected by the investigator and documented prior to patient randomization.

6.7.1 Assignments in the Infusion Sub-Study

The sub-study will start with a safety run-in group.

Stage A1

A cohort of about 9 patients will receive margetuximab as a 120-minute infusion time in Cycle 1. Of the subjects completing Cycle 1, 6 patients will go on to receive a 60-minute infusion time in Cycle 2 and beyond. Patients will be allocated to the reduced infusion time in order of their completion of Cycle 1 of treatment. Any remaining subjects in the cohort will continue to receive 120-minute infusions. If 2 or more patients in Stage A1 experience a Grade 3 or higher IRR during Cycle 2, the infusion acceleration will be abandoned and enrollment into the sub-study will be stopped. If no more than 1 of the 6 patients in Cycle 2 of Stage A1 experiences a Grade 3 or above IRR, an additional 9 patients will be enrolled to Stage A2.

Stage A2

As in Stage A1, about 9 patients will receive margetuximab infused at 120 minutes in Cycle 1. Six patients, in the order of their completion of Cycle 1, will go on to receive a reduced infusion time of 30 minutes in Cycle 2 and beyond. Any remaining subjects in the cohort will continue to receive 120-minute infusions. If no more than 1 of the 6 patients in Stage A2 experiences a Grade 3 or higher IRR during Cycle 2, the sub-study will enroll about 60 patients in Stage B to receive margetuximab infused at 120 minutes in Cycle 1 followed by 30 minutes in Cycle 2 and beyond. If 2 or more patients in Stage A2 experience a Grade 3 or higher IRR during Cycle 2 (30-minute infusion), patients in Stage B will be infused according to the method in Stage A1.

Stage B

Patients will be assigned to the shortest infusion schedule based on the stopping rules for Stages A1 and A2. In the absence of Grade 3 or higher IRRs, all patients in Stage A1 or Stage A2 may have a reduced infusion duration to the Stage B infusion schedule.

Backbone chemotherapy, if used, will be administered according to the instruction in **Section 6.1.2** and **Table 4**.

6.8 Blinding

This is an open-label study and no blinding of site personnel or patients will be employed. With exception of authorized Sponsor staff and other specified individuals not directly involved in the conduct of this study, clinical data provided to the Sponsor will remain blinded with respect to treatment assignment. Independent assessment of PFS will be blinded. The infusion sub-study is not blinded.

In this open-label study, clinical data provided to the Sponsor were blinded with respect to treatment assignment until primary PFS analysis. Following independent blinded PFS assessments to support the primary endpoint, the Sponsor was unblinded.

6.9 Concomitant Therapy

All concomitant medications and blood products administered during the patient's participation in the study until the End of Treatment visit (or 28 days after the last dose of study drug, whichever occurs later) must be recorded in the patient's source documents and eCRF.

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

- Any anti-neoplastic therapies not described in this protocol, including but not limited to chemotherapy or other small molecules, biologics, or hormonal or radiotherapy, are not allowed.
- Palliative radiotherapy is only allowed during the study treatment period for the treatment of bone lesions present at baseline. Radiation therapy to a new lesion would, per RECIST (**Appendix 8**), qualify as progressive disease and necessitate discontinuation of therapy. RECIST target lesions cannot be in the radiation field.
- Patients may not receive other investigational drugs during the period of study treatment.
- Vaccinations (with the exception of the annual inactivated influenza vaccine) are prohibited during study treatment.

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.
- Bisphosphonates or RANKL inhibitors provided such agents are approved in the local jurisdiction and treatment with the agent is begun before the start of study treatment.
- Use of granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor or other growth factors is allowed per local practice.
- 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.

6.10 Restrictions

6.10.1 Prior Therapy

Prior therapy restrictions are described in the inclusion/exclusion criteria specified in **Section 5**, Selection and Withdrawal of Patients.

6.10.2 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 ECGs will be obtained pre-meal.

6.10.3 Patient Activity Restrictions

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

6.11 Treatment Compliance

Study drugs and backbone chemotherapy of the investigator's choice will be administered by healthcare professionals under the supervision of the investigators. Records of dose calculation, administration, and dosing regimen will be accurately maintained by site staff for all administered therapies. A site study monitor, designated by the Sponsor, will review dose calculation, study drug administration and regimen, as well as medication accountability, during investigator site visits and at the completion of the study.

6.12 Packaging and Labeling

Chemotherapies will be obtained locally unless an alternate source for the selected agent is needed.

Margetuximab will be supplied in single-use vials. Normal saline in 250-mL IV bags will be obtained from the institution's usual commercial supplier for the dilution of margetuximab solution for administration. All investigational products will be labelled according to local regulatory health authority requirements. Please see the Pharmacy Manual for detailed information about the packaging of margetuximab.

Trastuzumab (marketed as HERCEPTIN® by Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990; Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel) is available as follows:

- 440 mg vial is supplied in a multi-use vial containing 440 mg trastuzumab as a lyophilized sterile powder, under vacuum. Each carton contains one vial trastuzumab and one vial (20 mL) of Bacteriostatic Water for Injection, USP, containing 1.1% benzyl alcohol as a preservative.
- 150 mg vial is supplied in a single-dose vial containing 150 mg trastuzumab as a white lyophilized powder for preparation of a concentrated solution for infusion. Each carton contains one vial trastuzumab 150 mg.

Trastuzumab (marketed as HERCEPTIN®) will be provided in the commercial packaging taken from commercial supply. Trastuzumab will be appropriately labeled and will comply with local legal requirements, as required. Please see the Pharmacy Manual for detailed information about the packaging and labeling of the trastuzumab.

Prepared margetuximab/trastuzumab IV bags should be labeled for administration per the institution's guidelines.

6.13 Storage and Accountability

Chemotherapies and trastuzumab will be stored and accounted for according to institutional guidelines and procedures, and according to the respective Prescribing Information. Trastuzumab must be stored at 2−8°C (36−46°F) prior to reconstitution.

Vials containing margetuximab must be stored under refrigeration at 2° to 8°C (36° to 46°F) and must not be frozen, and in an appropriate locked room accessible only to the pharmacy personnel or a duly designated person. Protect margetuximab from light during storage. Do not shake margetuximab vials. To ensure compliance, temperature logs will be maintained. The refrigerator must have a digital min/max thermometer or a continuous recording device.

Administration should begin immediately after preparation of the margetuximab solution and no later than 6 hours after preparation when stored at 2° to 8°C.

Accurate accounting of all study medication must be maintained. The Investigator agrees to keep an inventory of all study drugs received and used during the course of the study 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 study-related documentation for inspection by the study monitors. Additional details regarding storage, handling, and accountability can be found in the Pharmacy Manual.

6.14 Investigational Product Disposition at End of Study

Upon completion or termination of the study, all unopened vials of study drugs 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 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 study 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. The Schedule of Events (**Appendix 1**) details the schedule of assessments by study visit.

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 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.

7.2 Medical History

A complete medical history should be obtained during the Screening period. All concurrent medical conditions experienced during the last 60 days and any significant prior medical conditions (e.g., hospitalizations, surgeries, prior cancer history) should be collected. Any untoward event that occurs during the Screening period (prior to first dose of any study drug) should be recorded as concurrent medical history and not as an AE unless it is due to a protocol-related procedure. Any untoward event that occurs following the first dose of study drug (margetuximab or trastuzumab) 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 visit (or 28 days after the last dose of study drug, whichever occurs later) must be recorded in the source document and on the eCRF. To the extent possible, patients who receive anti-cancer agents, either approved or experimental, after removal from study treatment should have this information recorded in the eCRF, including the name of the agent and the duration of exposure.

Prior courses of chemotherapy will be documented in the medical records and on the eCRF.

7.4 Physical Examination

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

Physical exams will be performed at Screening, Day 1 of each treatment cycle, and on at the End of Treatment visit. Weight will be measured during Screening, Cycle 1 Day 1, Day 1 of each subsequent Odd treatment cycle, and at the End of Treatment visit.

7.5 Vital Signs

Vital sign evaluations will include blood pressure, heart rate, respiratory rate, and temperature. Vital signs will be collected as indicated in Schedule of Events (**Appendix 1**).

Vital signs will be performed at Screening. On the first dose of study treatment (Cycle 1, Day 1), vital signs will be taken at the following time points:

- Prior to initiation of margetuximab or trastuzumab infusion
- at end of margetuximab or trastuzumab infusion, and
- at 60 minutes (± 10 minutes) after infusion with margetuximab or trastuzumab.

For subsequent cycles, vital signs will be collected only at the start and end of margetuximab or trastuzumab infusion as indicated in **Appendix 1**.

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

7.6 Clinical Laboratory Tests

Local laboratories should be used for all clinical decision-making, including but not limited to, decisions regarding chemotherapy administration and dose adjustments, if needed. Necessary laboratory testing for patient safety should be performed as required by the clinical situation. Local laboratory testing will be used for confirmation of pregnancy status prior to dosing according to the protocol schedule.

