Official Title: A Two-Cohort, Open-Label, Multicenter, Study of Trastuzumab Emtansine (T-DM1) in HER2 Positive Locally Advanced or Metastatic Breast Cancer Patients Who Have Received Prior Anti-HER2 and Chemotherapy-Based Treatment

NCT Number: NCT01702571

Document Date: Protocol Version 6: 18-July-2019

PROTOCOL

TITLE: A TWO-COHORT, OPEN-LABEL, MULTICENTER, STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) IN HER2 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER PATIENTS WHO HAVE RECEIVED PRIOR ANTI-HER2 AND CHEMOTHERAPY-BASED TREATMENT

PROTOCOL NUMBER: MO28231 **VERSION NUMBER:** 6

EUDRACT NUMBER: 2012-001628-37

TEST PRODUCT: Trastuzumab emtansine (RO5304020)

MEDICAL MONITOR: [redacted], MD

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Name	Date and signature

Date and Time (UTC)	Title	Approver's Name
15-Jul-2019 10:15:57	EU QPPV	[redacted]
18-Jul-2019 21:45:46	Company Signatory	[redacted]

CONFIDENTIAL STATEMENT

PROTOCOL AMENDMENT, VERSION 6
RATIONALE

Protocol MO28231 has been amended to include the following changes as outlined below, along with the rationale for the change. Newly inserted text are indicated in italics within the document.

- Clarification about post-trial access to extension study has been provided in Synopsis, Sections 3.2, and 4.2.4. It is specified that, due to delay in activation of sites in China for the extension study BO25430, Chinese patients currently under trastuzumab emtansine treatment will continue to receive treatment under MO28231 protocol until 31 Dec 2019. After this date, or any earlier if site activation allows, these patients will be transferred to and treated under Kadcyla extension study protocol, BO25430.

- Following sections have been updated to reflect clarifications provided in the notes to file after protocol version 5: Synopsis, Sections 4.1.1, 4.4.2.3, 4.4.2.4, and Appendix 1

- Sections 4.3.1 and 4.3.2 were updated with clarifications regarding Chinese traditional medicines following the note to file after protocol version 5.

- The following sections were updated to reflect the revised pregnancy and post-study adverse event reporting language following the notes to file after protocol version 5: Sections 5.4.3.1 and 5.6

- Minor administrative changes to update the names of protocol signatories.

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PROTOCOL ACCEPTANCE FORM

TITLE: **A TWO-COHORT, OPEN-LABEL, MULTICENTER, STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) IN HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER PATIENTS WHO HAVE RECEIVED PRIOR ANTI-HER2 AND CHEMOTHERAPY-BASED TREATMENT**

PROTOCOL NUMBER: MO28231 **VERSION NUMBER:** 6

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TEST PRODUCT: Trastuzumab emtansine (RO5304020)

MEDICAL MONITOR: [redacted], MD

SPONSOR: F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please return a copy of the form as instructed by your local study monitor.
Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE: **A TWO-COHORT, OPEN-LABEL, MULTICENTER, STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) IN HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER PATIENTS WHO HAVE RECEIVED PRIOR ANTI-HER2 AND CHEMOTHERAPY-BASED TREATMENT**

PROTOCOL NUMBER:	MO28231	**VERSION NUMBER:**	6
EUDRACT NUMBER:	2012-001628-37		
TEST PRODUCT:	Trastuzumab emtansine (RO5304020)		
PHASE:	IIIb		
INDICATION:	HER2-positive metastatic breast cancer		
SPONSOR:	F. Hoffmann-La Roche Ltd		

Objectives

Primary Objective

- To evaluate the safety and tolerability of trastuzumab emtansine.

Secondary Objectives

- Progression Free Survival (PFS)
- Overall Survival (OS)
- Overall Response Rate (ORR)
- Clinical Benefit Rate (CBR)
- Duration of Response (DoR)
- Time to Response (TTR)

Pharmacoeconomics Outcome Objective

- Health Resource Utilization

Study Design

Description of Study

Two-cohort, open-label, international, multicenter, Phase IIIb study (see Figure 2 in the protocol).

- Cohort 1 (approximately 2000 patients)
- Cohort 2 (approximately 220 patients) will include only patients of Asian race

Enrollment into Cohort 2 will begin around the end of enrollment into Cohort 1.

Number of Patients

Approximately 2220 patients will be enrolled into this study, approximately 2000 patients in Cohort 1 and 220 patients in Cohort 2.

