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)**

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STATISTICAL ANALYSIS PLAN

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STUDY DRUG:	Pertuzumab (RO4368451), Trastuzumab (RO0452317)
IND NUMBER:	4517
SPONSOR:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080
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1. BACKGROUND

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).

2. STUDY DESIGN

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 in the protocol 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.

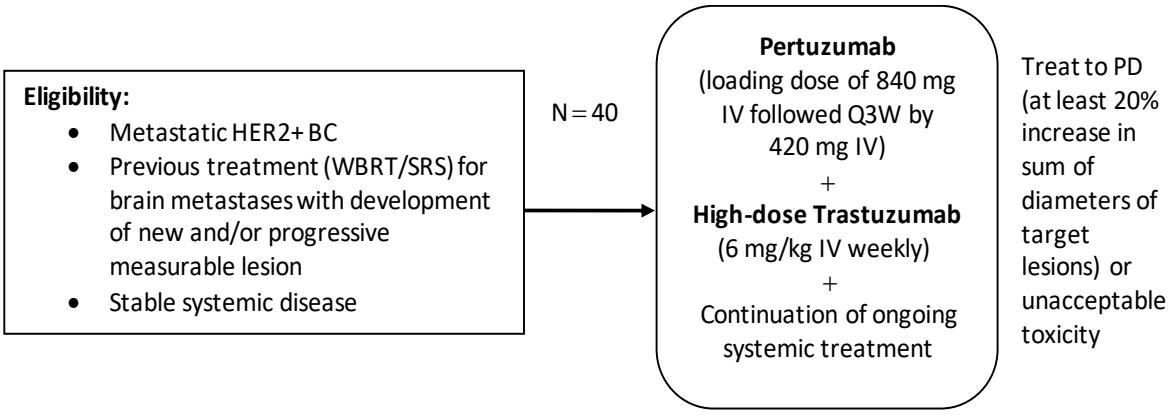
2. Patients receiving treatment with lapatinib

– 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 A.

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.

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.

Final Analysis

The study 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).

2.1 PROTOCOL SYNOPSIS (INCLUDING SCHEDULE OF ASSESSMENT)

Refer to the protocol for the protocol synopsis. See Appendix A for the schedule of assessments and Appendix B for the schedule of assessments for scans.

2.2 OUTCOME MEASURES

2.2.1 PRIMARY EFFICACY OUTCOME MEASURES

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

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

2.2.2 SECONDARY EFFICACY OUTCOME MEASURES

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

- 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)
  - Tumor response in CNS will be assessed per RANO-BM criteria (see Appendix 4 in the protocol).
  - Non-CNS tumor response will be assessed by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 5 in the protocol).

2.2.3 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 in the protocol)
- Characterization of changes in left ventricular ejection fraction (LVEF) and changes in LVEF from baseline over the course of the study (see Appendix 6 in the protocol)
- Clinically significant laboratory test abnormalities

2.2.4 PHARMACOKINETIC OUTCOME MEASURES

Blood samples for measurements of pertuzumab and trastuzumab serum concentrations will be collected from patients according to the schedule below:

– Week 1, Day 1 (pre-dose and at 30 minutes after the end of the infusions [maximum concentration (C_{max})])

– Week 4, Day 1 (pre-dose [trough])

– Week 10, Day 1 (pre-dose [trough])

– Week 16, Day 1 (pre-dose and at 30 minutes after the end of the infusions [C_{max}])

2.2.5 PATIENT-REPORTED OUTCOME MEASURES

The PRO outcome measure for this study is as follows:

- Scores from the MDASI-BT assessment

2.2.6 EXPLORATORY OUTCOME MEASURES

To explore the relationship between pertuzumab and high-dose trastuzumab exposure expressed as PK paramters and efficacy and safety endpoints.

2.3 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 1 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 1 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 2 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 2 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

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

This is an open-label, single arm study. There is no randomization in the study.