With Protocol Amendment 4, blood and urine samples for testing at a central laboratory will no longer be collected. Instead, blood and urine samples for safety will be collected according to institutional standard of care for patients who are receiving a HER2-targeted agent (margetuximab or trastuzumab). Local labs with units and normal ranges will be reported only as AEs, if clinically significant, or within Serious Adverse Event reporting. Clinically significant labs, in the Investigator's opinion, mean a disease and/or organ toxicity that is new, has worsened from baseline, or requires additional active management.

MacroGenics or its designee will provide the following blood sampling supplies for central lab ADA testing only: polypropylene transport tubes, labels, and shipping supplies. Serum tubes should be labeled with the Patient ID and date 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.

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

7.7 Samples for HER2 Testing

A pathologic specimen or unstained slides are requested whenever possible for central HER2 testing. There are two purposes for requesting samples. First, all patients will be requested to provide tissue samples for protocol-defined sensitivity analysis. Second, if a patient's previous HER2 testing does not meet protocol requirements (i.e., not performed at an accredited reference laboratory), or if previous results are not available, a sample is required for central HER2 testing to determine study eligibility. Samples can be from the patient's original biopsy or resection or be obtained from subsequent samples, but the most recently available specimen should be obtained. Samples can be from either primary or metastatic tissue. A testing report of a patient's most recently available HER2+ specimen is acceptable to determine patient study eligibility provided the testing was performed at an accredited laboratory. Details of sample acquisition requirements are provided in the Laboratory Manual.

7.8 Cardiac Evaluations

7.8.1 12-Lead Electrocardiograms

Analysis of electrocardiographic intervals and cardiac adverse events in this trial revealed no safety signal for margetuximab. With Protocol Amendment 4, ECGs will no longer be collected and analyzed centrally. Rather, ECGs should be collected and interpreted locally according to institutional standard of care. Findings will be reported only as AEs, if clinically significant in the view of the Investigator, or within Serious Adverse Event reporting.

7.8.2 Multigated Acquisition Ventriculography Scanning and Echocardiography

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

7.9 Adverse Events

7.9.1 Criteria for Evaluation

- Safety assessment will be based on the evaluation of AEs from the time of initiation of any study therapy through the End of Treatment visit (or 28 days after the last dose of study drug, whichever occurs later) and will be determined based on signs, symptoms, physical examination findings and/or laboratory test results from enrolled patients as appropriate. Local labs with units and normal ranges will be reported only as AEs, if clinically significant, or within Serious Adverse Event reporting. Clinically significant labs, in the Investigator's opinion, mean a disease and/or organ toxicity that is new, has worsened from baseline, or requires additional active management.
- All AEs (related to the protocol or not) will be collected from the time the patient receives the first dose of any study medication.
- AEs reported between the time the patient signed the informed consent and the administration of the first dose of any study medication will be captured as concurrent medical history unless due to a protocol-related procedure.
- AE and SAE recording will continue until the End of Treatment visit is performed (or 28 days after the last dose of study drug, whichever is later).
- 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 disease progression only, without any other SAE) will be documented as an anti-tumor activity outcome and not as an SAE. If an SAE occurs in a patient and it is unclear whether the event is related to progressive disease, the SAE should be reported

7.9.2 Definitions

7.9.2.1 Adverse Event

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

7.9.2.2 Adverse Drug Reaction

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 adverse event of special interest (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 of such events could be appropriate. An AESI may be a serious or non-serious AE, which may require further investigation to fully 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 drug 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 Product Quality Issue

Product quality issues are defined as abnormalities that may be introduced during the manufacturing/labelling, packaging, shipping, handling or storage of the products. They may occur with or without clinical consequences.

7.9.2.6 Serious Adverse Events

An SAE is any untoward medical occurrence 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) unless for an elective procedure unrelated to the study or underlying disease.
- Persistent or significant disability or incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- 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.

7.9.2.7 Immediately Reportable Event (IRE)

IREs are events that must be reported immediately to MacroGenics Product Safety, or assigned designee, **within 24 hours** of being identified. IREs include but are not limited to:

- SAEs
- Pregnancy in a study patient or partner of a study patient. (Note: If the female partner of a male patient becomes pregnant, the partner 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.
- AESI requiring immediate reporting include (see **Section 7.9.3** below):
  - Grade 3 or greater infusion-related reactions or Cytokine Release Syndrome (see **Section 6.6.1**)
  - Left ventricular dysfunction leading to dose delay or discontinuation (see **Section 7.8**)
- Administration of a dose significantly greater than the planned dose of any study agent (margetuximab, trastuzumab, or chemotherapy) resulting in an event of clinical consequence.
- Any suspected transmission of an infectious agent via study drug (margetuximab or trastuzumab)
- Withdrawal of the patient from study drug (margetuximab or trastuzumab) administration for any reason, including AE, other than disease progression.
- Any abnormal liver enzyme laboratory value meeting criteria for potential Hy's Law, defined as AST and ALT values of $\geq 3.0 \times$ ULN with total bilirubin level of $\geq 2.0 \times$ ULN without an alternate etiology for the abnormal values.
- Product Quality Issue with clinical consequences.

In those cases, in which the IRE is considered related to study drug and the event 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 is withdrawn from the study by the investigator). At any time after completion of the study, if an investigator becomes aware of an 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-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

7.9.4 Product Quality Issue with Clinical Consequences

If a product quality issue results in an event of clinical consequences, from the use of study product, it must be immediately reported to the sponsor/designee as an IRE. The sponsor will collect the information and evaluate accordingly to protect the safety of the study patients.

7.9.5 Performing Adverse Event Assessments

Medical evaluation and classification of the AE 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 criteria described below.

7.9.5.1 Assessment of Seriousness

Event *seriousness* will be determined according to the definition of an SAE in **Section 7.9.2.6**. Seriousness serves as a guide for defining regulatory reporting obligations for AEs.

7.9.5.2 Assessment of Severity

Event *severity* will be assigned according to the Investigator's assessment using the Common Terminology Criteria for Adverse Events (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 SAE criterion of "immediately life threatening." (See **Section 7.9.2.6**).

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.

7.9.5.3 Assessment of Causality

The Investigator is required to provide an assessment of causality or relationship of AEs to the study drug (margetuximab or trastuzumab) 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. If, in investigator's opinion the event is not related to the study drug but to the chemotherapy used in combination with margetuximab or trastuzumab, the investigator is also required to make causality relationship with the chemotherapy based on the product label for that specific country/region. 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.

7.9.5.4 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. AEs 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) for the study product.

7.9.6 Reporting of Adverse Events to the Sponsor

Throughout the study, the investigator must document all AEs and SAEs on the eCRF in a timely manner. AEs will be collected and followed from the time the patient provides informed consent for the study until the End of Treatment visit or 28 days after the last dose of study drug, whichever occurs later. 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 a protocol-related 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 SAE occurs in a patient and it is unclear if the event is due to progressive disease, the SAE should be reported.

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.

7.9.6.1 Changes in Clinical Laboratory Parameters

Safety laboratory assessments, whether performed locally at the discretion of the investigator or as the result of central testing will be evaluated by the Investigator to ensure patient safety. The Investigator is responsible for reviewing the results of all laboratory tests as they become available. Clinically important discrepancies between local and central testing results should be addressed as appropriate. 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. If the Investigator determines the laboratory value is an abnormal change from baseline and is of clinical significance for that patient, it is considered an AE.

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 11g/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 7.9.2.7** for immediately reportable event.)

7.9.7 Notification to the Sponsor of Events Requiring Immediate Reporting

IREs, as defined in **Section 7.9.2**, are events that must be reported immediately (**within 24 hours of identification**) to MacroGenics Product Safety or MacroGenics designee responsible for Product Safety (e.g., contract research organization [CRO]) by completing the appropriate eCRF(s)/forms. Throughout the study, the Investigator must ensure documentation of all AEs in the eCRF in a timely manner

In case of patient or patient partner pregnancy, the MacroGenics Pregnancy Exposure eCRF 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.

7.9.8 Emergency Unblinding

Not applicable.

7.10 Efficacy, Pharmacokinetic, Pharmacodynamic Assessments

7.10.1 Efficacy Assessments

7.10.1.1 Radiologic Evaluation

Tumor assessments will be obtained at Screening using CT (with contrast) and/or MRI scans of the chest, abdomen and pelvis at time intervals as specified in **Appendix 1** (Schedule of Events). Assessment of skin lesions identified at screening may be made by photography with a reference ruler or by caliper measurement as described in RECIST 1.1 and should be followed at regular intervals as for radiologic evaluation. Treatment will continue until disease progression, withdrawal from the study, or death. At each tumor assessment time point, radiologic assessment of tumor status will be made using RECIST 1.1 criteria. Investigators will assess tumor response(s) for determination of suitability for continued therapy and the secondary endpoint of Investigator Assessed PFS. All patients who have CR, PR, SD, or non-evaluable as their local radiological assessment are eligible for further therapy. Non-radiological evidence of disease progression should be clearly documented in the eCRF.