Target Population

This study will enroll patients with human epidermal growth factor receptor 2 (HER2) positive, unresectable, locally advanced breast cancer (LABC) or metastatic breast cancer (mBC) who have previously received prior anti-HER2 and chemotherapy treatment and have progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy.

Patients must meet the following criteria for study entry according to the timing specified in the schedule of assessments (see Appendix 1):

1. HER2-positive disease determined locally i.e., immunohistochemistry (IHC) 3 + and/or gene-amplified by in situ hybridization (ISH) as per institutional practice (however, both tests should be performed wherever possible and only one positive result is required for eligibility)
2. Histologically or cytologically confirmed invasive breast cancer (BC)
3. Prior treatment for BC in the adjuvant, unresectable, locally advanced or metastatic setting must include both chemotherapy, alone or in combination with another agent, and an anti-HER2 agent, alone or in combination with another agent (complementary hormonal therapy is allowed)
4. Documented progression of incurable, unresectable, locally advanced, or mBC, defined by the investigator: progression must occur during or after most recent treatment for locally advanced/mBC or within 6 months of completing adjuvant therapy
5. Measurable and/or non-measurable disease
6. Signed written informed consent approved by the institution's independent Ethics Committee (EC)
7. Age ≥ 18 years
8. Left ventricular ejection fraction (LVEF) ≥ 50% by either echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
10. Adequate organ function:
    - Absolute neutrophil count > 1,500 cells/mm^3
    - Platelet count > 100,000 cells/mm^3
    - Hemoglobin > 9.0 g/dL. Patients are allowed to be transfused red blood cells to this level
    - Albumin ≥ 2.5 g/dL
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) serum glutamic oxaloacetic transaminase (SGOT) or aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT) or alanine aminotransferase (ALT), and alkaline phosphatase ≤ 2.5 x ULN with the following exception: Patients with bone metastases: alkaline phosphatase ≤ 5 x ULN
    - Creatinine clearance (CL) > 50 mL/min based on Cockroft-Gault glomerular filtration rate (GFR) estimation: (140 – Age) x (weight in kg) x (0.85 if female)/(72 x serum creatinine)
    - International normalized ratio (INR) < *1.5* (unless on therapeutic anti-coagulation)
11. For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception such as surgical sterilization or two effective forms of non-hormonal contraception (see Section 5.2.4 of the protocol)
12. Negative serum pregnancy test for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.2.4 of the protocol)
13. For Cohort 2, only patients of Asian race will be enrolled

Patients who meet any of the following exclusion criteria will not be eligible for this study. Assessments must be performed according to the timing specified in the schedule of assessments (see Appendix 1):

1. History of treatment with trastuzumab emtansine
2. Prior enrollment into a clinical study containing trastuzumab emtansine regardless of having received trastuzumab emtansine or not

3. Peripheral neuropathy of Grade ≥ 3 per National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) Version 4.0
4. History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage 1 uterine cancer, synchronous or previously diagnosed HER2-positive BC
5. History of receiving any anti-cancer drug/biologic or investigational treatment within 21 days prior to first study treatment except hormone therapy, which can be given up to 7 days prior to first study treatment; recovery of treatment-related toxicity consistent with other eligibility criteria
6. History of exposure to the following cumulative doses of anthracyclines:
   - Doxorubicin or liposomal doxorubicin > 500 mg/m^2
   - Epirubicin > 900 mg/m^2
   - Mitoxantrone > 120 mg/m^2
   - If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin
7. History of radiation therapy within 14 days of first study treatment. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to first study treatment
8. Metastatic central nervous system (CNS) disease only
9. Brain metastases which are symptomatic. NOTE: a 14 day window after end of radiotherapy must be observed. Patient must not be receiving steroids to control symptoms
10. History of a decrease in LVEF to < 40% or symptomatic congestive heart failure (CHF) with previous trastuzumab treatment
11. History of symptomatic CHF (New York Heart Association [NYHA] Classes II−IV) or serious cardiac arrhythmia requiring treatment
12. History of myocardial infarction or unstable angina within 6 months of first study treatment
13. Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy
14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
15. Pregnancy or lactation
16. Currently known active infection with HIV, hepatitis B virus, or hepatitis C virus
17. History of intolerance (such as Grade 3−4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product
18. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol throughout

Length of Study

Cohort 1

Last Patient Last Visit (LPLV) for Cohort 1 will be approximately 4 years after enrollment of the first patient into Cohort 1. Enrollment is estimated to take 2 years and there will be 2 years of follow-up after the last patient has been enrolled into Cohort 1. Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after the last patient has been enrolled into Cohort 1, whichever occurs first.

