Official Title: **AN OPEN-LABEL, SINGLE-ARM, PHASE II STUDY OF PERTUZUMAB WITH HIGH-DOSE TRASTUZUMAB FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM PROGRESSION POST-RADIOTHERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER (PATRICIA)**

NCT Number: NCT02536339

Document Date: Protocol Version 3: 29-October-2018

PROTOCOL

TITLE:	**AN OPEN-LABEL, SINGLE-ARM, PHASE II STUDY OF PERTUZUMAB WITH HIGH-DOSE TRASTUZUMAB FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM PROGRESSION POST-RADIOTHERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER (PATRICIA)**
PROTOCOL NUMBER:	ML29366
VERSION NUMBER:	*3*
EUDRACT NUMBER:	Not applicable
IND NUMBER:	4517
TEST PRODUCT:	Pertuzumab (RO4368451), Trastuzumab (RO0452317)
MEDICAL MONITOR:	[redacted] Pharm.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 29 April 2015
DATE AMENDED:	Version 2: 16 August 2016 *Version 3: See electronic date stamp below*

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	29-Oct-2018 00:56:38

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

The ML29366 protocol is being amended to shorten the survival follow-up period from 24 months to 12 months and to shorten the safety follow-up after treatment discontinuation from 6 months to 1 month; as the median survival observed in this patient population is less than 24 months. Three patients remain on study and continue to receive treatment.

Changes to the protocol, along with a rationale for each change, are summarized below:

- In Section 3.2, the end of study definition has been revised as patients will be followed for 12, not 24, months after treatment discontinuation.
- In Section 4.5.5, language has been revised to reflect that patients will be followed for 12, not 24, months after treatment discontinuation.
- In Section 4.6.2.2, language has been revised to reflect that all patients will be followed for a minimum of 12, not 24, months from the date of the last dose of study drug or until death, whichever occurs first.
- In Section 5.1.2, language has been revised to reflect that patients will be followed for 12, not 24, months after treatment discontinuation.
- In Section 5.7, the Perjeta USPI and Herceptin USPI have been removed as the Investigators Brochure is the appropriate single reference document to determine reporting requirements for single adverse event cases.
- In Section 6.9, the language has been revised to reflect that the primary efficacy analysis will be performed when all enrolled patients have been followed for approximately 1 month after the last patient has disease progression or early discontinuation or has been at least 6 months on treatment, whichever occurs first.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN OPEN-LABEL, SINGLE-ARM, PHASE II STUDY OF PERTUZUMAB WITH HIGH-DOSE TRASTUZUMAB FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM PROGRESSION POST-RADIOTHERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER (PATRICIA)**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, SINGLE-ARM, PHASE II STUDY OF PERTUZUMAB WITH HIGH-DOSE TRASTUZUMAB FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM PROGRESSION POST-RADIOTHERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER (PATRICIA)**
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VERSION NUMBER:	*3*
EUDRACT NUMBER:	Not applicable
IND NUMBER:	4517
TEST PRODUCT:	Pertuzumab (RO4368451), trastuzumab (RO0452317)
PHASE:	Phase II
INDICATION:	HER2-positive MBC with CNS metastases
SPONSOR:	Genentech, Inc.

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of the study combination of pertuzumab with high-dose trastuzumab for the treatment of central nervous system (CNS) progression post-radiotherapy in patients with human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer (MBC), as measured by objective response rate (ORR) in the CNS

The secondary efficacy objective for this study is as follows:

- To evaluate the efficacy of pertuzumab with high-dose trastuzumab for these same patients, as measured by duration of response (DOR) in the CNS, clinical benefit rate (CBR) for the CNS, progression-free survival (PFS) in the CNS, PFS (CNS or non-CNS), and overall survival (OS)

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety of the study dose of pertuzumab (loading dose of 840 mg intravenous [IV] followed every 3 weeks thereafter by a dose of 420 mg IV) and high-dose trastuzumab (6 mg/kg IV weekly) for the treatment of patients with HER2-positive MBC with CNS progression post-radiotherapy

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the serum pharmacokinetics of pertuzumab (loading dose of 840 mg IV followed every 3 weeks thereafter by a dose of 420 mg IV) and high-dose trastuzumab (6 mg/kg IV weekly) for the treatment of patients with HER2-positive MBC with CNS progression post-radiotherapy

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objectives for this study are as follows:

- To evaluate the impact of treatment with pertuzumab and high-dose trastuzumab in patients with HER2-positive MBC with CNS progression post-radiotherapy on PROs, as measured by the M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT) assessment
- To evaluate the relationship of ORRs with PRO endpoints, as measured by the MDASI-BT

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To perform an exploratory analysis of the relationship between pertuzumab and high-dose trastuzumab exposure and efficacy and safety endpoints
- To collect (optional) tissue samples and plasma, which will be banked for future biomarker analysis

Study Design

Description of Study

This is a U.S.-based, Phase II, open-label, single-arm study designed to examine the safety and efficacy of pertuzumab (loading dose of 840 mg IV followed every 3 weeks thereafter by a dose of 420 mg IV) and high-dose trastuzumab (6 mg/kg IV weekly) administered to patients with HER2-positive, MBC-related CNS metastases (parenchymal) that have disease progression in the brain following radiotherapy (stereotactic radiosurgery [SRS] or whole brain radiotherapy [WBRT]). No changes will be made to the patient's current treatment (e.g., chemotherapy, hormonal therapy) for systemic disease in order to optimize the ability to detect any incremental benefits provided by the combination of pertuzumab and high-dose trastuzumab (see Section 4.3.1.1 for dosing information). The following exceptions, however, will be made:

- Patients receiving treatment with ado-trastuzumab emtansine (also known as T-DM1 or Kadcyla®)
  - Ado-trastuzumab emtansine will be discontinued 3 weeks prior to initiation of pertuzumab with high-dose trastuzumab.
- Patients receiving treatment with lapatinib
  - Lapatinib will be discontinued 1 week prior to initiation of pertuzumab with high-dose trastuzumab.

Patients may remain on study treatment until disease progression within the CNS or systemic progression, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Overall safety will be assessed on an ongoing basis during the conduct of the study.

Number of Patients

Approximately 40 patients will be enrolled in the study.

Target Population

Patients with HER2-positive MBC with documented CNS progression of disease post-radiotherapy (WBRT/SRS) and stable systemic disease will be enrolled in the study.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent
- Able and willing to comply with the study protocol
- Age $\geq$ 18 years
- Pathologically confirmed HER2-positive MBC by local laboratory with the following requirements:
  - HER2 overexpressed or amplified (immunohistochemistry of 3+ or HER2 gene amplification by in situ hybridization with a ratio of HER2-gene signals to centromere 17 signals $\geq$ 2.0 or average HER2 copy number $\geq$ 6.0 signals/cells)

- Unequivocal evidence of new and/or progressive brain metastases after completion of WBRT or SRS
- Completed previous SRS or WBRT $>$ 60 days
- At least one measurable CNS metastasis (lesion $\geq$ 10 mm per Response Assessment in Neuro-Oncology-Brain Metastases [RANO-BM] criteria)
- Confirmed tumor assessment demonstrating stable measureable/non-measureable systemic disease
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- LVEF $\geq$ 50% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 28 days before Day 1 of study
- Adequate bone marrow function, as indicated by the following:
  - ANC $>$ 1500/μL
  - Platelets $\geq$ 75,000/μL
  - Hemoglobin $\geq$9 g/dL
- Adequate renal function, as indicated by creatinine $\leq 1.5 \times$ upper limit of normal (ULN)
- Adequate liver function, as indicated by bilirubin $\leq 1.5 \times$ ULN
  - AST and ALT $< 2.5 \times$ ULN unless related to primary disease; up to $5 \times$ ULN if liver metastases are present
- Life expectancy $>$ 12 weeks
- Female patients of childbearing potential, including those who have had tubal ligation, and women $<$ 12 months after the onset of menopause, even if they have undergone surgical sterilization, must have a negative serum pregnancy test $<$ 7 days prior to initiation of study drug (with result available prior to dosing).
- Female patients of childbearing potential (who are not postmenopausal $\geq$ 12 months of non-therapy-induced amenorrhea or surgically sterile [absence of ovaries and/or uterus]) and male patients with female partners of childbearing potential must agree to use one highly effective or two effective methods of non-hormonal contraception, as specified in the protocol, during their participation in the study and for at least 7 months after last dose of study drug.

Exclusion Criteria

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

- Progression of systemic disease at time of screening
- Leptomeningeal disease (LMD)
  - LMD is a clinical diagnosis, defined as positive cerebrospinal fluid (CSF) cytology and/or unequivocal radiological or clinical evidence of clinically significant leptomeningeal involvement
  - Patients with leptomeningeal symptoms would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurological deficit
  - Patients who are asymptomatic or with nonspecific leptomeningeal enhancement would not be considered to have LMD. However, if there is clinical or radiographic suspicion of LMD, CSF confirmation to rule out LMD is at the investigator's discretion.
- History of intolerance ($\geq$ Grade 3) or hypersensitivity to trastuzumab or pertuzumab
- Current use or history of receiving a non-approved, investigational treatment within 21 days prior to study enrollment
- Current use of anthracyclines
- Patients unwilling to discontinue ado-trastuzumab emtansine or lapatinib therapy
- Active infection
- Pregnant or lactating women

- Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result < 7 days prior to initiation of study drug.

- History of significant cardiac disease, cardiac risk factors, uncontrolled arrhythmias, or uncontrolled hypertension
- Symptomatic intrinsic lung disease or extensive tumor involvement of the lungs, resulting in dyspnea at rest
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned

Length of Study

The total length of this study will be from screening of the first patient to completion of the last follow-up assessment of the last patient, which is estimated to occur approximately 3 years after the first patient is screened.

End of Study

The study will end when all patients have been followed for *12* months after the treatment discontinuation visit (inclusive of the safety and survival follow-up periods), unless they have been lost to follow-up, withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

Outcome Measures

Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is as follows:

- Objective response rate (ORR) in the CNS (assessed per RANO-BM criteria; see Appendix 4). Objective response is defined as complete response (CR) or partial response (PR).

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS
  - Tumor response in CNS will be assessed per RANO-BM criteria (see Appendix 4).
  - Non-CNS tumor response will be assessed by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 5).

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of all non-serious and serious adverse events
- Incidence and severity of Grade ≥ 3 adverse events and serious adverse events
- Incidence of adverse events leading to discontinuation or interruption of pertuzumab alone or the combination of pertuzumab and trastuzumab
- Cause of death while on study
- Incidence and severity of cardiac events, as assessed by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) and New York Heart Association (NYHA) classification for congestive heart failure (CHF; see Appendix 7)
- Characterization of changes in left ventricular ejection fraction (LVEF) and changes in LVEF from baseline over the course of the study (see Appendix 6)
- Clinically significant laboratory test abnormalities

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Observed serum concentrations for pertuzumab and trastuzumab at the following timepoints:
  - Week 1, Day 1 (1 sample pre-dose and 1 sample within 30 minutes after completion of both infusions [maximum concentration (C_{max})]) (total of 2 samples)
  - Week 4, Day 1 (pre-dose [trough])
  - Week 10, Day 1 (pre-dose [trough])
  - Week 16, Day 1 (1 sample pre-dose and 1 sample within 30 minutes after completion of both infusions [C_{max}]) (total of 2 samples)

Patient-Reported Outcome Measure

The PRO outcome measures for this study is as follows:

- Scores from the MDASI-BT assessment

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- To explore the relationship between pertuzumab and high-dose trastuzumab exposure and efficacy and safety endpoints
- Collection of (optional) tissue and plasma samples

Investigational Medicinal Products

Study treatment is defined as systemic, biologic agent for the treatment of CNS metastases due to HER2-positive breast cancer. Pertuzumab and trastuzumab are considered investigational medicinal products (IMPs) in this study.

Any background systemic agents for the management of disease (i.e., chemotherapy, hormone therapy) are considered non-IMPs in this study.

Test Product (Investigational Drugs)

Pertuzumab will be administered at a dose of 840 mg administered as a 60-minute IV infusion with an observation period of 60 minutes (loading dose), followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 – 60 minutes with an observation period of 30 – 60 minutes. For patients already receiving pertuzumab as part of their ongoing systemic therapy, no loading dose is required in the case of an interval $<$ 6 weeks between the last dose of pertuzumab and the first administration of on-study pertuzumab.

High-dose trastuzumab will be administered at a dose of 6 mg/kg weekly, infused intravenously over 30 – 90 minutes. No loading dose is required. Trastuzumab-naïve patients should receive their first dose over 90 minutes. Patients who are actively receiving trastuzumab prior to enrollment will have a dose increase to 6 mg/kg IV weekly. The dose of trastuzumab will be based on the patient's actual body weight measured at baseline. The dose need not be recalculated unless body weight has changed by $\geq$ 10% from baseline.

Non-Investigational Medicinal Products

For non-IMPs, refer to local prescribing information/institutional guidelines for detailed guidelines on administration, premedications, and dose delays/reductions for toxicities.

Statistical Methods

Efficacy Analyses

The primary efficacy endpoint is ORR in the CNS per RANO-BM criteria. To evaluate the ORR, two sets of analyses will be performed: one is based on the efficacy-evaluable population and the other is based on the safety population. The efficacy-evaluable population is the primary population for ORR in CNS. Any patient without sufficient data to determine response (e.g., non-evaluable patients) will be classified as a non-responder. The estimate of the ORR with 95% Clopper-Pearson exact confidence interval (CI) will be presented. Responses to study treatment will be based on investigator assessments.