3.2 DATA MONITORING

The Genentech team will monitor study data and will consult with an external Steering Committee. The purpose of the Genentech Study Team 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 Genentech team will include the CMM, MSDs, LSR, Drug Safety Scientist, Biostatistician, and Statistical Programmer. The Steering Committee will include at least 3 external disease-state experts and is governed by the Steering Committee Charter.

4. STATISTICAL METHODS

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

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

No formal statistical hypotheses will be tested in the study.

4.1 ANALYSIS POPULATIONS

The analysis populations are defined below.

4.1.1 INTENT-TO-TREAT POPULATION

Intent-to-Treat (ITT) population includes all enrolled patients in the study, regardless of whether they are exposed to study drugs (Pertuzumab or Trastuzumab).

4.1.2 EFFICACY EVALUABLE POPULATION

Efficacy evaluable population includes all patients in the ITT population who received any dose of Pertuzumab or Trastuzumab and had at least one follow-up CNS tumor assessment or who received any dose of Pertuzumab or Trastuzumab, but die without follow-up tumor assessment within 30 days from the last dose of study drug.

This will be the population used for efficacy analyses unless otherwise noted.

4.1.3 PHARMACOKINETIC EVALUABLE POPULATION

Pharmacokinetic evaluable population includes all patients in the ITT population who received any dose of Pertuzumab or Trastuzumab and had at least one PK assessment 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.

4.1.4 PATIENT-REPORTED OUTCOMES EVALUABLE POPULATION

Patient-reported outcomes evaluable population includes all patients in the ITT population who received any dose of Pertuzumab or Trastuzumab and had both a non-missing baseline and at least one post-baseline PRO assessment. Summary statistics of the symptom severity score and symptom interference score will be presented at each scheduled visit, and the change from baseline scores will be presented at each post-baseline visit.

4.1.5 SAFETY POPULATION

Safety population includes all patients in the ITT population who received any dose of Pertuzumab or Trastuzumab.

4.2 ANALYSIS OF STUDY CONDUCT

The number of enrolled patients will be tabulated by study site and overall. Analysis populations, patient disposition, primary reason for premature discontinuation, and protocol violations (including inclusion/exclusion criteria not met), and duration of follow-up will be tabulated for all patients enrolled. Eligibility, protocol violations, and premature discontinuations will be presented in data listings.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

This is a single-arm study and therefore no treatment group comparisons will be performed.

Demographic and baseline characteristics, such as age, sex, reproductive status, ethnicity, race, age category, height, weight, BMI, ECOG score, time from metastatic diagnosis to the first dose of study drug, time from metastatic diagnosis to CNS diagnosis, time from CNS metastases to the first dose of study drug, number of prior chemotherapy agents, and prior brain radiation therapy type will be summarized using mean, median, standard deviation, 25th percentile, 75th percentile, and range for continuous variables and using counts and percentages for categorical variables. Individual patient demographic and baseline characteristics will also be presented in a data listing.

Verbatim description of each medical history will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA, the most current version). The number (percentage) of patients in the ITT population reporting any medical condition will be summarized by SOC and preferred term. Subject data listings of general medical history, cardiac history, breast cancer history, prior EBC surgery, non-breast cancer related surgery and procedures history, EBC and MBC systemic treatment history will be presented.

All verbatim terms for medications recorded in the CRF will be coded by Genentech/Roche and assigned a preferred term and an anatomic therapeutic class (ATC) term using International Non-proprietary Name (INN) drug terms and procedures. Medications with (1) start date on or after the first dose of study drug up to 30 days after the last dose of study drug or (2) start date before the first dose of study drug and stop date on or after the first dose of study drug or ongoing are considered as *concomitant medications*. Medications with stop date before the first dose of study drug are considered as *prior medications*. Concomitant medications and prior medications will be summarized separately, based on the ITT population, with number (percentage) of patients in each ATC class and preferred drug name. Prior and concomitant medications will also be presented in a data listing. Listings of concomitant corticosteroids, screening systemic status, CNS treatment history, prior and on-study breast cancer radiotherapy, and on-study MBC systemic treatment will also be presented.