Cohort 2

LPLV for Cohort 2 and global End of Study will be also 4 years after enrollment of the first patient into Cohort 2. Enrollment is estimated to take 2 years and there will be 2 years of follow-up after the last patient has been enrolled into Cohort 2. Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after the last patient has been enrolled into Cohort 2, whichever occurs first. *Patients who are under trastuzumab emtansine treatment as of the date of version 6 of this protocol will continue under MO28231 protocol until 31 Dec 2019. After this date, or earlier if site activation in China allows, these patients will be transferred to and treated under the Kadcyla extension study protocol, BO25430.*

Overview of Cohort 1 and 2

Enrollment into Cohort 2 will begin around the end of enrollment into Cohort 1. Therefore, the entire length of the study (covering enrollment and follow-up period) is estimated to be 6 years.

End of Study

Last patient, last visit (LPLV) as per definition is the last data collection point, which can be a clinic visit or a laboratory sample (see above Length of Study).

Safety Outcome Measures

- Incidence, nature and severity by NCI CTCAE version 4.0 of adverse events (AEs) and serious AEs (SAEs), including AEs Grade 3 or higher for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, and also all other AEs Grade 3 or higher related to trastuzumab emtansine. Pneumonitis events of all grades will be analyzed.
- Incidence of CHF
- Cases of drug-induced liver injury meeting Hy's law criteria
- LVEF decrease over the course of the study as measured by ECHO or MUGA
- Laboratory test abnormalities
- Premature withdrawal from study and study medication
- Exposure to study medication

Efficacy Outcome Measures

- Efficacy will be assessed according to response evaluation criteria for solid tumors (RECIST) v1.1 as per investigator assessment
- Parameters measured will be: PFS, OS, ORR, CBR, DoR, and TTR

Pharmacoeconomics Outcome Measures

The resource expenditure due to hospitalizations that are not study-defined evaluations while on study treatment will be evaluated. The number of hospital visits, number of days admitted, and type of visits (emergency department versus inpatient care) will be collected. The reason for admission (disease progression versus AE) will also be assessed.

Investigational Medicinal Product

Test Product

Trastuzumab emtansine will be administered intravenously every 3 weeks at a dose of 3.6 mg/kg over approximately 90 minutes for the first dose and 30 (±10) minutes for subsequent doses.

The total trastuzumab emtansine dose will be calculated based on the patient's weight up to 28 days before each cycle with no upper limit. If within these 28 days a patient experiences a severe weight loss, the dose will be recalculated accordingly.

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after the last patient has been enrolled into the trial, whichever occurs first.

Patients who have not progressed at the end of the trial will be offered the following options to continue with treatment:

- Patients in countries in which trastuzumab emtansine is approved and reimbursed for this indication at the study end, may continue treatment outside this study in accordance with local labeling and reimbursement.
- Patients in countries in which trastuzumab emtansine is not approved and/or not reimbursed for this indication or local regulations do not allow patients to receive continued treatment in this way, will be offered the possibility to continue treatment in an extension study.

Non-Investigational Medicinal Product

Not applicable

Statistical Methods

Analysis populations

All safety and efficacy summaries will be presented for each cohort separately and for the pooled analysis of Cohorts 1 and 2.

Two Safety populations will be defined; Safety population 1 and Safety population 2, which will be used to summarize safety variables.

Safety population 1 will include all patients who have received at least one dose of study medication in Cohort 1 while Safety population 2 will include all patients who received at least one dose of study medication in Cohort 2.

Pooled analysis for safety will be performed on the Safety population that includes all patients in Safety population 1 and Safety population 2.

The efficacy variables will be summarized for the intent-to-treat (ITT) population 1 and ITT population 2. ITT1 will include all patients enrolled in Cohort 1, while ITT2 will include all patients in Cohort 2.

Pooled analysis for efficacy will be performed on the ITT population that includes ITT1 and ITT2.

Primary Analysis

The primary endpoint of Cohort 1, Cohort 2 and the pooled analysis of Cohorts 1 and 2 will be AEs Grade ≥ 3, specifically, hepatic events, allergic reactions, thrombocytopenia, hemorrhage events and all Grade ≥ 3 AEs related to trastuzumab emtansine. Pneumonitis events of all grades will be analyzed.