Secondary efficacy endpoints include DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS. The Kaplan-Meier approach will be used to estimate the

distribution of DOR, PFS, and OS. The 95% CI for the median time to event will be calculated using the Brookmeyer and Crowley method.

Determination of Sample Size

The emphasis of this study is estimation of the ORR with a given precision, rather than hypothesis testing. ORRs of 20% or higher will be deemed clinically significant because no other therapeutic options are available for this patient population.

With 35 evaluable patients, and assuming that the study treatment is expected to lead to an ORR in CNS of 20% (7 patients), the 95% CI around the estimated ORR will be 8.4%–36.9%.

Interim Analysis

An interim analysis will be performed when 15 patients are enrolled and have the following: 1) at least two LVEF measurements (at Week 6 and Week 12), 2) two cycles (3-week cycle) of study drug, and 3) two response measurements for review. Complete guidelines to assist in decision-making will be described in the Steering Committee charter. For this interim analysis, the safety endpoints will be of primary consideration. Efficacy endpoints will also be examined to identify potential treatment non-benefits.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	anthracycline plus cyclophosphamide
BBB	blood-brain barrier
CBR	clinical benefit rate
CHF	congestive heart failure
C_{max}	concentration maximum
C_{min}	concentration minimum
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CT	computed tomography
D5W	dextrose (5%) in water
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
HER2	human epidermal growth factor receptor-2
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
IXRS	interactive voice/web response system
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction

MBC	metastatic breast cancer
MDASI-BT	M.D. Anderson Symptom Inventory-Brain Tumor
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PET-CT	positron-emission tomography CT
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
RANO-BM	Response Assessment in Neuro-Oncology-Brain Metastases
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SRS	stereotactic radiosurgery
ULN	upper limit of normal
USPI	U.S. Package Insert
WBRT	whole-brain radiation therapy

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE CENTRAL NERVOUS SYSTEM METASTASES

Breast cancer is the second most prevalent malignancy metastasizing to the central nervous system (CNS), accounting for 20% of cases observed in cancer care (Boogerd et al. 1993). The incidence of clinically evident brain metastasis in patients with metastatic breast cancer (MBC) is estimated to be between 10% and 30% (Pivot et al. 2015). Patients who develop metastatic CNS disease have a poor prognosis and associated neurological complications that often lead to significant morbidity and mortality. The management of intracranial metastases from breast cancer has become a vital component of disease control, and increasingly patients are progressing in the CNS after radiotherapy, at which point the standard options become quite limited.

Human epidermal growth factor receptor-2 (HER2) is a member of the erb-B epidermal growth factor receptor tyrosine kinase family, and is overexpressed in 18%–20% of human breast cancers (Altaha et al. 2005; Stemmler et al. 2006; Yau et al. 2006; Pinder et al. 2007). Clinically, its overexpression is an independent adverse prognostic factor and is associated with an aggressive clinical course and poor survival in breast cancer patients. Advancements in HER2-targeted therapies have altered the natural landscape of HER2-positive breast cancer and improved systemic control and overall survival.

The incidence of CNS metastases (24%–48%) is higher in HER2-positive MBC patients than reported for other cancers (Altaha et al. 2005; Stemmler et al. 2006; Yau et al. 2006; Pinder et al. 2007). In an analysis of 10 adjuvant trials examining the sites of metastases in 9524 patients with early stage breast cancers treated without anthracyclines, taxanes, or trastuzumab in the pre-trastuzumab era, the 10-year incidence of CNS relapse at any time was almost double in patients with HER2-positive disease compared to those with HER2-negative breast cancer (6.8% versus 3.5%; $p < 0.01$) (Pestalozzi et al. 2006). In the epidemiological registHER (registry of HER2-positive patients) study of 1023 patients with newly diagnosed HER2-positive MBC, 37% of patients had a diagnosis of CNS metastases at a 29-month median follow-up (Brufsky et al. 2011). Of these, 7% had intracranial involvement at the time of their MBC diagnosis and 30% as a subsequent site of disease progression. Patients are not actively screened for CNS involvement. The actual incidence of CNS metastases may be greater than observed in retrospective studies. The CEREBEL trial compared the incidence of the CNS as the site of first relapse in patients with HER2-positive MBC treated with trastuzumab plus capecitabine to the incidence in patients treated with lapatinib plus capecitabine. At screening, asymptomatic CNS metastases were identified in 20% of the patients (Pivot et al. 2015).

In older studies, the one-year survival rate in patients with CNS metastases was 20% (Pestalozzi 2009). However, patients with HER2-positive brain metastases often live

longer, and in some multicenter series, median survival after a brain metastasis diagnosis is now in the range of 2 years in HER2-positive patients (Sperduto et al. 2012).

1.2 BACKGROUND ON PERTUZUMAB

Pertuzumab (Perjeta®), a humanized monoclonal antibody to the HER2 receptor, blocks ligand-dependent heterodimerization of HER2 with other HER family members. This results in the inhibition of ligand-initiated intracellular signaling. In addition, pertuzumab mediates antibody-dependent cellular cytotoxicity.

Pertuzumab has been shown in nonclinical settings to have superior anti-tumor effects when combined with trastuzumab than when used as monotherapy.

Trastuzumab and pertuzumab monoclonal antibodies bind to distinct epitopes on the HER2 receptor without competing with each other, resulting in distinctive mechanisms for disrupting HER2 signaling. These mechanisms are complementary and result in augmented therapeutic efficacy when pertuzumab and trastuzumab are given in combination. Pertuzumab binds to an epitope within subdomain 2 of HER2, whereas the epitope for trastuzumab is localized to subdomain 4 (Cho et al. 2003; Franklin et al. 2004). Pertuzumab acts by blocking dimerization of HER2 with other HER family members, thereby inhibiting ligand-initiated intracellular signaling through two major signaling pathways, MAPK and PI3K. Inhibition of these pathways can result in growth arrest and apoptosis (Hanahan and Weinberg 2000). In comparison, trastuzumab binds to the juxtamembrane epitope (subdomain 4), preventing cleavage and ligand independent signal transduction. Both antibodies are also capable of activating antibody-dependent, cell-mediated cytotoxicity (Spector and Blackwell 2009).

In the Phase III, pivotal study WO20698/TOC4129g (CLEOPATRA; N = 808) in patients with previously untreated HER2-positive MBC, a statistically significant and clinically meaningful improvement in progression-free survival (PFS), based on tumor assessments by an independent review facility (IRF), was observed in patients treated with pertuzumab, trastuzumab, and docetaxel (n = 406) compared with those receiving placebo, trastuzumab, and docetaxel (n = 402). PFS was prolonged at the median by 6.1 months, and the risk of disease progression or death was reduced by 38% (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.51, 0.75; $p < 0.0001$) with an improvement in median PFS from 12.4 months to 18.5 months. Results of the investigator-assessed PFS analysis (HR: 0.65 [0.54, 0.78]; $p < 0.0001$; median 12.4 vs. 18.5 months, respectively) were consistent with those observed for IRF-assessed PFS. A second interim analysis of overall survival (OS; performed one year after the primary analysis of efficacy) crossed the predefined stopping boundary for statistical significance ($p \leq 0.0138$), demonstrating that treatment with pertuzumab, trastuzumab, and docetaxel significantly improved OS when compared with the placebo arm (HR: 0.66; 95% CI: 0.52, 0.84; $p = 0.0008$). The updated analysis of investigator-assessed PFS demonstrated that the PFS benefit observed at the primary analysis was maintained after an additional year of follow-up. The HR of 0.69 and the increase in median PFS of

6.3 months (from 12.4 months in the placebo arm to 18.7 months in the treatment arm) were highly consistent with those from the first analysis of investigator-assessed PFS and consequently also with the primary IRF analysis (Swain et al. 2013).

Based on these data, pertuzumab was approved by the FDA for use in HER2-overexpressing MBC in combination with trastuzumab and docetaxel for first-line treatment metastatic disease.

Pertuzumab is also currently approved in the early breast cancer setting.

See the pertuzumab Investigator's Brochure for additional information.

1.3 BACKGROUND ON TRASTUZUMAB

Trastuzumab (Herceptin®) is a recombinant monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2. Trastuzumab has been shown to inhibit the proliferation of human tumor cells overexpressing HER2 both in vitro and in vivo.

The clinical benefit of trastuzumab in women with MBC has been demonstrated in two pivotal studies.

A Phase II trial (H0649g) assessed the activity of single-agent trastuzumab in 222 women with HER2-overexpressing MBC with progressive disease after one or more chemotherapy regimens (Cobleigh et al. 1999). An independent response evaluation committee identified 8 complete and 26 partial responses, for an objective response rate of 15% in the intent-to-treat population (95% CI: 11% to 21%). The median duration of response was 9.1 months, and the median duration of survival was 13 months. The most common adverse events, which occurred in approximately 40% of patients, were mild to moderate infusion-associated fever and/or chills. The most clinically significant event was cardiac dysfunction, which occurred in 4.7% of patients.

An open-label, randomized, Phase III study (H0648g) in 469 patients with HER2-positive MBC was conducted to evaluate the efficacy of trastuzumab in combination with chemotherapy as first-line treatment. Patients who were anthracycline-naïve were randomized to receive either anthracycline plus cyclophosphamide (AC) or trastuzumab plus AC. Patients who had received prior anthracyclines in the adjuvant setting were randomized to receive either paclitaxel or trastuzumab plus paclitaxel. As determined by an independent response evaluation committee, trastuzumab prolonged median time to disease progression from 4.6 months to 7.4 months ($p < 0.001$), improved the overall response rate (complete and partial responses) from 32% to 50% ($p < 0.001$), and increased median duration of response from 6.1 to 9.1 months ($p < 0.001$). Compared to chemotherapy alone, the addition of trastuzumab significantly lowered the incidence of death at one year from 33% to 22% ($p = 0.008$) and increased median overall survival 24% from 20.3 months to 25.1 months ($p = 0.046$) (Slamon et al. 2001). The observed

survival advantage remained despite crossover of 66% of patients initially randomized to chemotherapy alone who elected to receive trastuzumab upon disease progression (Tripathy et al. 2000). Fever/chills were observed with the initial trastuzumab infusion in approximately 25% of patients. Class III or IV cardiac dysfunction was observed in 16% of the trastuzumab + AC subgroup; increasing age was an associated risk factor for the development of cardiotoxicity in this treatment cohort (Slamon et al. 2001).

Based on these data, trastuzumab was approved by the U.S. Food and Drug Administration (FDA) for use in HER2-overexpressing MBC in combination with paclitaxel for first-line treatment and as a single agent for patients failing prior chemotherapy for metastatic disease.

Trastuzumab is also currently approved in the early breast cancer setting.

See the trastuzumab Investigator's Brochure for additional information.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The incidence of CNS disease in HER2-positive MBC is close to 50%. Tumors overexpressing HER2 may have a predilection for brain metastases. Kallioniemi and colleagues (1991) demonstrated that HER2-positive disease is associated with a different pattern of metastatic spread, and those with overexpression of the HER2 gene metastasized three times more often ($p = 0.0002$) to the brain. HER2 overexpression has shown to be a predictive factor for CNS metastases in advanced breast cancer (Miller at al. 2003).

Improvements in extra-cranial control with HER2-directed therapy may be a contributing factor to the observed increased risk of brain metastases as site of first relapse reported in multiple studies. A systematic review of trastuzumab-containing regimens from early breast cancer examined data from five randomized clinical trials (B-31, FinHer, HERA, N9831, and PACS-04). This analysis reported an increased risk of brain metastases as the site of first relapse in patients treated with trastuzumab (risk ratio: 1.75, 90% CI: 1.29 – 2.38; $p = 0.002$) compared to trastuzumab-naïve patients in the control arms, 73/3120 patients and 50/3761 patients, respectively (Moja et al. 2012). In a population-based registry study of 1458 patients with early stage breast cancer, CNS as the site of first recurrence was documented for 0.6% of patients with HER2-negative disease and for 4% and 1.2% of patients with HER2-positive disease who had and had not received adjuvant trastuzumab, respectively. Time to CNS as first recurrence from diagnosis, however, was significantly prolonged in patients with HER2-positive disease who received adjuvant (20.3 months) compared with patients with HER2-negative disease (19.8 months) and those with HER2-positive disease who did not receive trastuzumab (10.3 months) ($p = 0.018$) (Musolino et al. 2011).

Multiple retrospective studies have reported an OS benefit in patients with CNS metastases treated with trastuzumab. Dawood et al. (2008) reported findings

demonstrating that patients with HER2-negative disease and patients with HER2-positive disease who had never received trastuzumab had an increased hazard of death compared with patients with HER2-positive disease who had received trastuzumab before or at the time of CNS metastases diagnosis. The prospective observational registHER trial demonstrated continuation of trastuzumab after intracranial metastases to be associated with improved survival. The median survival for patients who received trastuzumab subsequent to CNS diagnosis was 17.5 months compared with 3.7 months for patients who did not (Brufsky et al. 2011). Results from the Phase III CLEOPATRA trial in HER2-positive, first-line MBC demonstrated significant improvements in PFS and OS with pertuzumab in combination with trastuzumab and docetaxel over placebo, trastuzumab, and docetaxel. A subsequent exploratory analyses of the incidence and time to development of CNS metastases in patients from CLEOPATRA suggest that pertuzumab added to trastuzumab and docetaxel delays the onset of CNS disease compared with the control arm, as well as an OS trend in favor of pertuzumab combined with trastuzumab and docetaxel in patients who developed CNS metastases as the first site of disease progression (Swain et al. 2014).