Patient treatment history, and current/previous brain MBC treatment will be summarized in separated tables.

4.4 EFFICACY ANALYSES

4.4.1 PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint is ORR (confirmed CR or confirmed PR) 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 the 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. Water fall plot of the percent change in the total sum of target lesion diameter will be presented.

Responses to study treatment will be based on investigator assessments.

4.4.2 SECONDARY EFFICACY ENDPOINTS

Secondary efficacy endpoints include DOR in the CNS, CBR for the CNS, PFS in the CNS, PFS in the systemic, PFS (CNS or systemic), 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.

4.4.2.1 Duration of Response

Among patients with an objective response, duration of response 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, relapse, or disease progression before the end of the study, duration of response will be censored on the last date the patient is known to be progression free.

Median duration of response and the corresponding 95% CI will be presented. Minimum, the first quartile, the third quartile, and maximum of the duration of response will also be presented. Swimmer plot of the duration of response will be presented for subjects with objective response.

4.4.2.2 Clinical Benenfit Rate

CBR (CNS), defined as a combination of confirmed CR, confirmed PR, or stable disease (≥ 4 months and ≥ 6 months, respectively) in CNS, will be calculated. A 95% Clopper-Pearson exact CI for CBR will be presented. Note that duration of CBR will be calculated with SD in ≥ 4 and ≥ 6 months, respectively. Swimmer plot of the duration of response will be presented for subjects with clinical benefit.

4.4.2.3 Progression-Free Survival in the CNS

PFS (CNS), defined as the time from the date of first dose 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. Median PFS (CNS) and the corresponding 95% CI will be presented. Minimum, the first quartile, the third quartile, and maximum of the duration of response will also be presented.

4.4.2.4 Progression-Free Survival in the Systemic

PFS (systemic), defined as the time from the date of first dose to disease progression in the systemic or death from any cause, will be calculated. If no progressive disease in the systemic and no death occurs, PFS (systemic) will be censored on the date of the last systemic tumor assessment. If a post-baseline assessment is not available, PFS (systemic) will be censored on Day 1. Median PFS (systemic) and the corresponding 95% CI will be presented. Minimum, the first quartile, the third quartile, and maximum of the duration of response will also be presented.

4.4.2.5 Progression-Free Survival (CNS or Systemic)

PFS (CNS or systemic), defined as the time from the date of first dose 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. Median PFS (CNS or systemic) and the corresponding 95% CI will be presented. Minimum, the first quartile, the third quartile, and maximum of the duration of response will also be presented.

4.4.2.6 Overall Survival

OS is defined as the period from the date of first dose 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.

Median OS and the corresponding 95% CI will be presented. Minimum, the first quartile, the third quartile, and maximum of the OS will also be presented.

4.4.3 SENSITIVITY ANALYSES

Sensitivity analysis is currently not planned.

4.4.4 SUBGROUP ANALYSES

Subgroup analysis is currently not planned.

4.4.5 EXPLORATORY ANALYSES

Analyses will be conducted to explore the relationship between Pertuzumab / Trastuzumab exposure and PK parameters and efficacy / safety endpoints.

4.5 SAFETY ANALYSES

Safety analyses will be performed on the safety population. Baseline value is defined as the last observation prior to the initiation of study drug.

Due to unscheduled laboratory or other safety assessments, the safety analyses will use the actual visit dates and the time windows shown below to define the visit cycles. Time window for screening (baseline) is defined from study day -28 up to study day -1. For post baseline visits, the time windows are generated in such a way that the windows are not overlapping. If more than one assessment is measured within the same visit window, the assessment closest to the scheduled day in the specific visit window will be used for the analysis for that visit. Abnormal values may have to be reported as Adverse Event. For all safety analyses, Day 1 is defined as the day on which the patient receives the first dose of study drug.