In addition, AEs leading to treatment interruption and discontinuation, SAEs, cause of death, incidence of CHF, premature discontinuation from study and treatment, laboratory parameters and exposure to study drug will be secondary safety variables.

Safety will be assessed through summaries of AEs, SAEs, deaths, and changes in laboratory test results.

There are no formal statistical hypothesis tests to be performed. There are no adjustments for multiplicity of endpoints or within-subgroup comparisons.

Efficacy is the secondary endpoint. Efficacy endpoints will be: PFS, OS, ORR, CBR, DoR, and TTR.

Safety Data Analysis

Summaries of safety data described below will be performed for Cohort 1, Cohort 2, and the pooled analysis.

All AEs will be assessed according to the NCI CTCAE v 4.0 grading system. The analysis of AEs will focus on treatment-emergent AEs i.e., AEs occurring on the day of or after first administration of study drug. Non-treatment-emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Based on the safety profile of trastuzumab emtansine, time to onset of the first episode of each AE described in Section 5 will also be summarized via Kaplan-Meier (KM) estimates. Additional summaries by frequency tables will also be provided for these AEs. Pneumonitis events of all grades will be analyzed.

AEs Grade 3 or higher for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, and also all other AEs Grade 3 or higher, AEs leading to treatment interruption and discontinuation, pneumonitis of all grades, and SAEs will be analyzed in a similar way to all AEs.

Cause of death will also be summarized and listed.

The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative study medication doses and duration of exposure.

LVEF over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time with associated 95% confidence interval (CI).

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI CTCAE version 4.0 grade at baseline versus worst grade during treatment period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will also be presented. The selected laboratory parameters will be graphically presented over time.

Efficacy Analyses

Summaries of efficacy will be performed for Cohort 1, Cohort 2 and the pooled analysis.

Estimates for the survivor function for PFS, OS, DoR and TTR will be obtained by the KM approach.

The analysis of ORR is based on the best (confirmed) overall response (BOR). The BOR will be assessed by the number and proportion of responders and non-responders, together with two-sided 95% CIs. Only patients with measurable disease at baseline will be included in the analysis of the BOR. Patients without a post-baseline tumor assessment will be considered to be non-responders.

Logistic analysis will be performed for BOR rate to assess the influence of baseline covariates, e.g., age (> 65, ≤ 65), ECOG 0–1 versus ECOG 2 in an exploratory manner.

In addition to these predictor factors, for the pooled analysis of Cohorts 1 and 2, a further factor will be added: region (Asian versus non-Asian regions).

More details will be specified in the statistical analysis plan.

CBR will be summarized in a similar way to BOR.

Exploratory Analyses

The following subgroup analyses will be performed for both cohorts and pooled across cohorts:

- AST or ALT increases that are > 3 × ULN and total bilirubin > 2 × ULN except in patients with documented Gilbert syndrome
- Country
- Race
- Region (Asia versus non-Asia regions)
- Age (> 65, ≤ 65)
- Age (>75, ≤75)
- ECOG 0–1 versus ECOG 2

Other Analyses

Baseline and disease characteristics such as demographics, medical history, etc. will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation, and 25th-75th quartiles for the continuous variables).

Pharmacoeconomics: the resource expenditure due to hospitalizations that are not study-defined evaluations while on study treatment will be also evaluated and summarized.

Determination of Sample Size

A sample size of approximately 2000 patients is planned for Cohort 1 of this study. For the purpose of the estimation of sample size, the incidence of AEs of Grade 3 or higher related to trastuzumab emtansine was chosen as a safety endpoint of primary interest.

If the observed incidence of AEs Grade ≥ 3 related to trastuzumab emtansine e.g., hepatic events, pneumonitis, thrombocytopenia or allergic reactions is between 5% and 10% (Study TDM4450g/BO21976), the precision for the estimation of the incidence of AE is presented in the table below by 95% Clopper-Pearson CIs.

Cohort 1: Clopper-Pearson 95% Confidence Intervals for the incidence of AEs Grade ≥ 3 based on 2000 patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
20 (1%)	0.6% - 1.5%
40 (2%)	1.4% - 2.7%
60 (3%)	2.3% - 3.8%
80 (4%)	3.2% - 5%
100 (5%)	4.1% - 6%
120 (6%)	5% - 7.1%
140 (7%)	5.9% - 8.2%
160 (8%)	6.8% - 9.3%
180 (9%)	7.8% - 10.3%
200 (10%)	8.7% - 11.4%

For the purpose of the sample size estimate of Cohort 2, the incidence of Grade ≥ 3 thrombocytopenia in Asian patients was chosen as a safety endpoint of primary interest.