The standard of care for the treatment of CNS metastasis consists of local modalities and includes surgery, whole brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS). These approaches can reduce tumor burden and palliate neurological symptoms but are often associated with neurocognitive and other morbidities. Current American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommendations for the systemic management of HER2-positive breast cancer are limited and based on low-level evidence.

CNS response to existing systemic anticancer therapies at standard dosages has been disappointing, in part due to the limited capacity of many of these drugs to cross the blood–brain barrier (BBB) effectively and the therapeutic concentration limitations resulting from active drug efflux proteins such as P-glycoprotein (Pgp), which are present in high concentrations in the luminal membranes of brain endothelium (Régina et al. 2001). Large monoclonal antibodies in particular are not believed to cross an intact BBB. However, the BBB may be subject to increased permeability/disruption associated with radiation effects and tumor invasion. The influence of WBRT on monoclonal antibody uptake in the brain was examined in a pilot study in patients with HER2-positive breast cancer-related brain metastases. This study demonstrated increased trastuzumab uptake after WBRT; the median serum cerebrospinal fluid trastuzumab concentration ratios were 420:1 and 76:1 pre- and post-WBRT (Stemmler et al. 2007). A study using positron electron tomography imaging demonstrated CNS penetration by 89Zr-trastuzumab in patients with MBC with an 18-fold higher uptake in brain tumors than in normal brain tissue (Dijkers et al. 2010).

Multiple studies have demonstrated in both retrospective and prospective observational data that patients treated with trastuzumab prior to the development of CNS metastases and/or after CNS metastases have improved survival outcomes. Incremental increases

in uptake of trastuzumab have been observed with standard systemic dosing when the BBB is disrupted by associated radiation effects and/or tumor invasion (Dijkers et al. 2010). Subtherapeutic trastuzumab levels achieved in the CNS may be related to insufficient dosing as opposed to the inability of trastuzumab to cross the BBB.

Phillips et al. (unpublished Genentech internal data) evaluated the relationship between dose-response in brain graft experiments in murine models. When evaluated in brain graft experiments, 4D5 (a murine equivalent of trastuzumab) doses up to three times the effective dose used in mammary grafts were required to achieve efficacy in brain grafts. These data suggest that an increased dose of trastuzumab could lead to improved efficacy against metastases in the CNS for HER2-positive MBC patients. Higher trastuzumab dosages have not been associated with increased cardiotoxicity or adverse events as observed in a Phase I study (8 patients received 500 mg intravenously every week for 8 weeks), and data from two Phase II studies (Vogel et al. 2002; Leyland-Jones et al. 2010) where patients received two (N = 57) and three times (N = 47) the standard dose.

The impact of a more comprehensive blockade of cell signaling associated with the addition of pertuzumab to trastuzumab has been demonstrated in the nonclinical and clinical settings. The combination of pertuzumab and trastuzumab with docetaxel demonstrated statistically significant and clinically meaningful improvements in outcomes (PFS and OS) without an observed increase in cardiotoxicity compared with trastuzumab and docetaxel in a pivotal, Phase III, randomized, controlled trial (CLEOPATRA; Perjeta U.S. Package Insert [USPI]). Pertuzumab and trastuzumab combinations are the current standard of care in first-line HER2-positive MBC. Data from CLEOPATRA also suggest that the addition of pertuzumab to trastuzumab and chemotherapy delays the onset of CNS disease compared with trastuzumab and chemotherapy alone (15 months vs. 11.9 months; hazard ratio: 0.58; 95% CI: 0.39 – 0.85; p = 0.0049), demonstrating that the two agents in combination may have improved activity in the CNS (Swain et al. 2014).

Currently, there is no clear standard of care that addresses recurring or multiple intracranial metastases in HER2-positive MBC. CNS metastasis is a stipulated exclusion criterion in most clinical trials of systemic therapies, and clinical data reporting the efficacy of systemic therapy for breast cancer brain metastases are limited. CNS response to existing systemic anticancer therapies at standard dosages has been disappointing, necessitating clinical investigations examining alternative dosing of efficacious therapies in patients with HER2-positive MBC with CNS progression post-radiotherapy.

This study will examine the safety and efficacy of pertuzumab (loading dose of 840 mg intravenous [IV] followed every 3 weeks thereafter by a dose of 420 mg IV) in combination with high-dose trastuzumab (6 mg/kg IV weekly) in patients with

HER2-positive MBC with CNS metastases that have disease progression in the brain following radiotherapy.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of the study combination of pertuzumab with high-dose trastuzumab for the treatment of CNS progression post-radiotherapy in patients with HER2-positive MBC, as measured by objective response rate (ORR) in the CNS

The secondary efficacy objective for this study is as follows:

- To evaluate the efficacy of pertuzumab with high-dose trastuzumab for these same patients, as measured by duration of response (DOR) in the CNS, clinical benefit rate (CBR) for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the safety of the study dose of pertuzumab (loading dose of 840 mg IV followed every 3 weeks thereafter by a dose of 420 mg IV) and high-dose trastuzumab (6 mg/kg IV weekly) for the treatment of patients with HER2-positive MBC with CNS progression post-radiotherapy

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the serum pharmacokinetics of pertuzumab (loading dose of 840 mg IV followed every 3 weeks thereafter by a dose of 420 mg IV) and high-dose trastuzumab (6 mg/kg IV weekly) for the treatment of patients with HER2-positive MBC with CNS progression post-radiotherapy

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- To evaluate the impact of treatment with pertuzumab and high-dose trastuzumab in patients with HER2-positive MBC with CNS progression post-radiotherapy on PROs, as measured by the M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT) assessment
- To evaluate the relationship of ORRs with PRO endpoints, as measured by the MDASI-BT

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To perform an exploratory analysis of the relationship between pertuzumab and trastuzumab exposure and efficacy and safety endpoints

- To collect (optional) tissue samples and plasma, which will be banked for future biomarker analysis

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a U.S.-based, Phase II, open-label, single-arm study designed to examine the safety and efficacy of pertuzumab (loading dose of 840 mg IV followed every 3 weeks thereafter by a dose of 420 mg IV) and high-dose trastuzumab (6 mg/kg IV weekly) administered to patients with HER2-positive, MBC-related CNS metastases (parenchymal) that have disease progression in the brain following radiotherapy (SRS or WBRT). No changes will be made to the patient's current treatment (e.g., chemotherapy, hormonal therapy) for systemic disease in order to optimize the ability to detect any incremental benefits provided by the combination of pertuzumab and high-dose trastuzumab (see Section 4.3.1.1 for dosing information). The following exceptions, however, will be made:

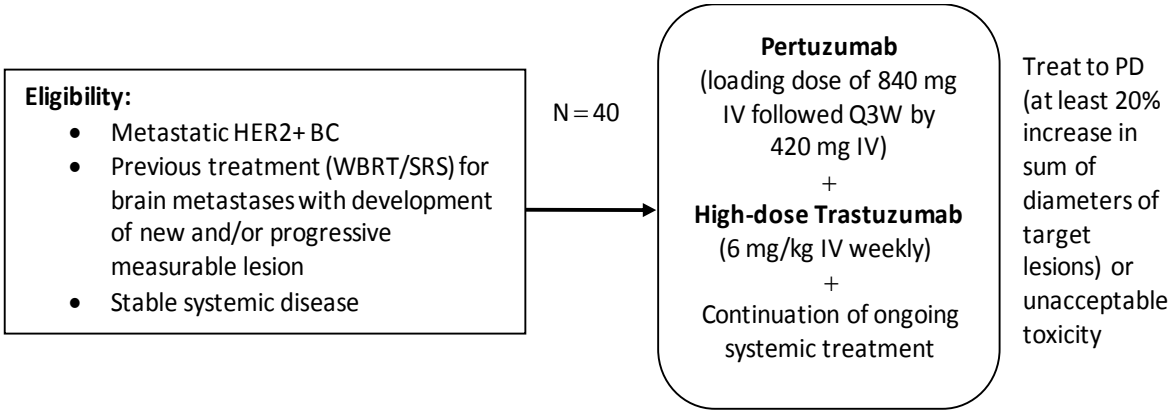
1. Patients receiving treatment with ado-trastuzumab emtansine (also known as T-DM1 or Kadcyla®)
   - Ado-trastuzumab emtansine will be discontinued 3 weeks prior to initiation of pertuzumab with high-dose trastuzumab.
2. Patients receiving treatment with lapatinib
   - Lapatinib will be discontinued 1 week prior to initiation of pertuzumab with high-dose trastuzumab.

Patients may remain on study treatment until disease progression within the CNS or systemic progression, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Overall safety will be assessed on an ongoing basis during the conduct of the study.

The study schema is presented in Figure 1. The schedule of assessments is provided in Appendix 1.

Figure 1 Study Schema



- **Primary efficacy endpoint:** ORR in the CNS
- **Secondary efficacy endpoint:** DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS
- **Safety endpoint:** Safety of pertuzumab and trastuzumab for the treatment of HER2-positive MBC with CNS progression post-radiotherapy

BC = breast cancer; CBR = clinical benefit rate; CNS = central nervous system; DOR = duration of response; HER2 = human epidermal growth factor receptor-2; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

3.2 END OF STUDY

The study will end when all patients have been followed for *12* months after the treatment discontinuation visit (inclusive of the safety and survival follow-up periods), unless they have been lost to follow-up, withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

At this time, the study will end and no further data will be collected in the clinical database for this study. The end of study is defined as the last patient last visit (LPLV) at the end of the follow-up period.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Pertuzumab and Trastuzumab Dose and Schedule

Currently, there is no clear standard of care that addresses recurring or multiple intracranial metastases post-radiotherapy in HER2-positive MBC. Despite incremental increases in uptake of trastuzumab observed with standard systemic dosing when the BBB is disrupted, subtherapeutic levels are achieved in the CNS. Brain graft experiments with 4D5 (a murine equivalent of trastuzumab) demonstrated that doses up to three times the effective dose used in mammary grafts were required to achieve efficacy in brain grafts.

The impact of a more comprehensive blockade of cell signaling associated with the addition of pertuzumab to trastuzumab has been demonstrated in the nonclinical and clinical settings, and may translate in to improved CNS activity. This study will examine the safety and efficacy of pertuzumab (loading dose of 840 mg IV followed every 3 weeks thereafter by a dose of 420 mg IV) in combination with high-dose trastuzumab (6 mg/kg IV weekly) in patients with HER2-positive MBC with CNS metastases that have disease progression in the brain following radiotherapy. Treatment will continue until disease progression in the CNS or systemic progression, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor (see Section 1.3).

3.4 OUTCOME MEASURES

3.4.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is as follows:

- ORR in the CNS (assessed per Response Assessment in Neuro-Oncology-Brain Metastases [RANO-BM] criteria; see Appendix 4). Objective response is defined as complete response (CR) or partial response (PR).

3.4.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS
  - Tumor response in CNS will be assessed per RANO-BM criteria (see Appendix 4).
  - Non-CNS tumor response will be assessed by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 5).

3.4.3 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of all non-serious and serious adverse events
- Incidence and severity of Grade $\geq$ 3 adverse events and serious adverse events
- Incidence of adverse events leading to discontinuation or interruption of pertuzumab alone or the combination of pertuzumab and trastuzumab
- Cause of death while on study
- Incidence and severity of cardiac events, as assessed by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0) and New York Heart Association (NYHA) classification for congestive heart failure (CHF; see Appendix 7)
- Characterization of changes in left ventricular ejection fraction (LVEF) and changes in LVEF from baseline over the course of the study (see Appendix 6)
- Clinically significant laboratory test abnormalities

3.4.4 Pharmacokinetic Outcome Measure

The PK outcome measure for this study is as follows:

- Observed serum concentrations for pertuzumab and trastuzumab at the following timepoints:
  - Week 1, Day 1 (1 sample pre-dose and 1 sample within 30 minutes after completion of both infusions [maximum concentration (C_{max})]) (total of 2 samples)
  - Week 4, Day 1 (pre-dose [trough])
  - Week 10, Day 1 (pre-dose [trough])
  - Week 16, Day 1 (1 sample pre-dose and at 1 sample within 30 minutes after completion of both infusions [C_{max}]) (total of 2 samples)

3.4.5 Patient-Reported Outcome Measure

The PRO outcome measure for this study is as follows:

- Scores from the MDASI-BT assessment

3.4.6 Exploratory Outcome Measures

The exploratory outcome measures for this study are follows:

- To explore the relationship between pertuzumab and high-dose trastuzumab exposure and efficacy and safety endpoints
- Collection of (optional) tissue and plasma samples

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with HER2-positive MBC with documented CNS progression of disease post-radiotherapy and stable systemic disease will be enrolled in the study. Written informed consent will be obtained before initiation of any study-specific, non-standard of care procedures. Unless otherwise noted, screening evaluations may be performed at any time within 28 days prior to Day 1 (time of the first study treatment), per the schedule of assessments in Appendix 1.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent
- Able and willing to comply with the study protocol
- Age $\geq$ 18 years

- Pathologically confirmed HER2-positive MBC by local laboratory with the following requirements:
  - HER2 overexpressed or amplified (immunohistochemistry of 3+ or HER2 gene amplification by in situ hybridization with a ratio of HER2-gene signals to centromere 17 signals ≥ 2.0 or average HER2 copy number ≥ 6.0 signals/cells)
- Unequivocal evidence of new and/or progressive brain metastases after completion of WBRT or SRS
- Completed previous SRS or WBRT > 60 days
- At least one measurable CNS metastasis (lesion ≥ 10 mm per RANO-BM criteria)
- Confirmed tumor assessment demonstrating stablesystemic disease
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- LVEF $\geq 50\%$ by echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 28 days before Day 1 of study
- Adequate bone marrow function, as indicated by the following:
  - ANC $> 1500/\mu L$
  - Platelets $\geq 75{,}000/\mu L$
  - Hemoglobin ≥ 9 g/dL
- Adequate renal function, as indicated by creatinine $\leq 1.5 \times$ upper limit of normal (ULN)
- Adequate liver function, as indicated by bilirubin $\leq 1.5 \times$ ULN
  - AST and ALT $< 2.5 \times$ ULN unless related to primary disease; up to $5 \times$ ULN if liver metastases are present
- Life expectancy > 12 weeks
- Female patients of childbearing potential, including those who have had tubal ligation, and women < 12 months after the onset of menopause, even if they have undergone surgical sterilization, must have a negative serum pregnancy test < 7 days prior to initiation of study drug (with result available prior to dosing).
- Female patients of childbearing potential (who are not postmenopausal ≥ 12 months of non-therapy-induced amenorrhea or surgically sterile [absence of ovaries and/or uterus]) and male patients with female partners of childbearing potential must agree to use one highly effective or two effective methods of non-hormonal contraception, as specified in the protocol, during their participation in the study and for at least 7 months after last dose of study drug.