Time Windows for Lab Data (Hematology, Serum Chemistry)			
Scheduled Visit Number	**Visit**	**Scheduled Study Day of Assessment (day)**	**Time interval (day)**
0	Screening/Baseline	<1	-28 to -1
1	Week 6	43	1 to 63
2	Week 12	85	64 to 105
3	Week 18	127	106 to 147
4	Week 24	169	≥ 148

Time Windows for Vital Signs			
Scheduled Visit Number	**Visit**	**Scheduled Study Day of Assessment (day)**	**Time interval (day)**
0	Screening/Baseline	<1	-28 to -1
1	Week 3	22	1 to 32
2	Week 6	43	33 to 53
3	Week 9	64	54 to 74
4	Week 12	85	75 to 95
5	Week 15	106	96 to 116
6	Week 18	127	117 to 137
7	Week 21	148	138 to 158
8	Week 24	169	≥ 159

4.5.1 EXPOSURE OF STUDY MEDICATION

Study drug exposure will be summarized descriptively (mean, median, standard deviation, 25th percentile, 75th percentile, and range) by total dose (mg) received, number of cycle received, average dose received per cycle, number of doses received, and treatment duration (weeks) for Pertuzumab or Trastuzumab, respectively. In addition, the number and percentage of patients experiencing dose missed, delayed, interrupted, slowed down, and discontinued (for reasons other than disease progression) will be tabulated.

Study drug administration data will also be presented in data listings.

4.5.2 ADVERSE EVENTS

Verbatim descriptions of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA, version 18.1 or newer) preferred terms (PT) and System Organ Classes (SOC).

AEs will also be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

All AEs occurring on or after Day 1 of study treatment until 30 days after the last dose of study treatment (i.e., treatment-emergent adverse events (TEAEs)) will be summarized by System Organ Classes, preferred terms, and NCI CTCAE grade. In the AE summaries, a patient having the same event more than once will be counted only once for that event type. For AEs of varying severity, the highest (worst) grade will be used in the summaries. AEs related to study drug are those suspected to be caused by Pertuzumab or Trastuzumab. Missing severity or relationship to study drug will be imputed as described in section 4.8.

Summaries of the following AEs will be provided:

1. Overall summary of TEAEs
2. Death and cause of death
3. TEAEs by NCI CTCAE grade
4. TEAEs related to study drug by NCI CTCAE grade
5. Serious TEAEs by NCI CTCAE grade
6. Serious TEAEs related to study drug by NCI CTCAE grade
7. TEAEs with incidence rate ≥ 5%
8. TEAEs related to study drug with incidence rate ≥ 5%
9. TEAEs with Grade 3 and above
10. TEAEs related to study drug with Grade 3 and above
11. TEAEs leading to any study drug discontinuation
12. TEAEs leading to Pertuzumab only discontinuation
13. TEAEs leading to Pertuzumab infusion delay, slow down, or interruption
14. TEAEs leading to Trastuzumab dose modification
15. TEAEs of special interest (defined below)
16. TEAEs of special interest related to study drug
17. Time to the first incidence of TEAEs of special interest

The following AEs are considered of special interest (AESIs):

- an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice
- Suspected transmission of an infectious agent by the study drug (to be defined)
- Congestive heart failure

- An asymptomatic decline in LVEF (a value 10 percentage points below baseline or lower, and < 45%) that requires treatment or that leads to discontinuation of study treatment

Overall summary of TEAEs will be presented for number of deaths, patients with any TEAE, serious TEAE, TEAE with severity Grade 3 or higher, TEAE of special interest, infusion related reaction, TEAE leading to interruption of any study drug, and TEAE leading to withdrawal of any study drug. All AEs of special interest will be summarized in another table. A separate table will summarize number and percentage of death and cause of death.