This is based on the pooled analysis of various trials TDM4370g/BO21977, TDM4450g/BO21976, TDM4373g/BO22495, TDM4374g, TDM4258g, TDM4688g, TDM3569g and TDM4529g/BO25430, and the results of a subset of 99 Asian patients (see the trastuzumab emtansine Investigator's Brochure).

If the observed incidence of Grade ≥ 3 thrombocytopenia in Asian patients is between 30% and 55%, the precision for the estimation of the incidence of AEs is presented in the table below by 95% Clopper-Pearson CIs.

Cohort 2: Clopper-Pearson 95% Confidence Intervals for the incidence Grade ≥ 3 thrombocytopenia based on 220 Asian patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
2 (1%)	0.1% - 3.6%
10 (5%)	2.4% - 9%
20 (10%)	6.2% - 15%
60 (30%)	23.7% - 36.9%
70 (35%)	28.4% - 42%
80 (40%)	33.2% - 47.1%
90 (45%)	38% - 52.2%
100 (50%)	42.9% - 57.1%
110 (55%)	47.8% - 62%

The sample size of approximately 2220 patients is planned for the pooled analysis of Cohorts 1 and 2.

Clopper-Pearson 95% Confidence Intervals for the incidence of AEs Grade ≥ 3 based on 2220 patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
22 (1%)	0.6% - 1.5%
44 (2%)	1.5% - 2.7%
66 (3%)	2.3% - 3.8%
88 (4%)	3.2% - 4.9%
110 (5%)	4.1% - 6%
132 (6%)	5% - 7.1%
154 (7%)	6% - 8.1%
176 (8%)	6.9% - 9.2%
198 (9%)	7.8% - 10.3%
220 (10%)	8.8% - 11.3%

Interim Analyses

Cohort 1, Cohort 2 and pooled analysis of Cohorts 1 and 2

The final analysis of each cohort will be performed when all patients within the respective cohort have been followed up for safety and efficacy for a period of up to 2 years after the last patient has been enrolled into the respective cohort, with further review of accumulating safety as required (see iDMC charter). The pooled analysis of Cohorts 1 and 2 will be conducted in parallel to the final analysis of Cohort 2.

Cohort 1

In addition to the final analysis, there will be five interim safety analyses for review by the independent Data Monitoring Committee (iDMC): after approximately 50 and 350 patients have completed Cycle 1, Day 1 and after approximately 1,000, 1,500, and 2,000 patients have completed the first cycle of study medication (Cycle 1, Day 21).

Cohort 2

In addition to the final analysis, there will be one interim safety analysis for review by the iDMC after approximately 100 patients have completed Cycle 1 (Cycle 1, Day 21).

In addition to the above interim analyses, there might be additional interim analyses for Health Authority purposes (e.g., to support SFDA [China]) after 150 Chinese patients have been enrolled and completed Cycle 1 (Cycle 1, Day 21) or by January 2017, whichever occurs first.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BOR	best overall response
BUN	blood urea nitrogen
BC	breast cancer
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DoR	duration of response
DLT	dose-limiting toxicity
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
EEA	European economic area
EU	European Union
FDA	Food and Drug Administration
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Conference on Harmonization
iDMC	independent Data Monitoring Committee
IHC	Immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (application)

INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ISH	in situ hybridization
ITT	Intent-to-treat
IV	intravenous
IxRS	interactive voice/web recognition system
KM	Kaplan-Meier
LABC	locally advanced breast cancer
LVEF	left ventricular ejection fraction
LPLV	last patient, last visit
mBC	metastatic breast cancer
MCC	maleimidylmethyl cylcohexane-1-carboxylate
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NRH	nodular regenerative hyperplasia
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
QT	measure between Q wave and T wave in the heart's electrical cycle
QTcF	heart rate-corrected QT interval using the Fridericia formula
q3w	every 3 weeks
qw	weekly
RECIST	response evaluation criteria for solid tumors
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system-organ class
SWFI	sterile water for injection

$t_{½}$	terminal half-life
T-DM1	trastuzumab emtansine
TTR	time to response
ULN	upper limit of normal
V_{ss}	apparent volume of distribution at steady state
WBC	white blood cells
WHO	World Health Organization