4.1.2 Exclusion Criteria

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

- Progression of systemic disease at time of screening
- Leptomeningeal disease (LMD)

  - LMD is a clinical diagnosis, defined as positive cerebrospinal fluid (CSF) cytology and/or unequivocal radiological or clinical evidence of clinically significant leptomeningeal involvement
  - Patients with leptomeningeal symptoms would be considered to have LMD even in the absence of positive CSF cytology, unless a parenchymal lesion can adequately explain the neurological deficit
  - Patients who are asymptomatic or with nonspecific leptomeningeal enhancement would not be considered to have LMD. However, if there is clinical or radiographic suspicion of LMD, CSF confirmation to rule out LMD is at the investigator's discretion.
- History of intolerance ($\geq$ Grade 3) or hypersensitivity to trastuzumab or pertuzumab
- Current use or history of receiving a non-approved, investigational treatment within 21 days prior to study enrollment
- Current use of anthracyclines
- Patients unwilling to discontinue ado-trastuzumab emtansine or lapatinib therapy
- Active infection
- Pregnant or lactating women
  - Women who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result $<$ 7 days prior to initiation of study drug.
- History of significant cardiac disease, cardiac risk factors, uncontrolled arrhythmias, or uncontrolled hypertension
- Symptomatic intrinsic lung disease or extensive tumor involvement of the lungs, resulting in dyspnea at rest
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label, Phase II, single-arm study. Randomization will not be performed. Once a patient's eligibility has been confirmed by the investigator, the study staff must ensure the patient is registered via the interactive voice/web response system (IXRS) to obtain a unique enrollment identification number prior to initiation of study treatment. A patient number will not be re-used if the patient leaves the study.

Under no circumstances will patients who enroll in this study and complete treatment as specified be permitted to re-enroll in the study. A Patient Enrollment and Identification Code List must be maintained by the Principal Investigator.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 **Pertuzumab** (Perjeta)

Pertuzumab drug product for IV administration is provided as a single-use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-mL vial contains 420 mg of pertuzumab (14.0 mL/vial). Pertuzumab does not contain any antimicrobial preservative. Therefore, care must be taken to ensure the sterility of the prepared solution for infusion and should be prepared by a healthcare professional using aseptic technique. A 14 mL of pertuzumab liquid concentrate should be withdrawn from the vial and diluted into a 250 mL PVC or non-PVC polyolefin infusion bag of 0.9% sodium chloride solution for infusion.

For information on the formulation, packaging, and handling of pertuzumab, see the Perjeta Investigator's Brochure.

Incompatibilities

No incompatibilities between pertuzumab and polyvinylchloride, polyethylene, or non-PVC polyolefin bags have been observed. Dextrose (5%) in water (D5W) solution should not be used to dilute pertuzumab since it has been shown to be chemically and physically unstable in such solutions (dilute formulations of pertuzumab liquid formulations in D5W IV bags did not maintain stable pH after storage at room temperature [27°C – 33°C] for 24 hours followed by 24 hours at refrigerator temperature [2°C – 8°C]).

Pertuzumab should not be mixed or diluted with other drugs unless stated in the clinical protocol and supported with compatibility data.

4.3.1.2 **Trastuzumab** (Herceptin)

Trastuzumab is supplied for use as a freeze-dried preparation at a nominal content of 440 mg per vial for parenteral administration. The drug is formulated in histidine/histidine-HCl, α,α-trehalose dihydrate, and polysorbate 20.

For IV administration, each vial of trastuzumab is reconstituted with 20 mL of bacteriostatic water for injection (BWFI; containing 1.1% benzyl alcohol), which is supplied with each vial. When reconstituted, this results in a 21 mg/mL solution of trastuzumab. This vial configuration and formulation is designed for multiple use and must be used within 28 days after reconstitution when stored at 2°C to 8°C. Each vial should be used for multiple doses for the same patient only. For patients who are sensitive to benzyl alcohol, trastuzumab may be reconstituted in 20 mL sterile water for injection (SWFI) for immediate use. The appropriate dose of trastuzumab should be withdrawn from the vial using aseptic techniques and added to 250 mL 0.9% sodium chloride for injection for subsequent patient administration.

For information on the formulation, packaging, and handling of trastuzumab, see the Herceptin Investigator's Brochure.

Incompatibilities

No incompatibilities between trastuzumab and polyvinylchloride, polyolefin, or polypropylene bags have been observed. Dextrose 5% solution should not be used because it causes aggregation of the protein. Trastuzumab should not be mixed or diluted with other drugs.

4.3.2 Dosage and Administration

Pertuzumab and trastuzumab may be given in any order. Other systemic therapy should be administered after pertuzumab and trastuzumab.

4.3.2.1 Pertuzumab

The loading dose of pertuzumab will be 840 mg administered as a 60-minute IV infusion with an observation period of 60 minutes, followed every 3 weeks thereafter by a dose of 420 mg administered over a period of 30 – 60 minutes with an observation period of 30 – 60 minutes. For patients already receiving pertuzumab as part of their ongoing systemic therapy, no loading dose is required in the case of an interval < 6 weeks between last dose of pertuzumab and the first administration of on-study pertuzumab.

Left Ventricular Ejection Fraction

Assess LVEF as per the algorithm for continuation and discontinuation of trastuzumab and pertuzumab based on LVEF assessments in Appendix 6.

Infusion-Related Reactions

Like other monoclonal antibodies, pertuzumab has been associated with infusion-related reactions (IRRs), such as chills, diarrhea, fatigue, headache, nausea, and pyrexia. The infusion rate of pertuzumab may be slowed or interrupted and appropriate medical therapies should be administered if the patient develops a significant IRR. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Hypersensitivity Reactions/Anaphylaxis

The infusion should be discontinued immediately if the patient experiences a serious hypersensitivity reaction.

4.3.2.1.1 Dose Modifications

Dose reductions are not allowed for pertuzumab in this study.

4.3.2.1.2 Delayed or Missed Doses

For delayed or missed doses, if the time between two sequential infusions is less than 6 weeks, the 420-mg dose of pertuzumab should be administered. Do not wait until the next planned dose. If the time between two sequential infusions is 6 weeks or more, the loading dose of 840 mg pertuzumab should be re-administered as a 60-minute IV

infusion followed every 3 weeks thereafter by a dose of 420 mg administered as an IV infusion over 30 – 60 minutes.

4.3.2.1.3 Treatment Discontinuations

If a patient experiences an adverse event deemed associated with high-dose trastuzumab that requires trastuzumab discontinuation, pertuzumab should also be discontinued.

Additional information and guidelines on treatment interruption or discontinuation are provided in the Perjeta USPI.

4.3.2.2 Trastuzumab

High-dose trastuzumab will be administered at a dose of 6 mg/kg weekly, infused intravenously over 30 – 90 minutes. No loading dose is required. Trastuzumab-naïve patients should receive their first dose over 90 minutes. Patients who are actively receiving trastuzumab prior to enrollment will have a dose increase to 6 mg/kg IV weekly.

The dose of trastuzumab will be based on the patient's actual body weight measured at baseline. The dose need not be recalculated unless the body weight has changed by ≥ 10% from baseline.

Weekly doses may be administered ± 2 days (no less than 5 days apart).

Left Ventricular Ejection Fraction

Assess LVEF as per the algorithm for continuation and discontinuation of pertuzumab and trastuzumab based on LVEF assessments in Appendix 6

Infusion-Related Reactions

Additional guidelines for treatment interruption or discontinuation related to IRRs are provided in the Herceptin USPI .

4.3.2.2.1 Dose Modifications

Dose reductions are not allowed for trastuzumab in this study.

4.3.2.2.2 Delayed or Missed Doses

If a patient misses a dose of trastuzumab, then the study dose of 6 mg/kg IV should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent trastuzumab IV maintenance doses of 6 mg/kg should be administered 7 days later according to the dosing schedule.

4.3.2.2.3 Treatment Discontinuations

If a patient experiences an adverse event deemed associated with high-dose trastuzumab that requires trastuzumab discontinuation, pertuzumab should also be discontinued. However, if a patient experiences a pertuzumab-associated adverse event requiring pertuzumab discontinuation, high-dose trastuzumab may be continued.

Guidelines for treatment interruption or discontinuation are provided in the Herceptin USPI.

4.3.3 Investigational Medicinal Product Accountability

Pertuzumab and trastuzumab, the investigational medicinal products (IMPs) required for completion of this study, will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the IXRS to confirm the shipment condition and content. Any damaged shipments must be reported and will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed or returned, and IMP destruction or return must be documented on the appropriate form.

Accurate records of all IMPs received, dispensed, destroyed, or returned must be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Pertuzumab and Trastuzumab

The Sponsor will offer post-trial access to the study drugs (pertuzumab and trastuzumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for CNS metastases from HER2-positive breast cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for CNS metastases from HER2-positive breast cancer
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

The following treatments are permitted throughout the duration of the study treatment phase and during follow-up:

- Current anti-cancer therapy and associated pre-medications that the patient is receiving for HER2-positive MBC resulting in stable systemic disease except ado-trastuzumab emtansine, which must be discontinued 3 weeks before the initiation of study treatment, or lapatinib, which must be discontinued 1 week before the initiation of study treatment
- Standard therapies for preexisting medical conditions unless listed as prohibited therapy in Section 4.4.1. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrheals, anti-depressants) may be used at the investigator's discretion.
- Local radiation therapy outside of the CNS for palliation of symptoms **is** allowed.
- Corticosteroids for treatment of CNS edema are allowed. Increasing doses of steroids alone will not be taken into account in determining CNS progression in the absence of persistent clinical deterioration (see RANO-BM criteria, Appendix 4).
- Hematopoietic growth factors (e.g., granulocyte-colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor) may be used at investigator's discretion for the primary prophylaxis and/or management of treatment-emergent neutropenia and/or for secondary prophylaxis per NCCN guidelines or local standard practice.
- Bisphosphonate or denosumab therapy (to be used in accordance with the approved labeled indication and/or nationally recognized treatment guidelines)

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 21 days prior to initiation of study treatment, unless otherwise specified below:

- A non-approved, investigational therapy
- Ado-trastuzumab emtansine
- Lapatinib (must be discontinued 1 week before initiation of study treatment)

- Anthracyclines
- Any newly initiated anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, immunotherapy, and biological or targeted (e.g., lapatinib, neratinib) anti-cancer therapy
- Any systemically active oral, injected, or implanted hormonal method of contraception except for progesterone coated intrauterine devices (IUDs) that had been previously implanted
- Estrogen-replacement therapy

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Original signed Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment/registration via IXRS. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Enrollment will be tracked via registration of patients in the IXRS. Re-screening of patients is permitted on a case-by-case basis, to be determined by the Medical Monitor.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, and cancer history (including prior cancer therapies and procedures). Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat; and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Neurological status should be performed as part of these exams.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.5.4 Vital Signs, Weight, and Height

Vital signs will include measurements of heart rate, systolic and diastolic blood pressures while the patient is in a seated position, respiratory rate, and temperature.

Vital signs and weight will be assessed before treatment on Day 1 of every cycle. Weight changes of $\geq$ 10% would require the dose of trastuzumab to be adjusted. Height will be collected at screening.

4.5.5 LVEF Evaluations

LVEF evaluations will be assessed at Screening, 6 and 12 weeks (after Cycle 1, Day 1), followed by LVEF evaluations every 3 months during the treatment period. LVEF evaluations will also be conducted every 6 months during the survival follow-up period (*12* months after the treatment discontinuation visit). Measurements will be done by either ECHO or MUGA scan (with ECHO as the preferred method). Patients should be reassessed with the same technique used for baseline cardiac evaluation throughout the study.

4.5.6 Performance Status

Performance status will be measured using the ECOG Performance Status scale at screening (see Appendix 8).