With Protocol Amendment 4, central review of radiographic images is discontinued. Investigator-assessed PFS and ORR will continue to be measured according to the protocol schedule.

All patients will have a bone scan performed at baseline and then as clinically indicated during the study for the assessment of bone metastasis. Patients with bone only disease should be followed at regular intervals by bone scan or CT or MRI scan at the same intervals as other patients. Patients with a history of treated brain metastasis who are otherwise eligible must have a baseline brain MRI or CT within 4 weeks prior to randomization and as clinically indicated thereafter.

Tumor evaluations will be performed at baseline (prior to treatment) and every 2 cycles for the first 24 weeks of treatment; thereafter, beginning with Cycle 9, tumor evaluations will be performed every 4 cycles while on treatment or every 3 months during post-treatment follow-up until documented progression, initiation of alternative anti-cancer therapy, lost to follow up, withdrawal of informed consent, death, or end of study. For patients who receive alternative anti-cancer therapy in absence of progression and have a new tumor assessment schedule for that anti-cancer therapy, every effort should be made to collect the date of the documented progression per that new tumor assessment schedule.

It is recommended that any accumulation of fluid (pleural or pericardial effusion and/or ascites) that is new or increased in size from baseline, and, when appropriate, any new lesions noted by radiography, be assessed by cytology or histology to document progression.

Progression can only be documented from new or increasing fluid collections if cytology confirms that the fluid is malignant.

7.10.1.2 Digital Imaging of Skin Lesions

When applicable, digital images of skin lesions will be obtained on the same schedule for radiographic evaluations.

7.10.1.3 Overall Survival

Patients who are discontinued from study treatment will be followed up for their survival status at 3-month intervals (± one week) until withdrawal of informed consent, loss to follow up, or the end of study is reached. Procedures for patients lost to follow-up are described in **Section 5.4.2**.

7.10.2 Immunogenicity

Immunogenicity evaluations will be performed only as indicated in the Schedule of Events (**Appendix 1**) for patients receiving margetuximab only. With Protocol Amendment 4, collection of samples for anti-drug antibody (ADA) assay will be decreased in frequency from once every 6 weeks (i.e., every 2 treatment cycles) to once every 12 weeks (i.e., every 4 treatment cycles), consistent with radiographic evaluation. ADA samples will continue to be collected at end of treatment and during follow-up.

The generation of ADA directed against margetuximab will be assayed using enzyme-linked immunosorbent assay (ELISA). The proportion of patients who are negative for ADA at baseline and become positive in this assay will be reported, as will 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. Samples with positive ADA will be evaluated for neutralizing activity. Immunogenicity samples from all patients may be retained for future evaluations of neutralizing antibodies as allowed per local requirements/regulations.

Blood samples will be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to the collection of blood sample for ADA assessment.

Procedures for the acquisition, handling and processing of ADA specimens are provided in the Laboratory Manual.

7.10.3 Pharmacokinetics

With Protocol Amendment 4, PK sample collection will be discontinued for patients who are still receiving study treatment.

7.10.4 Biomarkers

Specimens will be collected for the determination of Fc receptor genotype (CD16A, CD32A, and CD32B), as allowable per local requirements. Procedures for the acquisition, handling and processing of biomarker specimens are provided in the Laboratory Manual.

7.11 Health-Related Quality of Life

HRQoL will be evaluated using the EQ-5D-5L and NFBSI-16 **(10, 16)**. The NFBSI-16 is a new measure based on the Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index, with emphasis on patient-reported input regarding high-priority breast cancer–related symptoms (**Appendix 5**). The primary focus for analysis of NFBSI-16 HRQoL scale will be on the FBSI-16 score. EQ-5D-5L (**Appendix 6**) and NFBSI-16 data will be collected at baseline (prior to therapy administration on Cycle 1 Day 1), Day 1 of each Odd cycle thereafter, and at the End of Treatment visit. Patients participating in the infusion sub-study are exempt from completing the HRQoL assessments.

HRQoL data collection will continue until notification of discontinuation by the study Sponsor.

7.12 Sample Retention and Further Testing

Samples acquired for protocol specified assays retained for study purposes (analysis/re-analysis) may be retained up to 2 years after last approval of a marketing application in an International Conference on Harmonisation (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 allowed per local regulation/requirements, and patients consent to the use of their PK, ADA, and HER2 study samples for non-study research purposes, these samples may also be used for future research use (including assay development/optimization) and may be retained up to 15 years from the date of last patient enrolled. The DNA samples used for Fc Gamma receptor genotyping may be retained up to two years from the last patient enrolled.

7.13 Appropriateness of Measurements

Routine laboratory evaluations including hematology, chemistry, special chemistry, coagulation, and urinalysis will be performed in a central laboratory. Central laboratory testing should be used to determine patient eligibility and assess overall safety in the study, unless the medical monitor approves the use of a local laboratory in place of an unanalyzable central laboratory sample.

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

Serum concentrations of margetuximab will be monitored using an ELISA-based sandwich 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 will be performed and an appropriate model and model parameters will be described.

8 STUDY ACTIVITIES

A table of study activities including Screening, On-Study, and End of Treatment visits is presented in **Appendix 1**, Schedule of Events.

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. During the screening period, the Principal Investigator (PI) should review inclusion/exclusion criteria and verify that all assessments were performed within the protocol-specified windows and the patient is still eligible for the study. Only those patients who meet all inclusion/exclusion criteria specified in **Section 5.1** and **Section 5.2** will be entered into this study.

8.1.1 Up to 4 Weeks Prior to Randomization

The following evaluations are to be performed within 28 days (4 weeks) prior to randomization in this study.

- Perform radiographic tumor evaluations (**Section 7.10.1.1**) and digital imaging of skin lesions **Section 7.10.1.2**:
  - CT (with contrast) or MRI of chest, abdomen, and pelvis – all patients
  - Bone scan – all patients
  - CT or MRI of brain – patients with known, treated brain metastases or symptoms of brain metastases
  - Digital images of skin lesions – all applicable patients.

The above tumor assessments will be considered baseline **(Section 7.10.1.1**). Tumor assessments performed as standard of care prior to study registration may be considered baseline and need not be repeated if completed within 4 weeks prior to randomization.

- Perform MUGA scan or echocardiogram determination of LVEF **(Section 7.8.2**). A previous evaluation may be considered baseline if completed within 4 weeks prior to randomization.
- Request archival pathological material from primary or metastatic site for central HER2 testing (formalin-fixed paraffin embedded [FPPE] tissue block or 5 unstained slides). The most recent tumor biopsy from the patient should be obtained when available. If previous HER2 testing was performed at a reference laboratory and meets ASCO/CAP guidelines, the biopsy specimen is required only for efficacy sensitivity analyses, and the results are not required prior to randomization. If HER2 test results are not available from previous testing, this specimen may be used for eligibility purposes.

Procedures for the acquisition, handling and processing of specimens for central HER2 testing are provided in the Laboratory Manual.

- Obtain documentation of HER2 status from most recent result available.
- Perform toxicity review and AE assessment (with grading based on CTCAE, Version 4.03) (**Section 7.9**), and concomitant medications (**Section 7.3**).

8.1.2 Up to Two Weeks Prior to Randomization

The following evaluations are to be performed within 14 days (2 weeks) prior to randomization. Results of central laboratory and ECG evaluations must be reviewed and patient eligibility confirmed prior to randomization to study drug.

- Conduct medical history (**Section 7.2**).
- Conduct physical examination (PE), including height and weight (**Section 7.4**).
- Take vital signs (**Section 7.5**).
- Evaluate ECOG performance status (**Appendix 4**).
- Obtain ECG, standard 12-lead (in triplicate) (**Section 7.8.1**).
- Obtain specimen for complete blood count (CBC) with differential and platelet count.
- Obtain specimen for chemistry panel.
- Perform serum β-hCG pregnancy test for women of childbearing potential.
- Perform toxicity review and AE assessment (with grading based on CTCAE, Version 4.03) (**Section 7.9**), and concomitant medications (**Section 7.3**).

8.2 Registration and Randomization

Each patient must be randomized through an IxRS and dosed within 72 hours of randomization, with dosing preferably on the same day as randomization. Prior to randomization, the PI should review inclusion/exclusion criteria and verify that all screening assessments were performed within the protocol-specified screening windows and the patient is still eligible for the study. The date that informed consent is given is the first day of Screening.

The following information should be provided during registration:

- Patient Identification (ID) Number
- Date of signed informed consent
- Number of lines of therapy in the metastatic setting (≤2, >2)

- Number of metastatic sites (≤ 2, > 2)
- Choice of backbone chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).