All recorded AEs, SAEs, AEs leading to study drug discontinuation, deaths, and supplemental data for AEs of special interest will be presented in data listings. A glossary of AE verbatim terms and preferred terms will also be provided.

4.5.3 LABORATORY DATA

The incidence of NCI CTCAE, v4.0, Grade 3 and 4 hematology and serum chemistry abnormalities will be summarized at each protocol-specified collection timepoint for each parameter. Refer to Appendix F, Section 6.6.1 for the NCI CTCAE V4.0 Grades for laboratory paramaters.

Laboratory data (hematology and serum chemistry) will also be presented in data listings. Patients who became pregnant during the study period will be listed separately.

4.5.4 VITAL SIGNS

Vital signs assessments will be performed before treatment on Day 1 of every 3-week cycle. Descriptive statistics for vital signs parameters (i.e. heart rate, systolic and diastolic BP, respiratory rate, and temperature) at each cycle and changes from baseline (Cycle 1 Day 1) to each following cycle will be presented.

Vital signs data will also be presented in data listing.

4.5.5 ELECTROCARDIOGRAM

ECG data will be presented in data listing.

4.5.6 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).

LVEF results and interpretations will be summarized at each scheduled visit. The corresponding LVEF data will be presented in data listing.

4.6 PHARMACOKINETIC ANALYSES

Observed C_{max} and minimum concentration (C_{min}) values of pertuzumab and trastuzumab will be summarized at each specified sampling timepoint. Summary statistics, including arithmetic mean, geometric mean, median, standard deviation, and range, and coefficient of variation, will be presented for the PK-evaluable population.

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.

4.7 PATIENT REPORT OUTCOMES ANALYSES

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.” For details of the scoring algorithm, please refer to Appendix F, Section 6.6.2.

For each individual item and each scale, the data and their change from baseline values will be summarized descriptively at each protocol-specified timepoint. Data listings of individual scores and scale scores will also be presented.

To explore the relationship of ORR with PRO endpoints, subjects will be divided into two groups by symptom severity scale score, one group with score <= median and the other group with score > median. Similarly, subjects will be divided into two groups by symptom interference scale. ORR and the corresponding 95% CI will be presented.

4.8 HANDLING OF DROPOUTS, MISSING/INCOMPLETE DATA, OR OUTLIERS

No imputation will be performed for missing efficacy data.

AEs with missing relationship to study drug will be counted as 'Related', and AEs with missing CTCAE grade will be imputed as grade 3. Incomplete onset dates for AEs and concomitant medications will be imputed according to the following rules:

- In case the day is missing this will be replaced by the 1st of the month.
- In case of missing day and month this will be replaced by the January 1st.

If the imputation of the onset date leads to AEs or concomitant medications occurring before treatment start, the start date will be set to treatment start date.

Incomplete end dates will be imputed according to the following rules:

- In case the day is missing this will be replaced by the last day of the month.
- In case of missing day and month this will be imputed as December 31st.

If the imputation of the end date leads to AEs or concomitant medications ending after date of last contact, the end date will be set to date of last contact.

4.9 INTERIM ANALYSES AND/OR SAFETY REVIEWS

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. For this interim analysis, the safety endpoints will be of primary consideration. Overall summary of TEAEs, TEAEs and serious TEAEs by NCI CTCAE grade, TEAEs with Grade 3 and above, TEAEs lead to any study drug discontinuation, summary of the incidence of NCI CTCAE, v4.0, Grade 3 and 4 Lab results, summary of vital signs and ECG will be reviewed. Efficacy endpoints (ORR, DOR, PFS in CNS per RANO-BM criteria) will also be examined to identify potential treatment non-benefits. Complete details of the data outputs will be described in the Steering Committee charter. In addition, summary of all AEs, AEs and serious AEs by NCI CTCAE grade, AEs with Grade 3 and above, AEs lead to any study drug discontinuation will also be presented.