4.5.7 Tumor and Response Evaluations

Tumor response for CNS disease will be assessed by the investigator according to RANO-BM criteria (see Appendix 4). Tumor response of the brain will be evaluated by magnetic resonance imaging (MRI). Progression of systemic disease will be assessed according to RECIST v1.1 (see Appendix 5). Systemic evaluations of chest, abdomen, pelvis (and neck, if clinically indicated) will be measured using computed tomography (CT), MRI, or positron-emission tomography CT (PET-CT). (Use of spiral CT or MRI is required for baseline lesions $<$ 20 mm and must be documented in medical records and used consistently throughout the study.) The same assessment modality must be used throughout the study. All tumor measurement data and CNS response data must be documented on the appropriate eCRF.

The use of oral and intravenous contrast, etc., should, as long as it is clinically possible, be kept consistent. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that it is feasible.

4.5.7.1 Scheduling of Tumor Assessments

Baseline total tumor burden must be assessed at screening (within a maximum of 28 days before first dose of study drug).

Brain Metastases

All target and non-target CNS disease must be documented at screening and reassessed at each subsequent tumor evaluation. T1-weighted perfusion MRI will be used to evaluate changes in brain metastases that indicate treatment effects. Post-baseline MRI of the brain will be conducted every 6 weeks $\times 2$, followed by every 8 weeks $\times 2$, then every 12 weeks until progression. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. An additional assessment may be conducted at the treatment discontinuation visit. For further details, see the schedule of assessments in Appendix 1.

Response for brain metastases will be assessed by the investigator, based on MRIs of the brain, physical examinations, routine neurological examinations, and corticosteroid dosing using RANO-BM criteria (see Appendix 4). An objective response (CR, PR) and progressive disease in the CNS should be confirmed by repeat assessments $4-6$ weeks after initial finding or at the next scheduled tumor assessment if it is to occur $4-6$ weeks after the initial response.

Other Sites (non-CNS) of Disease

Tumor response of systemic disease will be measured using CT, MRI, or PET-CT of the chest, abdomen, and pelvis (and neck, if clinically indicated). Assessments will be performed every 8 weeks for the first 16 weeks, followed by assessments every 12 weeks. For patients with no evidence of systemic disease at baseline, additional systemic tumor assessments (chest, abdomen, and pelvis) will be performed every 8 weeks for the first 16 weeks, followed by systemic assessments every 12 weeks. All other known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

Disease progression will be assessed by the investigator on the basis of physical examinations and scans using RECIST v1.1 (see Appendix 5). The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans).

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Hematology and chemistry testing must be done during screening and every 6 weeks within ≤ 3 days (with results available) prior to the administration of study drug.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count [neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, and other cells])

- Serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, and LDH)
- Pregnancy test
  - All women of childbearing potential (including those who have had a tubal ligation and women < 12 months after the onset of menopause, even if they have undergone surgical sterilization) will have a serum pregnancy test at screening within 7 days before the first dose of study drug (with results available prior to dosing). Urine pregnancy tests will be performed at specified subsequent visits within 7 days before every 3rd pertuzumab cycle and at the treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug.

The following samples will be sent to the Sponsor or a central laboratory for analysis:

- PK assays
  - Serum pertuzumab and trastuzumab concentrations will be determined using validated assays.
- Optional samples for the Roche Clinical Repository (RCR; see Section 4.5.9)
  - Plasma (at screening and treatment discontinuation)
  - Tissue from primary tumor or metastatic site (at screening)

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

4.5.8.1 Pharmacokinetic Assessments

Blood samples for serial measurements of pertuzumab and trastuzumab serum concentrations will be collected from all patients, according to the schedule in Appendix 3.

On specified days of study drug administration, two pre-infusion PK samples should be drawn 0 – 4 hours before the start of the infusions, and two post-infusion PK samples should be drawn 0 – 30 minutes after the end of the infusions, unless otherwise specified.

Two separate 2-mL blood samples will be collected (one sample for each analyte, pertuzumab and trastuzumab) at each timepoint as follows:

1. Week 1, Day 1 (1 sample pre-dose [2 × 2 mL; trough] and 1 sample within 30 minutes after completion of both infusions [2 × 2 mL; C_{max}]) (total of 2 samples)
2. Week 4, Day 1 (pre-dose [2 × 2 mL; trough])
3. Week 10, Day 1 (pre-dose [2 × 2 mL; trough])
4. Week 16, Day 1 (1 sample pre-dose [2 × 2 mL; trough] and 1 sample within 30 minutes after completion of both infusions [2 × 2 mL; C_{max}]) (total of 2 samples)

Each blood sample will be 2 mL in volume, totaling 24 mL for PK sampling in each patient over approximately 16 weeks.

The date and actual start and end times of infusion, and the date and actual time of each sample collection, should be recorded in the PK sampling form. Any important information concerning the sample or its collection (e.g., missed or late sample, hemolysis, etc.) should also be recorded. Instructions for the processing and labeling of all PK samples, as well as shipping instructions, are provided in the Laboratory Manual.

PK samples will be destroyed no later than 15 years after the date of final closure of the associated clinical database.

4.5.9 Patient-Reported Outcomes

PROs will be collected in this study via paper questionnaire to evaluate the impact of treatment on the symptom severity and symptom interference with daily life, due to CNS metastases, as measured by the MDASI-BT assessment from the patient's perspective. To ensure instrument validity and data standards, the instrument will be completed directly by the patient and will be administered to patients at the study site prior to any study procedures and prior to receiving treatment. The PRO questionnaire will be administered at baseline (Day 1 prior to study treatment), at every brain MRI visit, every 6 weeks $\times$2, followed by every 8 weeks $\times$2, then every 12 weeks until progression. The MDASI-BT will also be administered at treatment discontinuation visit.

The MDASI-BT includes 13 core symptom items, 9 brain tumor-specific items, and 6 interference with life items. The 9 brain tumor-specific items are: weakness on one side of the body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel patterns, and irritability. See Appendix 11 for a sample of the PRO to be used in this study.

Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 5.3.5.11.

4.5.10 Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the RCR or designated repository vendor. Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

4.5.10.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Sample Collection

The following optional samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to HER2-positive breast cancer:

- Plasma (at screening and treatment discontinuation)
- Tissue from primary tumor or metastatic site (at screening)

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.2. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.10.3 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these

specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.10.4 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.10.5 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw

consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study ML29366 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study ML29366.

4.5.10.6 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Premature termination of the study by the Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Disease progression in the CNS or systemic progression
- Initiation of a non-protocol-specified anti-cancer treatment

- Unacceptable toxicity
- Withdrawal of consent
- Investigator discretion

Patients who discontinue from study treatment will be asked to return to the clinic within 30 days of the last infusion of trastuzumab for a treatment completion visit. The visit at which a response assessment showed disease progression may be used as the treatment completion visit.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.2.1 Progression-Free Survival Follow-Up

Patients who discontinue study treatment prematurely (i.e., without disease progression) will be followed for the assessments listed below as per standard of care until disease progression:

- MRIs of brain
- Assessments of the chest, abdomen, and pelvis (only scans that were abnormal at baseline need to be repeated)

The patient's physician will be contacted to collect follow-up information.

4.6.2.2 Survival and LVEF Follow-Up

All patients will be followed for a minimum of *12* months from the date of the last dose of study drug or until death, whichever occurs first, for the assessments listed below:

- Survival (every 3 months)
- LVEF (every 6 months)

Survival information may be gathered either by phone or by clinic visit.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Safety evaluations will consist of medical interviews, recording of adverse events of all grades of severity, physical examinations, cardiac assessments (ECHO/MUGA scans), electrocardiograms [ECGs] as clinically indicated, and laboratory measurements (hematology, chemistry, and pregnancy test).

Patients will be evaluated for adverse events (all grades according to NCI CTCAE v4.0), serious adverse events, and any adverse events requiring treatment interruption or discontinuation (for pertuzumab and/or trastuzumab). Patients who, at time of CNS or systemic progression, have an ongoing adverse event leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient has withdrawn consent, the patient is lost to follow-up, or the patient starts a different anti-tumor therapy.

5.1.1 General Safety Monitoring

This study will employ an Internal Monitoring Committee (IMC) with an external Steering Committee. The purpose of the IMC and Steering Committee will be to make recommendations regarding study conduct on the basis of trial safety and efficacy data to ensure patient safety while receiving study treatment. The IMC will include a Sponsor Medical Monitor, Drug Safety Scientist, Biostatistician, and Statistical Programmer. The Steering Committee will include three external disease-state experts.

Grade 4 and 5 adverse events assessed as not related to pertuzumab or trastuzumab will be reviewed to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event/safety signals.

In addition to the monthly assessment of the incidence and nature of adverse events, serious adverse events, and laboratory abnormalities by the Medical Monitor, the IMC will meet every 6 months or earlier, if needed, based on unexpected safety signals. The IMC will review all potential cases of left ventricular systolic dysfunction (LVSD), including CHF. In addition, the IMC will monitor data on serious adverse events at least once every 3 months.

The IMC and Steering Committee may make recommendations regarding study conduct including, but not limited to, the following: performing additional safety analyses,

amending the study protocol, holding patient enrollment pending further safety evaluations, holding/discontinuing study treatment, or terminating the study. Complete details of the IMC and Steering Committee will be described in the Steering Committee charter.

5.1.2 Cardiac Safety

All patients must have a baseline LVEF $\geq$ 50%. LVEF evaluations will be assessed at Screening, 6 weeks and 12 weeks (after Cycle 1, Day 1), followed by LVEF evaluations every 3 months during the treatment period. LVEF evaluations will also be conducted every 6 months during the survival follow-up period (*12* months after the treatment discontinuation visit). Measurements will be done by either ECHO or MUGA scan (with ECHO as the preferred method). Patients should be reassessed with the same technique used for baseline cardiac evaluation throughout the study. Study treatment will be adjusted if necessary according to the algorithm described in Appendix 6.

If an investigator is concerned that an adverse event may be related to cardiac dysfunction, an additional LVEF measurement should be performed. Study treatment will be discontinued permanently in any patient who develops clinical signs and symptoms suggesting symptomatic CHF, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. CHF should be treated and monitored according to standard medical practice.

At present, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. Study treatment must be held in all patients for whom a drop of LVEF to $<$40% or 40%$-$45% with a 10%-point or greater drop below baseline. If this value is confirmed or LVEF has not recovered to $>$45% or 40%$-$45% and LESS than 10% below baseline with a repeat assessment within 3 weeks of the first assessment, using the same assessment method, study drug must be discontinued (see Appendix 6).

Patients who resume therapy will resume pertuzumab at the study dose of 420 mg every 3 weeks (840 mg loading dose of pertuzumab required if study drug is held $>$6 weeks) and trastuzumab at the study dose of 6 mg/kg weekly. Patients will be allowed to hold and resume therapy for a maximum of three times, after which the study drug must be discontinued.

The incidence of CHF will also be recorded throughout the study.

See Appendix 7 for details of NYHA classification, Appendix 9 for LVSD according to NCI CTCAE v4.0 grading, and Appendix 10 for reporting conventions for LVSD/heart failure.

5.1.3 Management of Specific Adverse Events

5.1.3.1 Pertuzumab and Trastuzumab

Administration of trastuzumab may be delayed to assess or treat adverse events, such as changes in LVEF, as shown in Appendix 6.

Since pertuzumab is also associated with a risk for cardiac dysfunction, the management of cardiac safety for patients receiving both drugs in the study, as outlined in the next section, applies to both drugs.

For additional information regarding adverse events, see the Perjeta USPI and/or the Herceptin USPI.

Table 1 Actions to be Taken in Case of Pertuzumab- and Trastuzumab-Related Toxicity

Toxicity Related to Study Treatment	Action
1. Non-hematological, Grade 1 or 2 (NCI CTCAE v4.0; excluding cardiac[a]) toxicity	Continue study treatment.
2. Non-hematological, Grade 3 or 4 (NCI CTCAE v4.0; excluding cardiac[a]) toxicity	Hold study treatment (all medication in the cycle) until recovery to Grade ≤ 2. Toxicity resolved to Grade ≤ 1 within a maximum of 2 weeks calculated from **last** administration: resume study treatment. Toxicity did **not** resolve to Grade ≤ 2 within a maximum of 2 weeks calculated from last administration: discontinue the related study medication (pertuzumab or trastuzumab) permanently. Continue treatment as deemed suitable by the local investigator.
3. Recurrence of non-hematological, Grade 3 or 4 (NCI CTCAE v4.0; excluding cardiac[a]) toxicity upon rechallenge	Discontinue the related study medication (pertuzumab or trastuzumab) permanently. Continue treatment as deemed suitable by the local investigator.
4. Cardiac toxicity (asymptomatic drop in LVEF or symptomatic CHF)	Study treatment (all medication in the cycle) to be held, continued, or resumed according to the algorithm in Appendix 6. Related study medication (pertuzumab or trastuzumab) to be discontinued permanently in case of symptomatic CHF (refer to Management of Symptomatic Cardiac Changes).
5. Cardiac toxicity (NCI CTCAE or other cardiac toxicities not covered by the treatment algorithm in Appendix 6	Actions must follow rules 1 to 3 for non-hematological toxicities.
6. Hematological toxicity – neutropenia	Hold study treatment (all medication in the cycle) until neutrophils $\geq 1.5 \times 10^9$/L.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association.

[a] Severity corresponding to NYHA classification (see Appendix 7).

Management of Cardiac Safety. All patients must have a baseline evaluation of cardiac function including a measurement of LVEF by either ECHO or MUGA scan prior to study entry. Only patients with LVEF of $\geq 50\%$ should be entered into this study. While receiving treatment, all patients will have regular monitoring of LVEF with ECHO or MUGA (at screening, 6 weeks and 12 weeks [after Cycle1, Day 1], followed by LVEF evaluations every 3 months or as clinically indicated).