8.2.1 Registration for the Infusion Sub-Study

- Patient Identification (ID) Number
- Date of signed informed consent.

8.3 Cycle 1

8.3.1 Cycle 1 Day 1

8.3.1.1 Prior to First Dose of Study Treatment on Cycle 1 Day 1

For some assessments, if the corresponding screening assessment was performed within the specified number of days prior to initiating study treatment on Cycle 1 Day1, the assessment need not be repeated prior to dosing on Cycle 1 Day 1. When this is the case, details are provided below.

- Clinical assessments:
  - Review medical history (**Section 7.2**)
  - Conduct PE, including weight (**Section 7.4**)
  - Administer the NFBSI-16 and EQ-5D-5L questionnaire (**Section 7.11**; not required for infusion sub-study)
  - Perform toxicity review and AE assessment (**Section 7.9**), and review concomitant medications (**Section 7.3**).
- Laboratory assessments for local laboratory testing:
  - Perform local urine or serum pregnancy test for women of childbearing potential. Pregnancy test must be negative to administer chemotherapy or study drug.
  - Local chemistry and hematology should be performed prior to dosing for all cycles as needed if the results of central testing are not yet available.
- Laboratory assessments for central laboratory testing:
  - Obtain specimen for CBC with differential and platelet count
    - Not required if the Screening CBC with differential and platelet count (**Section 8.1.2**) was performed within 3 days of dosing with study treatment
  - Obtain specimen for chemistry panel

- Not required if the Screening chemistry panel (**Section 8.1.2**) was performed within 3 days of dosing with study treatment
- Obtain specimen for PT, aPTT
- Obtain specimen for urinalysis
- Obtain specimen for PK sampling (margetuximab arm only, **Section 7.10.3**)
- Obtain specimen for FcγR genotyping – specimen must be obtained at the Cycle 1 Day 1 visit
- Obtain specimen for ADA (margetuximab arm only, **Section 7.10.2**).

8.3.1.2 During and Following Administration of Study Treatment

The following evaluations should be performed only after ALL pre-treatment evaluations described in **Section 8.3.1.1** have been completed:

- Administer chosen chemotherapy – per specific chemotherapy regimen (see **Table 4**) according to institutional guidelines, including guidelines for premedications.
- Prior to initiation of margetuximab or trastuzumab infusion:
  - Obtain ECG (standard 12-lead in triplicate, **Section 7.8.1**)
  - Take vital signs (**Section 7.5**)
- Administer margetuximab or trastuzumab (**Section 6.3**)
- Following completion of margetuximab or trastuzumab infusion:
  - Obtain specimen for PK sampling (margetuximab arm only, **Section 7.10.3**)
  - Obtain ECG (standard 12-lead in triplicate, **Section 7.8.1**)
  - Take vital signs (**Section 7.5**):
    - At end of margetuximab or trastuzumab infusion,
    - At 60 minutes after end of margetuximab or trastuzumab infusion.

8.3.2 Cycle 1 Day 8

If the patient is required to return to the study site on Cycle 1 Day 8 for chemotherapy administration, a toxicity review and AE assessment (**Section 7.9**), and review of concomitant medications (**Section 7.3**) should also be performed. Local laboratory evaluations should be performed as needed according to local practice and institutional guidelines.

8.4 Study Evaluations for Even Cycles (e.g., Cycles 2, 4, 6, 8)

Procedures required each visit during Even treatment cycles are described below (see also Schedule of Events in **Appendix 1**). All procedures should be performed on the scheduled study day with exception of MUGA/ECHO/radiology assessments, which may be performed within 14 days pre-dose (chemotherapy and study drug), unless otherwise specified. Day 8 procedures are to be performed only if patients are required to return to the study site for chemotherapy administration.

8.4.1 Even Cycle Treatment Visits: Day 1

8.4.1.1 Prior to Administration of Study Treatments

- Clinical assessments:
  - Conduct PE (**Section 7.4**)
  - Take vital signs (**Section 7.5**)
  - Obtain ECG according to institutional standard of care, as clinically indicated
  - Perform toxicity review and AE assessment (**Section 7.9**), and review concomitant medications (**Section 7.3**).
- Laboratory assessments for local laboratory testing
  - Perform serum or urine pregnancy test for women of childbearing potential. Pregnancy test must be negative to administer chemotherapy or study drug.
  - Chemistry and/or hematology test(s) should be performed locally according to institutional standard of care prior to dosing for all cycles as needed.

8.4.1.2 Administration of Study Treatments

- Administer chosen chemotherapy – per specific chemotherapy regimen (see **Table 4**)
- Administer margetuximab or trastuzumab.

8.4.1.3 Following Administration of Study Treatments

- Laboratory assessments for central laboratory testing
  - Obtain specimen for PK sampling (margetuximab arm only, **Section 7.10.3**)
    - *Cycles 2 – 6 only*
- Clinical assessments:

- Take vital signs (**Section 7.5**)
- Obtain ECG according to institutional standard of care as clinically indicated.

8.4.2 Even Cycle Treatment Visits: Day 8 (as needed)

- Perform toxicity review and AE assessment (**Section 7.9**), and review concomitant medications **(Section 7.3**)
- Administer chosen chemotherapy – per specific chemotherapy regimen (see **Table 4**).

8.5 Study Evaluations for Odd Cycles >1 (e.g., Cycles 3, 5, 7)

Procedures required each visit during Odd treatment cycles are described below (see also Schedule of Event in **Appendix 1**). All procedures should be performed on the scheduled study day with exception of central laboratory assessments, which may be performed within 3 days pre-dose (chemotherapy and study drug) and MUGA/ECHO/radiology assessments, which may be performed within 14 days pre-dose (chemotherapy and study drug), unless otherwise specified. Day 8 procedures are to be performed only if patients are required to return to the study site for chemotherapy administration.

8.5.1 Odd Cycle Treatment Visits: Day 1

8.5.1.1 Prior to Administration of Study Treatments

- Clinical assessments:
  - Conduct PE, including weight **(Section 7.4**)
  - Take vital signs (**Section 7.5**)
  - Obtain ECG according to institutional standard of care as clinically indicated
  - Obtain MUGA scan or echocardiogram for determination of LVEF (**Section 7.8.2**) – *within 7 days prior to Day 1 visit: Cycle 3, Cycle 5, and every 4th cycle thereafter (e.g., Cycles 9, 13, 17) while on treatment*
  - Administer the NFBSI-16 and EQ-5D-5L questionnaire **(Section 7.11; not** required for infusion sub-study)
  - Perform toxicity review and AE assessment **(Section 7.9**), and review concomitant medications **(Section 7.3**).
- Laboratory assessments for local laboratory testing
  - Perform serum or urine pregnancy test for women of childbearing potential. Pregnancy test must be negative to administer chemotherapy or study drug.

- Chemistry and/or hematology test(s) should be performed locally per institutional standard of care prior to dosing for all cycles as needed.
- Obtain specimen for ADA (margetuximab arm only, **Section 7.10.2**)

- Radiographic tumor evaluations and digital imaging of skin lesions – within 14 days prior to Day 1 visit:
  - Obtain CT and/or MRI scan(s) (**Section 7.10.1.1**)
  - Obtain digital images of skin lesions (if applicable, **Section 7.10.1.2**).

8.5.1.2 Administration of Study Treatments

- Administer chosen chemotherapy – per specific chemotherapy regimen (see **Table 4**)
- Administer margetuximab or trastuzumab.

8.5.1.3 Following Administration of Study Treatments

- Clinical assessments:
  - Take vital signs (**Section 7.5**)
  - Obtain ECG according to institutional standard of care as clinically indicated
  - Perform toxicity review and AE assessment (**Section 7.9**), and review concomitant medications (**Section 7.3**).

8.5.2 Odd Cycle Treatment Visits: Day 8 (as needed)

- Perform toxicity review and AE assessment **(Section 7.9**), and review concomitant medications **(Section 7.3**)
- Administer chosen chemotherapy-per specific chemotherapy regimen (see **Table 4**).

8.6 End of Treatment Visit

Criteria for triggering the End of Treatment visit are specified in **Section 4.1.5**. The End of Treatment visit should be performed after the patient has met off-treatment criteria or has been followed for up to 28 days after the last dose of study drug. Procedures required for the End of Treatment Visit include the following (see also Schedule of Events in **Appendix 1**):

- Clinical assessments:
  - Conduct PE, including weight (**Section 7.4**)
  - Take vital signs (**Section 7.5**)

- Evaluate ECOG performance status (**Appendix 4**)
- Obtain MUGA scan or echocardiogram for determination of LVEF (**Section 7.8.2**)
- Administer the NFBSI-16 and EQ-5D-5L questionnaire (**Section 7.11**; not required for infusion sub-study).
- Perform toxicity review and AE assessment (**Section 7.9**), and review concomitant medications (**Section 7.3**).