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.

5. REFERENCES

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6. APPENDICES

6.1 APPENDIX A: 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	x	x	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					

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**	
Pregnancy test [l]	x	See footnote l				x	
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			x				
Administration of trastuzumab [q]		x					

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)			
Day	**Day – 28 to Day – 1**	**Day 1**	**Day 1**	**Day 1**	**Day 1**	**Within 30 Days after Last Dose**	
Adverse events [r]	x	x				x	
Survival status [s]							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.

[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 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.

[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 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 16 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, magnesium, phosphorus, total and direct bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase, LDH, and uric acid.

[l] All women of childbearing potential (including those who have had a tubal ligation and women $<$ 12 months after the onset of menopause unless 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 prior to every 3rd pertuzumab cycle ($<$ 7days) 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 (pre-dose and at 30 minutes after the end of the infusions [C_{max}]); Week 4, Day 1 (pre-dose [trough]); Week 10, Day 1 (pre-dose [trough]); Week 16, Day 1 (pre-dose and at 30 minutes after the end of the infusions [C_{max}]). 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 4 weeks for the first 16 weeks, and every 8 weeks thereafter while the patient is receiving study treatment.

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

[r] 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.

[s] 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.

6.2 APPENDIX B: 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 Discont-inuation 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) 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 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 16 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).

6.3 APPENDIX C: 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 up to 30 minutes after end of infusion.

6.4 APPENDIX D: STATISTICAL METHODS REQUIRING INPUT

There is no statistical method requiring input.

6.5 APPENDIX E: DOCUMENTATION OF ADDITIONAL ANALYSES PERFORMED AFTER DATABASE LOCK

There are no additional analyses planned at this point.

6.6 APPENDIX F: DATA HANDLING RULES

6.6.1 NCI CTCAE V4.0 GRADES FOR LABORATORY PARAMETERS

Panel: Chemistry

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline Phosphatase	U/L	(ULN, 2.5*ULN]	(2.5*ULN, 5*ULN]	(5*ULN, 20*ULN]	>20*ULN
ALT (increased)	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
AST (increased)	U/L	(ULN, 3.0*ULN]	(3.0*ULN, 5.0*ULN]	(5*ULN, 20*ULN];	>20*ULN
Bilirubin	umol/L	(ULN, 1.5*ULN]	(1.5*ULN, 3*ULN]	(3*ULN, 10*ULN]	>10*ULN
Calcium high (Hypercalcemia)	mmol/L	(ULN, 2.9]	(2.9, 3.1]	(3.1, 3.4]	>3.4
Calcium low (Hypocalcemia)	mmol/L	[2.0, LLN)	[1.75, 2.0)	[1.5, 1.75) ; hospitalization indicated	[0, 1.5); life threatening consequences
Creatinine (increased)	umol/L	(1 – 1.5*baseline]; (ULN, 1.5*ULN]	(1.5 – 3.0* baseline]; (1.5*ULN, 3*ULN]	>3.0*baseline; (3*ULN, 6*ULN]	>6*ULN
Glucose high (hyperglycemia)	mmol/L	(ULN, 8.9]	(8.9, 13.9]	(13.9, 27.8] ; hospitalization indicated	>27.8; life threatening consequences
Glucose low (hypoglycemia)	mmol/L	[3.0, LLN)	[2.2, 3.0)	[1.7, 2.2)	[0, 1.7); life threatening consequences; seizures
Magnesium high (Hypermagnesemia)	mmol/L	(ULN, 1.23]	UNDEFINED	(1.23, 3.30]	>3.30; life threatening consequences
Magnesium low (Hypomagnesemia)	mmol/L	[0.5, LLN)	[0.4, 0.5)	[0.3, 0.4)	[0, 0.3); life threatening consequences
Phosphate (hypophosphatemia)	mmol/L	[0.8, LLN)	[0.6, 0.8)	[0.3, 0.6)	[0, 0.3); life-threatening consequences
Potassium high (hyperkalemia)	mmol/L	(ULN, 5.5]	(5.5, 6]	(6, 7]; hospitalization indicated	>7; life-threatening consequences
Potassium low (hypokalemia)	mmol/L	[3, LLN)	[3, LLN); symptomatic; intervention indicated	[2.5, 3) ; hospitalization indicated	[0, 2.5); life-threatening consequences
Sodium high (hypernatraemia)	mmol/L	(ULN, 150]	(150, 155]	(155, 160]; hospitalization indicated	>160; life-threatening consequences
Sodium low (hyponatraemia)	mmol/L	[130, LLN)	UNDEFINED	[120, 130)	[0, 120); life-threatening consequences