During the course of therapy with pertuzumab and trastuzumab, patients should be monitored for signs and symptoms of heart failure (i.e., dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). The diagnosis must be confirmed using the same method used to measure LVEF at baseline (either ECHO or MUGA).

Management of Symptomatic Cardiac Changes. Patients who develop signs and symptoms of heart failure NCI CTCAE v4.0 Grade 2, 3, or 4 should have pertuzumab and trastuzumab held and should receive treatment for heart failure as prescribed by the Heart Failure Society of American (HFSA 2010; e.g., ACE inhibitors, angiotensin-II receptor blockers, β-blockers, diuretics, and cardiac glycosides, as needed). Consideration should be given to obtaining a cardiac consultation. LVEF should be reassessed after 3 weeks (using the same method of measurement).

If the symptoms of heart failure resolve with treatment, and cardiac function (as measured by ECHO or MUGA) improves, pertuzumab and trastuzumab may be restarted after discussion with the patient concerning the risks and benefits of continued therapy. If the patient is benefiting clinically from HER2-targeted study treatment, the benefit of continued treatment may outweigh the risk of cardiac dysfunction. If pertuzumab and trastuzumab are restarted, continued surveillance with noninvasive measures of LVEF (ECHO or MUGA) will continue per protocol.

Management of Asymptomatic Decreases in LVEF. If routine LVEF measurements document asymptomatic LVEF decreases during treatment, patient management should follow guidelines outlined in Appendix 6.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, performing protocol-specified safety laboratory assessments, performing protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.3.5.13.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including 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
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE

criteria; see Section 5.3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.5)
- Suspected transmission of an infectious agent by the study drug, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Congestive heart failure

Note: In general, asymptomatic declines in LVEF should not be reported as adverse events since LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF to a value 10 percentage points below baseline or lower, and $<$45% must be reported as an adverse event
- An asymptomatic decline in LVEF that requires treatment or that leads to discontinuation of study treatment must be reported in an expedited manner by using the Serious Adverse Event form and classifying the event as a Non-Serious Event of Special Interest

In both cases, it should be reported as "left ventricular systolic dysfunction" and graded according to NCI CTCAE v4.0.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.3.5.13 – Section 5.5.2.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.1 for seriousness criteria), severity (see Section 5.3.2), and causality (see Section 5.3.3).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.1 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.5.2).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.1 for reporting instructions), per the definition of serious adverse event in Section 5.2.1.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.1 for reporting instructions), per the definition of serious adverse event in Section 5.2.1.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.1 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
  - Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.1).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3) that are attributed by the investigator solely to progression of disease (progression of CNS or systemic disease) should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of HER2-positive MBC should be recorded only on the Survival eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Central Nervous System Metastases

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RANO-BM criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.1), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1).

No safety data related to overdosing of pertuzumab or trastuzumab are available.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.1 for further details)
- Non-serious adverse events of special interest (see Section 5.4.1 for further details)
- Pregnancies (see Section 5.4.2.2 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], Pharm.D.

Telephone No.: [redacted] ([redacted]; cell)

Alternatively, please contact the CRO Clinical Lead.

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 30 calendar days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.3.5.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified

as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

Additional information on any pertuzumab- or trastuzumab-exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (i.e., after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life). In case of a report of a congenital abnormality, a guided questionnaire will be sent out by Roche Drug Safety.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of

Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Perjeta Investigator's Brochure
- Herceptin Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Two analysis populations are defined for this study:

- Efficacy-evaluable population: includes all treated patients who have at least one follow-up CNS tumor assessment or who die without follow-up tumor assessment within 30 days from the last dose of study drug
- Safety population: includes all patients receiving any dose of study drugs

Details of the analyses will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The emphasis of this study is estimation of the ORR with a given precision, rather than hypothesis testing. ORRs of 20% or higher will be deemed clinically significant because no other therapeutic options are available for this patient population.

With 35 evaluable patients, and assuming that the study treatment is expected to lead to an ORR in CNS of 20% (7 patients), the 95% CI around the estimated ORR will be 8.4%–36.9%.

Table 4 below shows the estimated CIs for additional assumed ORRs. The final sample size will be approximately 40 patients, allowing for dropouts and loss to follow-up.

Table 4 Estimated Confidence Intervals for Additional Assumed Objective Response Rates

N	Number of Patients who Achieve CNS ORR	Rate	Lower Bound Exact 95% CI	Upper Bound Exact 95% CI	Half-Width of CI
35	1	2.86	0.07%	14.92%	7.43%
35	2	5.71	0.70%	19.16%	9.23%
35	3	8.57	1.80%	23.06%	10.63%
35	4	11.43	3.20%	26.74%	11.77%
35	5	14.29	4.81%	30.26%	12.73%
35	6	17.14	6.56%	33.65%	13.55%
35	7	20.00	8.44%	36.94%	14.25%
35	8	22.86	10.42%	40.14%	14.86%
35	9	25.71	12.49%	43.26%	15.39%
35	10	28.57	14.64%	46.30%	15.83%

CI = confidence interval; CNS = central nervous system; ORR = objective response rate.
CI based on Clopper Pearson method.

Table 5 below contains the probabilities of a particular adverse event occurring with a sample size of 40. The range of adverse event rates includes published cardiac event rates in metastatic patients receiving trastuzumab in combination with chemotherapy (Telli et al. 2007).

Table 5 Probability of Adverse Events

Incidence of Adverse Event	Probability of at Least One Adverse Event Occurring	Probability of at Least Two Adverse Events Occurring
1.00%	0.33	0.06
2.00%	0.55	0.19
3.00%	0.70	0.34
4.00%	0.80	0.48
5.00%	0.87	0.60
8.00%	0.96	0.84
10.00%	0.99	0.92
13.00%	1.00	0.97
16.00%	1.00	0.99
27.00%	1.00	1.00

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, duration of follow-up, and discontinuation from the study and discontinuation reasons will be summarized for all enrolled patients.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Patients will not be randomized in this study; all enrolled patients will receive study medication.

Demographic characteristics, medical history, baseline disease characteristics, patient treatment history, and current and previous brain MBC treatment will be summarized.

Descriptive statistics (mean, median, standard deviation, 25^{h} percentile, 75th percentile, and range) will be presented for continuous variables, such as age and time since metastatic diagnosis.

Frequency counts will be presented for categorical variables such as sex, race, age category, ECOG Performance Status, number of prior chemotherapy agents, and prior brain radiation therapy type.

Enrolled patients who are later found to be ineligible will be discontinued from the study and the reason for discontinuation will be recorded on the CRF.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR in the CNS per RANO-BM criteria. To evaluate the ORR, two sets of analyses will be performed: one is based on the efficacy-evaluable population and the other is based on the safety population. The efficacy-evaluable population is the primary population for ORR in CNS. Any patient without sufficient data to determine response (e.g., non-evaluable patients) will be classified as a non-responder. The estimate of the ORR with 95% Clopper-Pearson exact CI will be presented.

Responses to study treatment will be based on investigator assessments.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS (CNS or non-CNS), and OS.

- Among patients with an objective response, DOR will be defined as the time from documentation of the first CR or PR to the time of disease progression, relapse, or death from any cause. If a patient does not experience death or disease progression before the end of the study, DOR will be censored on the last date the patient is known to be progression free.

- CBR (CNS), defined as a combination of CR, PR, or stable disease $\geq$ 6 months in CNS, will be estimated. A 95% Clopper-Pearson exact CI for CBR will be presented.
- PFS in the CNS, defined as the time from the date of enrollment to disease progression in the CNS or death from any cause, will be calculated. If no progressive disease in the CNS and no death occurs, PFS (CNS) will be censored on the date of the last CNS tumor assessment. If a post-baseline assessment is not available, PFS (CNS) will be censored on Day 1.
- PFS (CNS or systemic), defined as the time from the date of enrollment to disease progression in the CNS or systemically, or death from any cause, will be calculated. If no progressive disease in the CNS or systemically and no death occurs, PFS will be censored on the date of the last CNS or systemic tumor assessment, whichever occurs first. If a post-baseline assessment is not available, PFS will be censored on Day 1. Progression will be recorded as the first documented progression in the CNS (for PFS CNS) or as the first documented progression at any site (for CNS or systemic disease PFS).
- OS is defined as the period from the date of enrollment until the date of death from any cause. If no death occurs, OS will be censored on the last date the patient is known to be alive.

The Kaplan-Meier approach will be used to estimate the distribution of DOR, PFS, and OS. The 95% CI for the median time to event will be calculated using the Brookmeyer and Crowley method.

6.5 SAFETY ANALYSIS

All patients who receive any amount of either study drug will be included in the safety analysis.

Exposure will be described by a summary of number of doses received, length of therapy, number of patients experiencing dose interruptions, and dose discontinuation for reasons other than disease progression.

Adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) terms and will be graded according to NCI CTCAE v4.0. Serious adverse events and non-serious adverse events of special interest, pregnancies, and serious adverse events considered related to a protocol-mandated procedure during screening will also be summarized separately by mapped terms.

NCI CTCAE v4.0 severity grade, study treatment discontinuations, and deaths will be summarized as well. Laboratory results will be summarized by using NCI CTCAE v4.0 grade.

6.6 PHARMACOKINETIC ANALYSES

Observed C_{max} and minimum concentration (C_{min}) values of pertuzumab and trastuzumab will be summarized at each specified sampling timepoint. Descriptive

statistics will be captured and compared, as appropriate, including means, medians, standard deviations, and ranges of values as appropriate. All patients who have measurable concentrations will be included in the PK analysis unless there are major protocol deviations or if information impacting PK evaluation (e.g., exact blood sampling time, labeling error, technical failure in sample analysis) are unavailable.

All pertuzumab and trastuzumab concentration data will be reported, but observed C_{min} values measured on days other than those scheduled, and similar outlier values that do not allow comparability with data from other patients, may be excluded from the analyses.

Relationships between observed and/or population model-predicted PK and safety, and between PK and efficacy, will also be examined as part of the exploratory analyses.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

PROs will be collected in this study to evaluate the impact of treatment on the CNS metastases (MDASI-BT assessment per the patient's perspective). The instrument will be completed directly by the patient and will be administered to patients upon arrival for their visit prior to receiving treatment or brain MRI procedure, every 6 weeks $\times$2, followed by every 8 weeks $\times$2, then every 12 weeks until progression.

MDASI-BT

Symptom Severity Score: A component score for the MDASI-BT symptom severity scale will be calculated by averaging of the 22 items. A prorated total score will be derived when patients score at least 12 of the 22. The score will be considered missing if less than 12 items are not completed.

Symptom Interference Score: The mean of the interference items will be calculated to represent overall symptom distress. A prorated total score will be derived when patients score at least 4 of the 6 items on a given administration. The score will be considered missing If less than 4 items are not completed.

Further details on the change from baseline analyses, as well as the time to symptom deterioration analyses based on the MDASI-BT scores, will be provided in the Statistical Analysis Plan. Further exploratory analyses will be conducted on the association of PRO scores (neurologic symptom deterioration) with response to therapy or with PFS.

6.8 INTERIM ANALYSIS

6.8.1 Planned Interim Analysis

An interim analysis will be performed when 15 patients are enrolled and have the following: 1) at least two LVEF measurements (at Week 6 and Week 12), 2) two cycles (3-week cycle) of study drug, and 3) two response measurements for review. Complete guidelines to assist in decision-making will be described in the Steering Committee

charter. For this interim analysis, the safety endpoints will be of primary consideration. Efficacy endpoints will also be examined to identify potential treatment non-benefits.

Accrual will be suspended and the study will be stopped if it is confirmed that the following scenarios have occurred:

- Two or more CHF events considered related to pertuzumab or trastuzumab in the first 15 patients treated
- None of the 15 patients with objective response or stable disease in the CNS

With this stopping rule (zero objective responses or stable disease in the CNS out of 15 efficacy-evaluable patients), the probabilities of stopping the study are 1.3%, 3.5%, 8.7%, 20.6%, and 46.3% when the true ORRs in the CNS are 25%, 20%, 15%, 10%, and 5%, respectively.

6.9 FINAL ANALYSIS

Primary efficacy analysis will be performed when all enrolled patients have been followed for *approximately 1* month after the last patient has disease progression or early discontinuation *or has been at least 6 months on treatment, whichever occurs first*. Follow-up data analysis will be performed when all the follow-up data are entered into the EDC system (or clinical database).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Both CRF and non-CRF data will be sent directly to the CRO, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.4.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms")

before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal

Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

Genentech, Inc., a member of the Roche group, will sponsor this study. A clinical research organization will provide clinical operations, data management, IXRS, day-to-day clinical science monitoring, and statistical programming. Approximately 20 study centers in the U.S. will participate in the study to enroll approximately 40 patients.

Electronic data capture will be utilized for this study. An IXRS will be used to assign patient numbers. A central laboratory will be used to manage and analyze laboratory samples for PK and biological samples.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Assessments	Screening	Study Treatment Period				Treatment Discontinuation [a]	Q3 Month Survival Follow-Up (±15 days)
		Every Week Until Progression (±2 days)	Every 3 Weeks Until Progression (±2 days)	Every 4 Weeks Until Progression (±2 days)	Every 8 Weeks Until Progression (±2 days)		
Day	**Day −28 to Day −1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Within 30 Days after Last Dose**	
Written informed consent [b]	x						
Medical history and demographic data [c]	x						
Physical examination [d]	x		x				
Vital signs, height, and weight [e]	x [e]		x				
Concomitant medications [f]	x	x				x	
LVEF monitoring [g]	x	See footnote g					x [g]
ECOG Performance Status	x						
Tumor Response and Evaluations							
MRI brain [h]	x	See footnote h					
CT, MRI, PET-CT of chest, abdomen, pelvis (and neck, if clinically indicated) [i]	x				x		
Laboratory, Biomarker, and Other Biological Sample Evaluations							
Hematology [j]	x	See footnote j					
Chemistry [k]	x	See footnote k					
Pregnancy test [l]	x	See footnote l				x	

Appendix 1
Schedule of Assessments (cont.)