- Laboratory assessments:
  - Perform serum or urine pregnancy test locally for women of childbearing potential.
  - Obtain specimen for ADA (margetuximab arm only, **Section 7.10.2**).

Safety Follow-up: Ongoing AEs at the time of study drug discontinuation will be followed to the End of Treatment visit or 28 days after the last dose of study drug, whichever occurs later. SAEs will be followed to resolution (see **Section 7.9.2.6**).

8.7 Post-Treatment Follow-up and Observation of Survival

Follow-up information regarding disease and vital status (including dates of progression and death [including appropriate documentation such as a death certificate, if allowed by local regulations]), and additional cancer treatment(s) received will be requested by the Sponsor at 3-month intervals (± 1 week) after treatment discontinuation until death, withdrawal of consent, lost to follow-up, or the end of study (**Appendix 1**). Procedures for patients lost to follow-up are described in **Section 5.4.2**.

For patients discontinued from the study treatment for any reason other than disease progression, initiation of alternative anti-cancer therapy, lost to follow-up, withdrawal of informed consent, or death, radiologic tumor evaluations (**Section 7.10.1.1**) and digital imaging of skin lesions (if applicable, **Section 7.10.1.2**), should be performed every 3 months until one of the aforementioned criteria to stop tumor assessments is met.

With Protocol Amendment 4, blood samples for immunogenicity will be obtained 3 months and 6 months after the last dose of margetuximab. Details for acquisition, handling, and shipping of the specimens will be provided in the Laboratory Manual.

Belgium only: monthly urine or serum pregnancy tests should be performed locally in women of childbearing potential for 7 months during the post-treatment follow-up period.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All statistical inferences will be based on two-sided tests with an α-level of 0.05 unless otherwise noted.

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, 25th, and 75th quartile. Time-to-event endpoints will be summarized by median durations, hazard ratios, and corresponding 95% confidence intervals (CIs).

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 9.2 or higher. A detailed analysis plan (SAP) will be prepared and submitted to regulatory health authorities, as per local requirements, before study initiation.

9.2 Independent Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will oversee the ongoing monitoring and interpretation of the safety and efficacy data from this study. A DSMC charter will be created, reviewed, and approved by the committee prior to study initiation. The independent DSMC will review safety data, with the first assessment to occur approximately 90 days after enrollment of the first patient, the second assessment to occur 30 days after enrollment of the 30th patient and the third assessment to occur 30 days after enrollment of the 60th patient, or 90 days after the second DSMC assessment (i.e., following enrollment of the 30th patient), whichever is later. If no adverse safety signal is identified, the DSMC will meet on a bi-annual basis thereafter. If, according to this schedule, a DSMC meeting is expected to occur near the time of a planned interim analysis (see **Section 9.9.1**), the timing of the DSMC meeting will be adjusted to align with the interim analysis. More frequent assessments may be used if emergent safety data warrant. The DSMC will evaluate aggregate safety data comparing the two arms and also evaluate safety within each baseline chemotherapy to ensure patient safety. For these reviews, the committee will be provided with safety tables and data listings. When approximately 100 PFS events have occurred, the DSMC will be asked to make a recommendation regarding continuation of full enrollment to the study or early termination of the study for either safety or futility reasons. The DSMC will be empowered to recommend changes to the study, including discontinuation or modification of an arm or overall discontinuation of the study as appropriate.

The DSMC meetings will be based on enrollment to the randomized cohorts only.

Sub-study patient safety monitoring will be conducted by the MacroGenics Product Safety group.

After the final DSMC meeting to oversee final protocol-specified OS analysis, MacroGenics Product Safety will oversee all study patient safety monitoring.

9.3 Determination of Sample Size

There are 2 primary endpoints in this study. The first primary endpoint is centrally determined PFS and the second primary endpoint is OS. These two endpoints will be assessed in a hierarchical manner 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 and chemotherapy is 4 months. To detect a 2-month improvement in median PFS from 4 months to 6 months (hazard ratio [HR]=0.67) in patients treated with margetuximab plus chemotherapy, a total of 257 PFS events are required to provide 90% power at a 2-sided alpha=0.05. The analysis of the primary PFS endpoint will occur when about 257 events have occurred or when all patients have been randomized, whichever occurs later.

The sample size 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 OS 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 the trastuzumab plus chemotherapy arm and 16 months for the margetuximab plus chemotherapy arm, 2 interim analyses are performed as described in **Section 9.9.1**, 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 about 530 patients will be accrued to achieve this number of events. Patients will be enrolled over 24 months, and estimated to remain on study for an average of 16 months, for a total anticipated study duration of approximately 40 months.

The planned sample size for the infusion sub-study is approximately 78 patients, approximately 18 patients for Stage A and about 60 patients for Stage B. The sample size of 60 patients for Stage B of the infusion sub-study is derived to provide adequate assessment of primary safety endpoint for the sub-study.

The overall total number of patients enrolled for the entire study is expected to be approximately 608.

9.3.1 Analysis Populations

Three analysis populations are defined:

- Intent-to-Treat Population – all patients randomized. Patients will be analyzed according to the treatment (margetuximab or trastuzumab) assigned during randomization. This population will be used to summarize baseline data and evaluate PFS, OS, and HRQoL.

- Response Evaluable Population — all patients who are randomized who have measurable disease at baseline. This population will be used to evaluate ORR and CBR.
- Safety Population – all patients who are randomized and receive any amount of any 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, PD, and immunogenicity analyses.

9.4 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.

9.5 Safety Endpoint(s) and Analyses

9.5.1 Adverse Events

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

- All AEs by CTCAE grade
- Drug-related AEs by CTCAE grade by onset of cycle (as a separate table)
- All SAEs (this may be a listing if there are few events)
- Drug-related SAEs by onset of cycle (as a separate table)
- Fatal AEs (this may be a listing if there are few events)
- AEs that result in study drug discontinuation
- AESI by onset of cycle (as a separate table)
- AEs which lead to dose interruption by onset of cycle (as a separate table)
- AEs that lead to withdrawal of study drug by onset of cycle (as a separate table)

All of these tables will display the number and percent of patients that experience the given event and will display events by System Organ Class (SOC) and preferred term. Events will be displayed alphabetically for SOC and in descending order of overall preferred term incidence within each SOC.

An overall summary of AEs will display the number and percent of patients who experience at least one event of each of the following types:

- Any AE
- Any drug-related AE
- Any AE ≥Grade 3
- Any drug-related AE ≥Grade 3
- Any SAE
- Any drug-related SAEs
- AEs which lead to dose interruption
- Any AE that results in study drug discontinuation
- Any AEs that result in withdrawal from study drug
- Any fatal AE
- Any AESIs

9.5.2 Laboratory Values

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

In cases where an abnormality resulted in a repeat laboratory test, the repeat value will be used for the summaries. A list of repeated laboratories including original values and repeat values will be included.

Graphs of mean values over time may also be generated.

9.5.3 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. LVEF will be evaluated by echocardiogram or MUGA and changes from baseline summarized.

With Protocol Amendment 4, ECGs will no longer be collected and analyzed centrally. Instead, ECGs will be collected and interpreted locally according to institutional standard of care.

9.6 Efficacy Endpoints and Analyses

Progression-free survival – defined as the time from randomization date to the date of first documented disease progression or death from any cause, whichever occurs first. For patients who are not known to be dead or progressed at time of data cut-off for PFS analysis, the PFS will be censored at the last tumor assessment.

Incomplete or missing data can complicate interpretation of PFS. **Appendix 3** describes the handling of these data for the PFS analysis.

Overall survival – defined as the time from 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 are last known to be alive.

Objective response rate – the proportion of patients in the response evaluable population achieving a best response of CR or PR when such responses are confirmed at least 28 days after initial observation of response. Patients who have baseline measurable disease but no post-baseline radiographic assessment will be considered as non-responders.

Duration of response – defined as the time from initial response to date of first documented disease 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.

Clinical benefit rate – the proportion of patients in the response evaluable population achieving a best response of CR, PR, or SD of duration >6 months.

HRQoL – Patients will be administered the EQ-5D-5L and NFBSI-16 quality of life questionnaires at baseline, Day 1 of each odd cycle, and at study completion. Change from baseline on global scores will be assessed. HRQoL data collection will continue until notification of discontinuation by the study Sponsor.

9.6.1 Primary Endpoints

The primary analysis for PFS will be conducted when about 257 PFS events have occurred or when all patients have been randomized, whichever occurs later. OS will be conducted at the time of PFS analysis and subsequently when 70% of the OS events and a final OS analysis when about 385 survival events have occurred.

For both PFS and OS, Kaplan-Meier methods will be used to generate survival curves and estimate the median OS and PFS along with corresponding 95% CIs for each treatment group. A log-rank test stratified by protocol defined stratification factors will be used to compare both time-to-event endpoints between the two treatment groups. In addition, hazard ratios and 95% CIs will be assessed using stratified Cox proportional hazards models with treatment as the only covariate. Sensitivity analyses of PFS and OS will be performed; further details are provided in the SAP.