Panel: Hematology

Lab Test	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (decreased)	g/L	[100, LLN)	[80, 100)	[0, 80); transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet count (decreased)	10^9/L	[75, LLN)	[50, 75)	[25, 50)	[0, 25)
WBC (decreased)	10^9/L	[3, LLN)	[2, 3)	[1, 2)	[0, 1)
Lymphocytes (decreased)	10^9/L	[0.8, LLN)	[0.5, 0.8)	[0.2, 0.5)	[0, 0.2)
Neutrophil count (decreased)	10^9/L	[1.5, LLN)	[1, 1.5)	[0.5, 1)	[0, 0.5)

Reference: (National Institute of Health, 2010)

6.6.2 MDASI-BT SCORING ALGORITHM

Symptom Severity Score: The MDASI-BT symptom severity scale score will be calculated by (total scores of non-missing items)/(number of non-missing items), if patients answer at least 12 of the 22 severity scale items. The score will be considered missing if less than 12 items are completed.

Symptom Interference Score: The MDASI-BT symptom interference scale score will be calculated by (total scores of non-missing items)/(number of non-missing items), if patients answer at least 4 of the 6 interference scale items. The score will be considered missing If less than 4 items are completed.

6.7 APPEDNDIX G: PROGRAMMING CODES FOR STATISTICAL ANALYSIS

Programming of the tables, listings and figures will be performed using SAS Version 9.3 or higher, running under UNIX environment. The following table presents the SAS code for the efficacy analysis.

Endpoints	Analysis Methods	SAS Codes

Objective response rate, clinical benefit rate, and AE of special interest rate.	95% Clopper-Pearson confidence interval	`Proc freq data=xx;`
		`  table response/ binomial`
		`  alpha=0.05;`
		`run;`
		
		(By default, PROC FREQ provides Wald and exact (Clopper-Pearson) confidence limits for the binomial proportion.)

Duration of response, PFS, OS	Kaplan-Meier method and 95% confidence interval for median calculated using the method of Brookmeyer and Crowley	`Proc lifetest data=xx;`
		`  TIME duration*censor(1);`
		`Run;`
		
		Note 0=event, 1=censored.

Statistical Analysis Plan (SAP) Initial Sign-Off Sheet

Study 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 #:	ML29366	**DAP Version:**	Final Draft
Authors:			
[redacted], Ph.D.			
Study Statistician		**Signature**	**Date**
[redacted], Ph.D.			
CRO Study Statistician		**Signature**	**Date**
Reviewers:			
[redacted]	[redacted]		May 1, 2019
Study Statistical Programmer		**Signature**	**Date**
Study Outcome Researcher		**Signature**	**Date**
[redacted]		**Signature**	**Date**
[redacted], Pharm.D.			
Approvers:			
[redacted], Pharm.D.			
[redacted]		**Signature**	**Date**
[redacted], Ph.D.			
Study Statistician*		**Signature**	**Date**

* The Biostatistics approver has ensured that key team members have been involved, contributed and reviewed the content of the List of Planned Outputs as described in the SAP Module guideline.