Assessments	Screening	Study Treatment Period				Treatment Discontinuation [a]	Q3 Month Survival Follow-Up (±15 days)
		Every Week Until Progression (±2 days)	Every 3 Weeks Until Progression (±2 days)	Every 4 Weeks Until Progression (±2 days)	Every 8 Weeks Until Progression (±2 days)		
Day	**Day −28 to Day −1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Within 30 Days after Last Dose**	
Laboratory, Biomarker, and Other Biological Sample Evaluations (cont.)							
Serum pertuzumab and trastuzumab levels [m]	See footnote m						
Optional biomarker plasma sample [n]	x					x	
Optional archival tumor sample [o]	x						
Patient-Reported Outcomes							
MDASI-BT [p]	x				x	x	
Treatment							
Administration of pertuzumab [q]			x				
Administration of trastuzumab [r]		x					
Adverse events [s]	x	x				x	
Survival status [t]							x

C_{max} = maximum concentration; CNS = central nervous system; CR = complete response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; LVEF = left ventricular ejection fraction; MDASI-BT = M.D. Anderson Symptom Inventory-Brain Tumor; MRI = magnetic resonance imaging; PET-CT = position-emission tomography CT; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome.

Appendix 1
Schedule of Assessments (cont.)

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[a] Patients who experience clinical benefit (stable disease, PR, or CR) may continue to receive treatment with pertuzumab and trastuzumab on study until disease progression (in the CNS or systemically) or intolerable toxicity. Patients who discontinue from study treatment will be asked to return to the clinic within 30 days of the last infusion of study treatment for a treatment completion visit. The visit at which a response assessment showed disease progression may be used as the treatment completion visit.

[b] Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations, and may be obtained more than 28 days before initiation of study treatment (Day 1).

[c] Medical history includes clinically significant diseases, surgeries, and cancer history (including prior cancer therapies and procedures). Demographic data will include age, sex, and self-reported race/ethnicity.

[d] A complete physical examination will be performed at baseline. Physical examination includes evaluation of the head, eyes, ears, nose, and throat; and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits (Day 1 of each 3-week cycle or as clinically indicated), limited, symptom-directed physical examinations should be performed (record changes in patient notes). Neurological status should be performed as part of these examinations. As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Record new or worsened clinically significant abnormalities as adverse events on the Adverse Event eCRF.

[e] Vital sign assessments include measurements of heart rate, systolic and diastolic blood pressures while the patient is in a seated position, respiratory rate, and temperature. Vital signs and weight will be assessed before treatment on Day 1 of every 3-week cycle. Record abnormalities on the Adverse Event eCRF. Height and weight will be measured at screening. Weight changes of $\geq 10\%$ would require the dose of trastuzumab to be adjusted.

[f] Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[g] LVEF evaluations will be assessed at Screening, 6 and 12 weeks (after Cycle 1, Day 1), followed by LVEF evaluations every 3 months during the treatment period. LVEF evaluations will also be conducted every 6 months during the survival follow-up period (*12* months after the treatment discontinuation visit).

[h] All target and non-target CNS disease must be documented at screening and reassessed at each subsequent tumor evaluation. T1-weighted perfusion MRI will be used to evaluate changes in brain metastases that indicate treatment effects. Post-baseline MRI of the brain will be conducted every 6 weeks $\times 2$, followed by every 8 weeks $\times 2$, then every 12 weeks until progression. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. An additional assessment may be conducted at the treatment discontinuation visit. An objective response (CR, PR) in the CNS should be confirmed by repeat assessments $4-6$ weeks after initial finding or at the next scheduled tumor assessment if it is to occur $4-6$ weeks after the initial response.

Appendix 1
Schedule of Assessments (cont.)

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[i] Tumor response of systemic disease will be measured using CT, MRI, or PET-CT of the chest, abdomen, pelvis (and neck, if clinically indicated). Assessments will be performed every 8 weeks for the first 16 weeks, then every 12 weeks. For patients with no evidence of systemic disease at baseline, additional systemic tumor assessments (chest, abdomen, and pelvis) will be performed every 8 weeks for the first 16 weeks, followed by systemic assessments every 12 weeks. All other known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

[j] Hematology testing must be done during screening and every 6 weeks within ≤ 3 days (with results available) prior to the administration of study drug. Hematology testing includes: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, and other cells).

[k] Chemistry testing must be done during screening and every 6 weeks within ≤ 3 days (with results available) prior to the administration of study drug. Chemistry testing includes: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, and LDH.

[l] All women of childbearing potential (including those who have had a tubal ligation and women $<$ 12 months after the onset of menopause, even if they have undergone surgical sterilization) will have a serum pregnancy test at screening within 7 days before the first dose of study drug (with results available prior to dosing). Urine pregnancy tests will be performed at specified subsequent visits within 7 days before every 3rd pertuzumab cycle and at the treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug.

[m] On specified days of study drug administration, pre-infusion PK samples should be drawn $0-4$ hours before the start of the first infusion and post-infusion PK samples should be drawn $0-30$ minutes after the end of the infusions, unless otherwise specified. Two separate 2-mL blood samples will be collected (one sample for each analyte, pertuzumab and trastuzumab) at each timepoint as follows: Week 1, Day 1 (1 sample pre-dose and 1 sample within 30 minutes after completion of both infusions [C_{max}]) (total of 2 samples); Week 4, Day 1 (pre-dose [trough]); Week 10, Day 1 (pre-dose [trough]); Week 16, Day 1 (1 sample pre-dose and 1 sample within 30 minutes after completion of both infusions [C_{max}]) (total of 2 samples). Each blood sample will be 2 mL in volume, totaling 24 mL for PK sampling in each patient over approximately 16 weeks.

[n] Two optional exploratory biomarker plasma samples may be taken.

[o] Tissue from primary tumor or metastatic site.

[p] The PRO questionnaire will be administered at baseline (Day 1 prior to study treatment), every 6 weeks $\times 2$, followed by every 8 weeks $\times 2$, then every 12 weeks until progression.

Appendix 1
Schedule of Assessments (cont.)

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[q] A loading dose of pertuzumab will be given on Day 1 on study. Subsequent pertuzumab doses will be given every 3 weeks. However, for patients already receiving pertuzumab as part of their ongoing systemic therapy, no loading dose is required in the case of an interval < 6 weeks between last dose of pertuzumab and the first administration of on-study pertuzumab.

[r] Safety assessments should be performed and results reviewed prior to administration of trastuzumab. Note: Weight changes ≥ 10% require the dose of trastuzumab to be recalculated. Weekly doses should be no less than 5 days apart.

[s] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 5.4). After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 30 calendar days after the last dose of study drug. LVEF events will be reported for 2 years after the last dose of study drug.

[t] For PFS survival follow-up, patients who discontinue study treatment will be followed per standard of care, including MRIs of the brain and assessments of the chest, abdomen, and pelvis (only scans that were abnormal at baseline need to be repeated). For survival and LVEF follow-up, all patients will be followed for a minimum of *12* months from the date of the last dose of study drug or until death, whichever occurs first, every 3 months for survival and every 6 months for LVEF.

Appendix 2
Schedule of Assessments for Scans

Assessments	Screening Day −28 to Day −1	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32 & Every 8 Weeks until Progression	Week 36 & Every 12 Weeks until Progression	Week 40 & Every 12 Weeks until Progression	Treatment Discontinuation Within 30 Days after Last Dose	Q3 Month Survival Follow-Up (±15 days)
MRI brain [a]	X	X		X		X		X			X	X	
Scans of chest, abdomen & pelvis (neck if clinically indicated) [b]	X		X		X			X			X		
LVEF monitoring [c]	X	X		X			X			X			X

CNS = central nervous system; CR = complete response; CT = computed tomography; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET-CT = positron-emission tomography CT.

[a] All target and non-target CNS disease must be documented at screening and reassessed at each subsequent tumor evaluation. T1-weighted perfusion MRI will be used to evaluate changes in brain metastases that indicate treatment effects. Post-baseline MRI of the brain will be conducted every 6 weeks ×2, followed by every 8 weeks ×2, then every 12 weeks until progression. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. An additional assessment may be conducted at the treatment discontinuation visit. An objective response (CR, PR) and progressive disease in the CNS should be confirmed by repeat assessments 4 – 6 weeks after initial finding or at the next scheduled tumor assessment if it is to occur 4 – 6 weeks after the initial response.

[b] Tumor response of systemic disease will be measured using CT, MRI, or PET-CT of the chest, abdomen, pelvis (and neck, if clinically indicated). Assessments will be performed every 8 weeks for the first 16 weeks, then every 12 weeks. For patients with no evidence of systemic disease at baseline, additional systemic tumor assessments (chest, abdomen, and pelvis) will be performed every 8 weeks for the first 16 weeks, followed by systemic assessments every 12 weeks. All other known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

[c] LVEF evaluations will be assessed at Screening, 6 and 12 weeks (after Cycle 1, Day 1), followed by LVEF evaluations every 3 months during the treatment period. LVEF evaluations will also be conducted every 6 months during the survival follow-up period (*12* months after the treatment discontinuation visit).

Appendix 3
Schedule of Pertuzumab and Trastuzumab Pharmacokinetic Assessments

Visit	Timepoint	Sample Types
Week 1, Day 1	Pre-dose (trough)	PK trastuzumab, PK pertuzumab (serum)
	Post-infusions (C_{max})	PK trastuzumab, PK pertuzumab (serum)
Week 4, Day 1	Pre-dose (trough)	PK trastuzumab, PK pertuzumab (serum)
Week 10, Day 1	Pre-dose (trough)	PK trastuzumab, PK pertuzumab (serum)
Week 16, Day 1	Pre-dose (trough)	PK trastuzumab, PK pertuzumab (serum)
	Post-infusions (C_{max})	PK trastuzumab, PK pertuzumab (serum)

C_{max} = maximum concentration; PK = pharmacokinetic.

At each timepoint, 2 × 2 mL samples will be collected, totaling 24 mL for PK sampling in each patient over approximately 16 weeks.

Pre-dose samples can be collected up to 4 hours prior to infusion. Post-infusion samples can be collected within 30 minutes after completion of both infusions.

Appendix 4
Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria: Modified Excerpt from Original Publication

Definitions

Definition of Measurable Disease: Measurable disease is defined as a contrast enhancing lesion that can be accurately measured in at least one dimension with a minimum size of 10 mm, visible on two or more axial slices that are preferably $\leq$ 5 mm apart with 0-mm skip (and ideally $\leq$ 1.5 mm apart with 0-mm skip). In addition, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. In the event the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least two times the slice thickness. If there are interslice gaps, this also needs to be considered in determining the minimum size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring $\geq$ 10 mm in longest diameter and $\geq$ 5 mm in the perpendicular plane. The cystic or surgical cavity should not be measured in determining response (Figure 1 in the original publication).

Definition of Non-measurable Disease: All other lesions, including lesions with longest dimension $<$ 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

Specifications of Methods of Measurement

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. It is important to use imaging techniques that are consistent across all imaging timepoints in order to ensure that the assessment of interval appearance or disappearance of lesions or of change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging (for example, Appendix A of the original publication) is particularly important when evaluating lesions $<$ 10 mm in LD and/or small changes in lesion size.

Imaging Modality: Gadolinium-enhanced MRI is the best currently available, sensitive, and reproducible method to measure CNS lesions selected for response assessment. Suggested brain MRI specifications are detailed in Appendix A of the original publication.

A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD). All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not

Appendix 4
Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria: Modified Excerpt from Original Publication (cont.)

required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'.

Definition of Best Overall CNS Response

Best overall CNS response represents a composite of radiographic CNS target and non-target response (see definitions above), corticosteroid use, and clinical status. In non-randomized trials where CNS response is the primary endpoint, confirmation of PR or CR at least 4 weeks later is required to deem either one the best overall response.

At each protocol-specified timepoint, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 1 shows the additional corticosteroid and clinical status requirements to deem a PR or CR.

Evaluation of Target Lesions

Complete response (CR): Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.

Partial response (PR): At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive disease (PD): At least a 20% increase in the sum LD of CNS 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%, at least one lesion must increase by an absolute value of $\geq$5 mm to be 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 LD while on study.

Evaluation of Non-Target Lesions

Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

CR: Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

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

Appendix 4
Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria: Modified Excerpt from Original Publication (cont.)

PD: Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

Special Notes on the Assessment of Target and Non-Target CNS Lesions:

a) *Target lesions that become too small to measure:* While on study, all CNS target lesions should have their actual measurement recorded, even when very small (*e.g.*, 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) that the radiologist does not feel comfortable assigning an exact measure, a default value of 5 mm should be recorded on the case report form.

b) *Lesions that coalesce on treatment:* As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum LD of each individual lesion. 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 maximum LD for the 'coalesced' lesion.

c) *Definition of new lesion(s):* The finding of a new CNS lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with ≤ 1.5 mm slice thickness, then the new lesion should also be visible in axial, coronal, and sagittal reconstructions of ≤ 1.5 mm projections. If a new lesion is equivocal, for example because of its small size (*i.e.*, ≤ 5 mm), continued therapy may be considered, 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 showing the new lesion. In the case of immunotherapy, new lesions alone may not constitute progressive disease (see "Guidance in the case of new lesion(s) while on immunotherapy" below).

d) *Definition of Unequivocal Progression of Non-Target Lesion(s): When the patient also has measurable disease*, to achieve 'unequivocal progression' on the basis of non-target disease alone, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. *When the patient has only non-measurable disease,* there must be an overall level of substantial worsening to merit discontinuation of therapy.