The following are pre-defined stratification factors:

- Number of metastatic sites (0-2, >2)
- Number of lines of prior therapy in the metastatic setting (≤2, >2)
- Choice of backbone chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)

In addition, the hazard ratios and 95% CIs for PFS and OS in each subgroup of the above three stratification factors as well as the following subgroups will be assessed using unstratified Cox proportional hazards model with treatment as only covariate and presented by forest plots:

- Prior use of T-DM1 (yes, no)
- Region (North America, Europe, Other)
- HER2 status (3+ or ISH amplified, Other)
- Age (≤60 and >60 years)
- Race (White, Black, Asian, Other)
- ECOG (0 and 1)
- ER and PR status (ER+ and/or PR+, ER- and PR-, Unknown)
- CD16A haplotypes (FF, FV, or VV)
- CD32A haplotypes (HH, HR, or RR)
- CD32B haplotypes (II, IT, or TT)

9.6.1.1 Primary Endpoint for the Infusion Sub-Study

The number of patients with Grade 3 or higher IRR by the end of Cycle 2 will be assessed using descriptive statistics.

9.6.2 Secondary Endpoints

The secondary endpoints of investigator-assessed PFS and independent review-assessed ORR will be assessed using the Hochberg step-up procedure for multiplicity adjustment. P-values will be assessed in descending order. If the least significant p-value<0.05, then 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.

Investigator-assessed PFS will be analyzed using the same methods as described above for the primary endpoint of PFS.

Independent review-assessed ORR will be compared between groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors.

9.6.2.1 Secondary Endpoint for Infusion Sub-study

The number of patients with any grade IRR will be assessed using descriptive statistics.

9.6.3 Tertiary Endpoints

No multiplicity adjustment will be used for tertiary endpoints.

Direct reports from patients will be obtained using the NFBSI-16 and EQ-5D-5L Questionnaires **(10, 16)**. Responses Data will be collected at baseline, Day 1 of each Odd cycle, and at the End of Treatment visit. The primary patient-reported outcome (PRO) endpoint for analysis will be the NFBSI-16 total score, with secondary analysis of the subscales that add to the total (disease related symptoms, treatment side effects, and function/well-being. Analyses using mixed model repeated measures using the baseline score and protocol defined stratification factors are planned as covariates. Subscale scores will be tabulated and summarized. Data from the EQ-5D-5L scale will be summarized by study visit. To minimize missing data, sites will be instructed and patients educated on the importance of recording the direct patient experience in order to appreciate the positive and negative aspects of treating advanced breast cancer, and they will specifically be trained on best practices for patient enrollment, adherence to endpoint data collection requirements, and methods to ensure complete data capture and management. Every effort will be made to collect survey data at all defined visits including at early withdrawal. Reasons for missing data will be summarized.

Duration of response, where response is assessed by study investigators and by independent review, respectively, will be analyzed using Kaplan-Meier methods and compared between two treatment groups using a stratified log-rank test.

Investigator assessed ORR will also be compared between two treatment groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors.

Clinical benefit rate, where response is assessed by study investigators and by independent review, respectively, will also be compared between two treatment groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors.

Change in tumor size over time will be summarized and the best percentage change from baseline will be presented by waterfall plots. Change calculations will be based on target lesions only.

9.6.4 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 the subgroup portion of **Section 9.6.1**.

In addition, an exploratory analysis will be performed to evaluate the impact of subsequent use of T-DM1 on the effect of margetuximab on OS. The details will be provided in the SAP.

9.7 Pharmacokinetic and Exposure-Response Analyses

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

Summary statistics will be tabulated for serum PK parameters by margetuximab dose. Geometric means and percent coefficients of variation will be reported for C_{max}, AUC_{tau}, AUC_{inf}, and C_{trough}; arithmetic means and standard deviations will be reported for T_{half}, CL, and V_{ss}; and medians, minimum, and maximum will be reported for T_{max}.

Exposure-response analyses will be conducted separately using key efficacy and safety parameters of interest. An analysis plan will be created prior to analysis.

9.8 Immunogenicity Analyses

The proportion of patients who are negative for ADA at baseline and become positive in this assay, the proportion of patients who are negative at baseline and remain negative, and those patients who have positive ADA at baseline that increases or decreases in titer over the course of treatment will be summarized. Neutralizing activity will be determined for samples with positive ADA. The effects of ADA on key PK, efficacy, and safety parameters will be investigated.

9.9 Timing of Analyses

Patients in the infusion sub-study are not included in the interim analysis of OS, futility, and final analysis.

9.9.1 Interim Analyses

9.9.1.1 Interim Analyses for OS

Two interim analyses of OS will be conducted for the randomized population. The first will occur at the time of the primary PFS analysis, when approximately 257 PFS events have occurred, assuming all patients have been enrolled and had at least one post-baseline assessment or in the absence of a post-baseline tumor assessment, have experienced clearly documented clinical disease progression. The second interim analysis will occur when 70%

of the target of 385 OS events have occurred unless that threshold was met at the time of PFS analysis.

The overall type 1 error rate is controlled at 2-sided 0.05 using the sequential analysis of PFS followed by OS if PFS is statistically significant and using the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries for the OS analyses. 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 5 Planned Interim 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

9.9.1.2 Interim Futility Analysis for PFS

When approximately 100 PFS events have occurred in the randomized population, a futility analysis will be conducted. The DSMC will be asked to make a recommendation to continue or terminate the study for either a safety or futility reason. Futility will be assessed using conditional power conducted both under the initial study design and under the current trend of the data.

The DSMC will evaluate study conduct and patient safety as well as conditional power. The committee may recommend study termination if the conditional power is low (as guidance, it is considered low if the conditional power is less than 20%), if there are safety issues, or if under the current conduct of the study, study objectives are unlikely to be achieved.

9.9.2 Final Analysis

The final analysis of PFS will take place when about 257 PFS events have occurred in the randomized population or when all patients have been randomized, whichever occurs later. The final OS analysis will take place when about 385 events have occurred.

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 CRFs, 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 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 11.6** 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 CRFs against source documents at the study site. The Investigator will also ensure that the monitor is given access to all the above noted study-related documents, source documents (regardless of media) and study-related facilities (e.g., investigational pharmacy, etc.), and has adequate space to conduct the monitoring visit. Queries may be raised if any datum is unclear or contradictory. The Investigator and 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 Entry and Computerized Systems

An electronic data capture system will be used in this study. Other data assessments, such as central laboratory assays, immunohistochemistry, 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, computer discs, or tapes. The anonymity of participating patients must be maintained. For data collection and data 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 necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Site personnel record all data for each study patient through eCRFs using an Electronic Data Capture (EDC) system approved by the sponsor. Sites must complete the eCRFs in a timely manner and the Investigator must promptly review the completed eCRFs for each patient. As the person ultimately responsible for the accuracy of all eCRF data, the Investigator must e-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, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also posted from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. 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 or Independent Ethics Committee Approval

The Investigator should provide the Sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and ICH. Any documents that the IRB/IEC may need to fulfill its responsibilities, such as the protocol and any amendments, 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 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 under a US Investigational New Drug (IND) application according to the Protection of Human Subjects United States Code of Federal Regulations, Title 21 (21 CFR 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 in accordance with ethical principles that have their origin in the Declaration of Helsinki, and all other applicable local regulations and/or guidelines.

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 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 study, or the Sponsor's representative. The Investigator must also comply with all local applicable privacy regulations [e.g., US Health Insurance Portability and Accountability Act of 1996 (HIPAA)], on protection of individuals with regard to personal data.

11.5 Case Report Forms and Study Records

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the patient's medical file, original laboratory reports, histology, and pathology reports (as applicable). The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered 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 CRFs. Electronic CRFs should be filled out completely by the Investigator or his/her designee. Prior to CRF 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 CRF. 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, 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 CRFs on file at MacroGenics, Inc. MacroGenics 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.

11.7 Retention of Data

Per ICH guidelines, all essential documents, including CRFs, 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. 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., 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 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 with any changes in reported information up to 1 year following the end of the study (as defined in **Section 4.3.2**)

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.

MacroGenics intends to publish the results of this study in an international peer-reviewed journal following completion of all primary endpoints. Interim results may be published prior to completion if warranted. If appropriate, results may be presented at scientific conferences prior to publication. MacroGenics will adhere to all relevant regulatory guidelines and best practices during preparation of any manuscripts or other scientific presentations.

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 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 study may be terminated if there is evidence of futility, an unacceptable safety signal, or failure to achieve a primary endpoint. Patients who are enrolled in the study and continue to receive benefit from treatment as defined in the protocol at the time of study termination may continue to receive treatment as described until a reason to discontinue treatment is indicated.

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 PI will be appointed by the Sponsor Medical Monitor prior to the end of the study.