Appendix 4
Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria: Modified Excerpt from Original Publication (cont.)

e) *Guidance in the Case of Uncertain Attribution of Radiographic Findings and/or Equivocal Cases:* The RANO-BM group acknowledges that in the case of patients followed after SRS or during immunotherapy-based approaches, there may be radiographic evidence of enlargement of target and non-target lesions which may not necessarily represent tumor progression. If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is required to distinguish true progression versus treatment effect as standard MRI alone is not sufficient. The methods used to distinguish between the two entities should be specified prospectively in the clinical protocol. Patients may be continued on protocol therapy pending further investigation with one or more of the following options: (1) Repeat the scan at the next protocol scheduled evaluation or sooner, and generally within ~6 weeks. An investigator may choose a shorter time interval in the case of progressive symptoms or other clinically concerning findings. If there is continued increase in enhancement concerning for tumor growth, then this may be consistent with radiographic progression and the patient should be taken off study (Figure 2 in the original publication). If the lesion is stable or decreased in size, then this may be consistent with treatment effect and the patient may remain on study (Figure 3 in the original publication). For patients with equivocal results even on the next restaging scan, the scan may be repeated again at a subsequent protocol scheduled evaluation or sooner although surgery and/or use of an advanced imaging modality (in the case of SRS) are strongly encouraged. (2) Surgical pathology obtained via biopsy or resection. (3) For SRS treated lesions, an advanced imaging modality such as perfusion MR imaging, MR spectroscopy, or ^{18}FLT or ^{18}FDG positron emission tomography (PET) may be used as additional evidence of tumor progression or treatment effect/radionecrosis. Upon review of the literature and extensive discussions by the Working Group, we were not able to conclude that any one modality or approach can be recommended across all patients to distinguish between radiation necrosis versus true progression, as the literature is not sufficiently robust, and recommend clinical judgment and involvement of a multidisciplinary team. We recognize this is less than satisfactory and agree that developing more sensitive and specific methods for distinguishing between treatment effect and tumor progression are needed. We should also note that these advanced imaging modalities have not been extensively studied with regards to immunotherapy-based approaches and therefore are cannot be recommended for distinguishing tumor progression versus immune-related changes at this time. Regardless of the additional testing obtained, if subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised. Patients may also have an equivocal finding on a scan (for example, a small lesion that is not clearly new). It is

permissible to continue treatment until the next protocol scheduled evaluation. If the subsequent evaluation demonstrates that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

f) *Guidance in the Case of New Lesion(s) while on Immunotherapy:* For patients receiving immunotherapy-based approaches, an initial increase in the number and size of metastases may be followed by radiographic stabilization or regression. This may be related to the mechanism of action for immunotherapy, including immune infiltrates as well as the time required for development of an effective immune response. Thus, progressive disease will be defined not solely by the appearance of new lesions but by at least a 20% increase in the sum of the LD of CNS target lesions and the new lesion(s); or unequivocal progression of existing enhancing non-target CNS lesions; or unequivocal progression of existing non-enhancing (T2/FLAIR) CNS lesions; or clinical decline related to tumor. If immune-related radiographic changes are suspected, we advise not changing treatment until a short interval scan is obtained. If the subsequent evaluation confirms that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Notes Regarding Corticosteroid Use and Clinical Deterioration:

a) An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression.

b) The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Appendix 4
Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) Criteria: Modified Excerpt from Original Publication (cont.)

Table 1

Summary of the Proposed RANO Response Criteria for CNS Metastases

Criterion	CR	PR	SD	PD
Target lesions	None	≥30% decrease in sum LD relative to baseline	<30% decrease relative to baseline but<20% increase in sum LD relative to nadir	≥20% increase in sum LD relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA+
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any+

Abbreviations: CNS=central nervous system; CR=complete response; LD=longest dimension; NA=not applicable; PD=progressive disease; PR=partial response; RANO=Response Assessment in Neuro-Oncology; SD=stable disease.

*Progression occurs when this criterion is met.

**New lesion=new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, 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 showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression (See "Guidance in the Case of New Lesion(s) while on Immunotherapy").

+Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

a. Measurable Tumor Lesions

Tumor Lesions. 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 as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). In addition, lymph nodes in the pelvis must measure $\geq$ 2 cm in greatest diameter to be considered target lesions. At baseline and 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.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 10 but $<$ 15 mm) 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, peritoneal spread, and abdominal

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring 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 malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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 usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, with use of 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 treatment.

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication (cont.)

b. 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 the study. Imaging-based evaluation should always be the preferred option.

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

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 on the basis of 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.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine whether substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication (cont.)

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

When 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. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, in addition, should 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 lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the 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 whether 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, 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 that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of <10 mm are considered non-pathological and should not be recorded or followed.

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication (cont.)

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 of 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 of diameters will be used as a 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 Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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 of 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 (nadir), including baseline
  - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  - 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 on study

b. 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 < 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 CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Target Lesions That Become Too Small to Measure. During the 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 that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- 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 and below measurable limit (BML) should be ticked. (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 is too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.

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 lesion. 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 maximum longest diameter for the coalesced lesion.

c. 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. Whereas some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size (<10 mm short axis).

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication (cont.)

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions
  - The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the 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 in a magnitude that, even in the 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 qualify 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. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have 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 whether 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; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or 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. Although 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.

Bone Only Disease: Since bone lesions are not considered measurable, patients with bone only disease will be evaluated for progression only. Progression is defined as the appearance of new lytic lesions or other new bone destruction thought to be related to cancer by X-ray, MRI, or CT scan or a bone event requiring intervention (surgery) if not

associated with trauma or other obvious cause. Changes in bone scan or ^{18}F-sodium fluoride (NaF) PET scan should not be used to define progression. Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. The appearance of new lesions on bone scan or ^{18}F-NaF PET scan may constitute progressive disease if associated with clinical symptoms suggestive of disease progression. The occurrence of a pathologic fracture at a site previously recognized bone disease may constitute progressive disease if not associated with trauma or other obvious cause. Bone pain requiring radiation will constitute progressive disease. Increase in pain at a site of previously recognized bone disease may constitute progressive disease if it is persistent and not associated with other obvious cause.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal; that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR. 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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify whether 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 RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication (cont.)

Table 1
Timepoint Response: Patients with Target Lesions
(with or without Non-Target Lesions)

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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2
Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint 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 during the study 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, since this equates with the case being not evaluable at that timepoint.

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1): Modified Excerpt from Original Publication (cont.)

Table 3
Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the 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 timepoint. Under these circumstances, the original CR should be changed to PR, and the best response is PR.

c. 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 CRF.

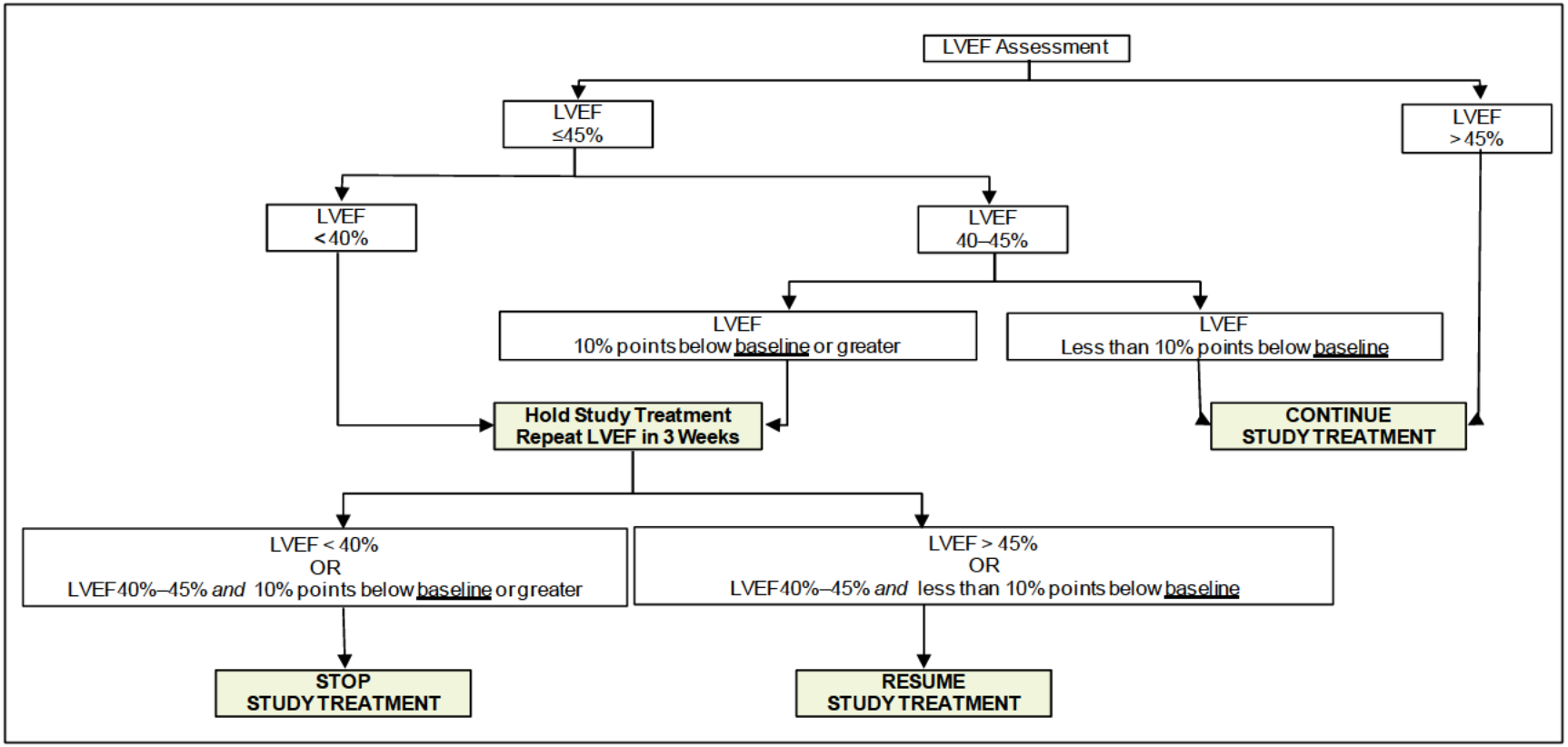
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a

descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and Table 3.

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.

In studies for which patients with advanced disease are eligible (e.g., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 6
Asymptomatic Decline in LVEF:
Algorithm for Continuation and Discontinuation of Pertuzumab and Trastuzumab Based on LVEF Assessments



Appendix 7
New York Heart Association Classification of Functional Cardiac Capacity

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 8
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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 housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 9
Left Ventricular Systolic Dysfunction Grading

NCI CTCAE Grade	Left Ventricular Systolic Dysfunction Severity
1	–
2	–
3	Symptomatic due to drop in ejection fraction responsive to intervention
4	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated
5	Death

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

LVSD Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

Appendix 10
Reporting Conventions for Left Ventricular Systolic Dysfunction/Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF $<10\%$ points from baseline or tan an LVEF $\geq 45\%$	No additional reporting required, LVEF results to be reported on eCRF	N/A	N/A
Asymptomatic decline in LVEF $\geq 10\%$ points from baseline or tan an LVEF $<45\%$	AE (eCRF)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of pertuzumab and trastuzumab	AE (eCRF) and on-serious AESI (reported on an SAE form)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure/CHF (symptomatic LVSD)	AE (eCRF) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA Class

AE = adverse event; CHF = congestive heart failure; eCRF = electronic Case Report Form; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; N/A = not applicable; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA = New York Heart Association; SAE = serious adverse event.

Note: Any symptomatic LVSD event must be reported as "heart failure."

[a] Report the status "asymptomatic" and the LVEF value in the comments field as appropriate.

Appendix 11
M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT)

The MDASI-BT consists of 28 items and is a multi-symptom measure of cancer-related symptoms (Cleeland et al. 2000) that are sensitive to disease and treatment changes. The MDASI-BT is composed of the symptom severity scale and the symptom interference scale. In the symptom severity scale, patients rate the severity of their symptoms in the last 24 hours on 0 – 10 numeric scales, ranging from “not present” to “as bad as you can imagine.” In the symptom interference scale, patients rate interference with daily activities caused by their symptoms on 0 – 10 numeric scales ranging from “did not interfere” to “interfered completely.” This instrument is brief, takes less than five minutes to complete, is easily understood and validated in the cancer population (Cleeland 2008).

Appendix 11
M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT) (cont.)

Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____

Protocol #: _____

PI: _____

Subject Initials: ☐☐☐

MD Anderson # : ☐☐☐☐☐☐

PDMS # : ☐☐☐☐

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Appendix 11
M.D. Anderson Symptom Inventory-Brain Tumor (MDASI-BT) (cont.)

Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: _____

MD Anderson # : ☐☐☐☐☐☐ PDMS # : ☐☐☐☐

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your quality of life?

Symptoms frequently interfere with how well we function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○