As part of his or her responsibilities, the Coordinating PI will review the final Clinical Study Report. Agreement with the final Clinical Study Report will be documented by the dated signature of the Coordinating PI.

13 REFERENCE LIST

1. **Andersson M, E Lidbrink, K Bjerre, E Wist, K Enevoldsen, AB Jensen, et al.**, Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol, 2011. 29(3): p. 264-71.
2. **Baselga J, J Cortes, SB Kim, SA Im, R Hegg, YH Im, et al.**, Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N. Engl. J. Med, 2012. 366(2): p. 109-119.
3. **Blackwell KL, HJ Burstein, AM Storniolo, H Rugo, G Sledge, M Koehler, et al.**, Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J. Clin. Oncol, 2010. 28(7): p. 1124-1130.
4. **Cardoso F, A Costa, L Norton, E Senkus, M Aapro, F Andre, et al.**, ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast, 2014. 23(5): p. 489-502.
5. **Carter P, L Presta, CM Gorman, JB Ridgway, D Henner, WL Wong, et al.**, Humanization of an anti-p185HER2 antibody for human cancer therapy. Proc Natl Acad Sci U S A, 1992. 89(10): p. 4285-9.
6. **Cortes J, J O'Shaughnessy, D Loesch, JL Blum, LT Vahdat, K Petrakova, et al.**, Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet, 2011. 377(9769): p. 914-23.
7. **Dear RF, K McGeechan, MC Jenkins, A Barratt, MHN Tattersall, and N Wilcken**, Combination versus sequential single agent chemotherapy for metastatic breast cancer (Review). The Cocharane Library, 2013. 2013(Issue 12).
8. **Dzimitrowicz H, M Berger, C Vargo, A Hood, O Abdelghany, AS Raghavendra, et al.**, T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2-Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab. J. Clin. Oncol, 2016.
9. Eisenhauer EA, P Therasse, J Bogaerts, LH Schwartz, D Sargent, R Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), in *Eur J Cancer*. 2009. p. 228-247.
10. **Garcia SF, SK Rosenbloom, JL Beaumont, D Merkel, JH Von Roenn, D Rao, et al.**, Priority symptoms in advanced breast cancer: development and initial validation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI-16). Value. Health, 2012. 15(1): p. 183-190.
11. **Genentech**, Herceptin Prescribing Information. Genentech, 2014.
12. **Geyer CE, J Forster, D Lindquist, S Chan, CG Romieu, T Pienkowski, et al.**, Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med, 2006. 355(26): p. 2733-2743.
13. **Gianni L, T Pienkowski, YH Im, L Roman, LM Tseng, MC Liu, et al.**, Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a

randomised multicentre, open-label, phase 2 trial. Lancet Oncol, 2012. 13(1): p. 25-32.
14. **Giordano SH, S Temin, JJ Kirshner, S Chandarlapaty, JR Crews, NE Davidson, et al.**, Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J. Clin. Oncol, 2014. 32(19): p. 2078-2099.
15. **GLOBOCAN**. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. GLOBOCAN 2012 2012; Available from: **http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx**.
16. **Herdman M, C Gudex, A Lloyd, M Janssen, P Kind, D Parkin, et al.**, Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res, 2011. 20(10): p. 1727-1736.
17. **Krop IE, SB Kim, A Gonzalez-Martin, PM Lorusso, JM Ferrero, M Smitt, et al.**, Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol, 2014. 15(7): p. 689-699.
18. **Musolino A, N Naldi, B Bortesi, D Pezzuolo, M Capelletti, G Missale, et al.**, Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. J Clin Oncol, 2008. 26(11): p. 1789-1796.
19. **NCCN**. Clinical Practice Guidelines in Oncology: Breast Cancer. 2014 2014; Available from: NCCN.org.
20. **Nordstrom JL, S Gorlatov, W Zhang, Y Yang, L Huang, S Burke, et al.**, Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fc-gamma receptor binding properties. Breast. Cancer Res, 2011. 13(6): p. R123.
21. **Piccart-Gebhart MJ, M Procter, B Leyland-Jones, A Goldhirsch, M Untch, I Smith, et al.**, Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med, 2005. 353(16): p. 1659-1672.
22. **Pivot X, A Manikhas, B Zurawski, E Chmielowska, B Karaszewska, R Allerton, et al.**, CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J. Clin. Oncol, 2015.
23. **Society AC**, Cancer Facts & Figures. Atlanta: American Cancer Society, 2014.
24. **Swain SM, MS Ewer, J Cortes, D Amadori, D Miles, A Knott, et al.**, Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study. Oncologist, 2013. 18(3): p. 257-264.
25. **Verma S, D Miles, L Gianni, IE Krop, M Welslau, J Baselga, et al.**, Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med, 2012. 367(19): p. 1783-91.
26. **von Minckwitz G, A du Bois, M Schmidt, N Maass, T Cufer, FE de Jongh, et al.**, Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol, 2009. 27(12): p. 1999-2006.

27. **Wilks S, S Puhalla, J O'Shaughnessy, L Schwartzberg, E Berrak, J Song, et al.**, Phase 2, multicenter, single-arm study of eribulin mesylate with trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer. Clin. Breast Cancer, 2014. 14(6): p. 405-412.
28. **Yardley DA, HA Burris, III, S Hanson, FA Greco, DR Spigel, J Barton, et al.**, Weekly gemcitabine and trastuzumab in the treatment of patients with HER2-overexpressing metastatic breast cancer. Clin. Breast Cancer, 2009. 9(3): p. 178-183.

Appendix 1 Schedule of Events

All procedures should be performed on the scheduled study day with exception of laboratory assessments, which may be performed within 3 days pre-dose (chemotherapy and study drug) and MUGA/ECHO/radiology assessments, which may be performed within 14 days pre-dose (chemotherapy and study drug), unless otherwise specified. Day 8 procedures are to be performed only if patients are required to return to the study site for chemotherapy administration. All procedures to be performed pre-dose (chemotherapy and study drug) unless otherwise specified.

	Screening		**Cycle 1**		**Cycle 2 and Even Cycles**		**Cycle 3 and Odd Cycles**		**End of Treatment**	**Post-Treatment Follow-Up[17]**
DAY	*-28 to -1*	*-14 to - 1*	*1[18]*	*8[19]*	*1*	*8[19]*	*1*	*8[19]*		
Study Treatment Dosing Window[1]					±3		±3			
CLINICAL ASSESSMENTS										
Informed Consent for Study Participation	X									
Medical History[2]		X	X							
Physical Examination[3]		X	X		X		X		X	
Weight		X	X				X		X	
Vital Signs[4]		X	X		X		X		X	
ECOG Performance Status		X							X	
ECG[5]		X	X		X		X		X	
MUGA or Echocardiography[6]	X						X		X	
NFBSI-16 Breast Cancer Symptom Index[22]			X				X		X	
EQ-5D-5L[22]			X				X		X	
Review of Concomitant Medications		X	X	X	X	X	X	X	X	
Review of Adverse Events		X	X	X	X	X	X	X	X	
LABORATORY EVALUATIONS										
HER2 status documentation[7]	X									

	Screening		Cycle 1		Cycle 2 and Even Cycles		Cycle 3 and Odd Cycles		End of Treatment	Post-Treatment Follow-Up[17]
DAY	*-28 to -1*	*-14 to - 1*	*1*[18]	*8*[19]	*1*	*8*[19]	*1*	*8*[19]		
Study Treatment Dosing Window[1]					±3		±3			
Tumor tissue sample[8]	X									
Serum β-hCG pregnancy test[9]		X								
Fc receptor genotyping			X							
Local serum or urine pregnancy test			X		X		X		X	X[20]
CBC with differential and platelet count[10]		X	X		X		X		X	
Chemistry[10]		X	X		X		X		X	
PT, aPTT			~~X~~		~~X~~		~~X~~		~~X~~	
Urinalysis			~~X~~		~~X~~		~~X~~		~~X~~	
PK/ADA										
Margetuximab PK (margetuximab arm only)[11]			X		X		X		X	X
ADA Sampling (margetuximab arm only)[12]			X				X		X	X
THERAPEUTIC ACTIVITY										
Radiographic Tumor Evaluations, Digital Imaging of Skin Lesions[13]	X[21]						X			X
Disease and Vital Status[14]										X
STUDY DRUG ADMINISTRATION										
Chemotherapy Administration[15]			X	X	X	X	X	X		
Margetuximab or Trastuzumab Administration[16]			X		X		X			

1. Beyond Cycle 1, Day 1, the study treatments window will be +/- 3 days from the scheduled day. The next treatment should revert to the original schedule.
2. Medical history at screening to cover last 60 days prior to study enrollment and previous cancer treatment history.
3. Physical examination to include: height (Screening only) and examination of skin, HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, and the neurologic system. Interval physical exams (symptom-directed) noting any changes from baseline will be recorded after the initial exam.

4. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) are to be collected as follows: at Screening; Cycle 1 Day 1 - before margetuximab or trastuzumab infusion, at end of margetuximab or trastuzumab infusion, and at 60 minutes after end of trastuzumab or margetuximab infusion; all subsequent Cycles – before and at end of margetuximab or trastuzumab infusions; and at the End of Treatment visit.
5. With Protocol Amendment 4, ECGs will no longer be collected and analyzed centrally. Instead, ECGs will be collected and interpreted locally according to institutional standard of care.
6. MUGA or echo to be performed at Screening; Cycle 3 Day 1; Cycle 5 Day 1, and on Day 1 of each 4th cycle thereafter (e.g., 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 14 days prior to the scheduled study visit.
7. HER2 results not required for randomization.
8. Tumor samples may be submitted for HER2 central testing if results are unavailable or if testing was not performed at an appropriate laboratory.
9. Serum pregnancy test results must be obtained within 14 days prior to randomization for women of childbearing potential.
10. With Protocol Amendment 4, blood and urine samples will no longer be collected and analyzed centrally. Instead, blood and/or urine samples for safety will be collected according to institutional standard of care for patients who are receiving a HER2-targeted agent (margetuximab or trastuzumab).
11. With Protocol Amendment 4, all PK sample collection will be discontinued for patients who are still receiving study treatment at the time of the amendment.
12. With Protocol Amendment 4, collection of samples for ADA assay will be decreased in frequency from once every 6 weeks (every 2 treatment cycles) to once every 12 weeks (every 4 treatment cycles), consistent with radiographic imaging. ADA samples will continue to be collected at end of treatment and during follow-up at 3 months and 6 months following the last dose of margetuximab. ADA samples for the infusion sub-study will be obtained according to the same schedule as the margetuximab arm.
13. Tumor evaluations (radiology and digital imaging of skin lesions) to be performed at Screening and Day 1 of every 2 cycles thereafter for the first 24 weeks of study treatment. Following 24 weeks on study treatment, tumor evaluations will be performed every 4 cycles (beginning with Cycle 9) while on treatment or every 3 months during post-treatment follow-up until documented progression, initiation of alternative anti-cancer therapy, lost to follow-up, withdraw of informed consent, death, or end of study. For all patients: CT (with contrast) or MRI of chest, abdomen, and pelvis for all evaluations; bone scan at screening and as clinically indicated thereafter. For patients with known, treated brain metastases and/or signs or symptoms of brain metastasis: CT or MRI of brain at Screening only and as clinically indicated thereafter. Tumor evaluations may be performed up to 14 days prior to the scheduled study visit.
14. Information collected to include disease and vital status (including dates of progression and death, if appropriate) and additional cancer treatment(s) received following the End of Treatment visit.
15. Patients to receive one of 4 backbone chemotherapy options (capecitabine, eribulin, gemcitabine, or vinorelbine) to be selected by the investigator (see **Section 6.1** and **Table 4**.) Selected chemotherapy must be allowed for use per local regulations. The Day 8 study visit is only required if the patient is assigned to a backbone chemotherapy requiring administration on this day.
16. Margetuximab or trastuzumab may be administered after completion of chemotherapy administration. Two consecutive doses should be a minimum 18 days apart.
17. Post-treatment Follow-up to occur at 3-month intervals ± 1 week.
18. Randomization must occur within 72 hours of Cycle 1 Day 1, with dosing preferably on the same day as randomization.
19. Day 8 evaluations to be performed only if patients are required to return to the study site for administration of backbone chemotherapy.
20. For Belgium sites only: monthly urine or serum pregnancy tests should be performed locally in women of childbearing potential during the post-treatment follow-up period.
21. Tumor assessments performed as standard of care may be considered baseline and need not be repeated if completed within 4 weeks prior to randomization.
22. HRQoL assessments are not required for patients assigned to the infusion sub-study.

Appendix 2 Principal Investigator's Agreement

Study Title:	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
Study Number:	CP-MGAH22-04

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: _____

Appendix 3 Censoring Rules for Primary PFS Analysis

Situation	Date	Outcome
No baseline tumor assessments	Randomization 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	Randomization date	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 4 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 5 NCCN/FACT Breast Symptom Index-16 (FBSI-16)

NCCN-FACT FBSI-16 (Version 2)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
DRS-P	GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	GP5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	N6	I have mouth sores	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
	GF1	I am able to work (include work at home)	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010
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NCCN/FACT Breast Symptom Index-16 (FBSI-16)
Scoring Guidelines (Version 2)

Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Scale	Item Code	Reverse item?		Item response	Item Score
FBSI-16 Total	GP1	4	-	_____	=_____
	GP4	4	-	_____	=_____
	GP6	4	-	_____	=_____
	B1	4	-	_____	=_____
Score range: 0-64	GP3	4	-	_____	=_____
	HI7	4	-	_____	=_____
	BP1	4	-	_____	=_____
	GF5	0	+	_____	=_____
	GE6	4	-	_____	=_____
	GP2	4	-	_____	=_____
	N6	4	-	_____	=_____
	GP5	4	-	_____	=_____
	B5	4	-	_____	=_____
	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 16: _____
Divide by number of items answered: _____=**FBSI-16 score**

Subscale	Item Code	Reverse item?		Item response	Item Score
FBSI-DRS-P (Disease Related Symptoms-Physical)	GP1	4	-	_____	=_____
	GP4	4	-	_____	=_____
	GP6	4	-	_____	=_____
	B1	4	-	_____	=_____
Score range: 0-32	GP3	4	-	_____	=_____
	HI7	4	-	_____	=_____
	BP1	4	-	_____	=_____
	GF5	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 8: _____
Divide by number of items answered: _____=**FBSI-DRS-P score**

FBSI-DRS-E (Disease Related Symptoms-Emotional)	GE6	4	-	_____	=_____=**FBSI-DRS-E score**

Score range: 0-4

FBSI-16 scoring template, 2008

Subscale	Item Code	Reverse item?		Item response	Item Score
FBSI-TSE (Treatment Side Effects)	GP2	4	-	_____	=_____
	N6	4	-	_____	=_____
	GP5	4	-	_____	=_____
	B5	4	-	_____	=_____
Score range: 0-16					

Sum individual item scores: _____
Multiply by 4: _____
Divide by number of items answered: _____ =**FBSI-TSE score**

FBSI-F/WB (Function/ Well-Being)	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF7	0	+	_____	=_____
Score range: 0-12					

Sum individual item scores: _____
Multiply by 3: _____
Divide by number of items answered: _____ =**FBSI-F/WB score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

FBSI-16 scoring template, 2008

Appendix 6 EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

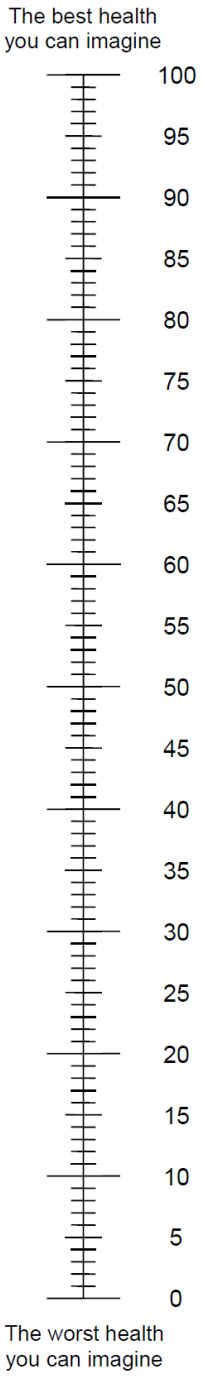
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7 Laboratory Testing Blood Volumes

Blood Requirements (mL)							
Laboratory Specimens	**Tube Type & Volume**	**Screen**	**D1, Odd Cycles 1-7**	**D1, Even Cycles 1-7**	**D1, Odd Cycles >7**	**End of Treatment**	**Post-Treatment Follow-up**
Serum β-hCG pregnancy test	Serum, clot activator 4 mL	4					
Hematology (CBC with differential, platelet count)	K_2EDTA 2 mL	2	2	2	2	2	
Serum Chemistry	Serum, clot activator 4 mL	4	4	4	4	4	
PT, APTT	NaCitrate, 2.7 mL		2.7	2.7	2.7	2.7	
FcReceptor Genotyping	K_2EDTA 6 mL		6				
PK sampling	Serum, clot activator 4 mL		8	8	8	4	4
ADA (Anti-MGAH22)	Serum, clot activator 4 mL		4		4	4	4
Total Required (mL)		**10**	**26.7**	**16.7**	**20.7**	**16.7**	**8**

Appendix 8 RECIST 1.1 Guidelines

(Adapted from Eisenhauer et al. 2009 **(9)**)

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 examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

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

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-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable 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 measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

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 examination 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. 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, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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

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

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

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<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 measurable 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 is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

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.

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