1. BACKGROUND

1.1 HER2-POSITIVE, METASTATIC BREAST CANCER

Breast cancer (BC) is the most common cancer in women worldwide, both in the developed and the developing world (WHO, World Health Statistics. 2011), with approximately 1.38 million new cases diagnosed in 2008. It is also the leading cause of cancer death in females, accounting for 458,400 deaths (14% of all cancer deaths) in 2008 (Jemal et al. 2011). Almost 100,000 of these BC-related deaths occurred in patients whose tumors overexpressed the human epidermal growth factor receptor 2 (HER2). Metastatic breast cancer (mBC) is incurable, with the primary goal of treatment to extend life and palliate symptoms while preserving quality of life.

The HER tyrosine kinase receptor family is comprised of four receptors: HER1, HER2, HER3, and HER4. These receptors are important mediators of cell growth, survival, and differentiation (Sundaresan et al. 1999). Activation of HER receptors leads to receptor dimerization and cell signaling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation.

Overexpression of HER2 is observed in approximately 15–20% of human BCs. Several lines of scientific and clinical evidence support a direct role for HER2 overexpression in the aggressive growth and poor clinical outcomes associated with these tumors (Slamon et al. 1987). The development of trastuzumab in the 1990s provided women with HER2-overexpressing tumors with a markedly better outcome than was possible with chemotherapy alone. Increases in response rate, response duration, and progression-free survival (PFS) were associated with a 5-month survival advantage when trastuzumab was given in the first-line metastatic setting, as demonstrated in the initial Phase III trial (Slamon et al. 2001).

For patients with HER2-positive mBC, the combination of trastuzumab and a taxane is a globally accepted first-line treatment, based on the survival advantage demonstrated in two large pivotal trials (Slamon et al. 2001; Marty et al. 2005). However, virtually all patients with HER2-positive mBC develop progressive disease (PD) and require additional therapies. Importantly, such tumors continue to express high levels of HER2 (Spector et al. 2005), and neither the process of internalization nor the level of surface expression is altered when HER2 is bound by trastuzumab (Austin et al. 2004). HER2-directed combination therapy beyond progression for HER2-positive mBC is an accepted palliative treatment approach.

An accepted example of second-line therapy for HER2-positive mBC therapy is lapatinib in combination with capecitabine as a treatment for patients who have received trastuzumab and a taxane for advanced disease. In a Phase III trial involving patients with advanced HER2-positive BC previously treated with an anthracycline, a taxane, and trastuzumab, the addition of lapatinib to capecitabine resulted in an increased response rate (24% versus 14%) and

time to disease progression (6.2 months versus 4.3 months) (Geyer et al. 2006).

1.2 BACKGROUND ON TRASTUZUMAB EMTANSINE

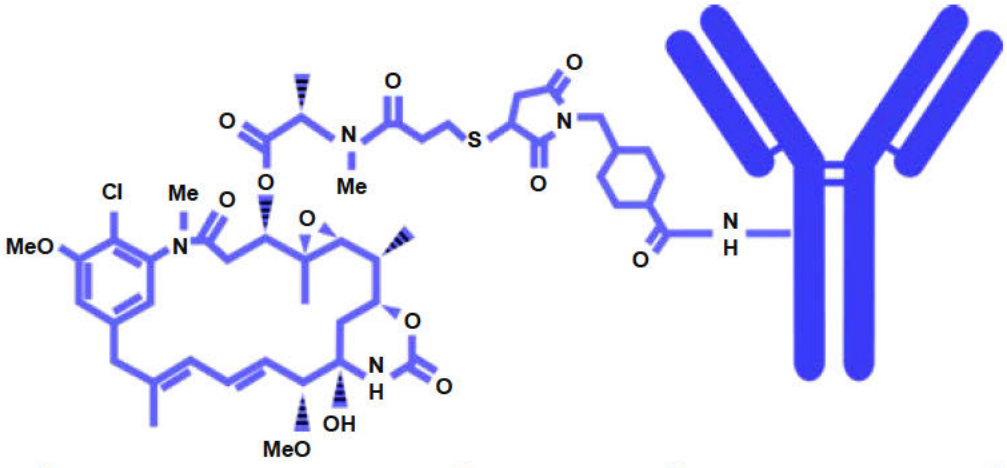
The study drug, trastuzumab emtansine (also known as T-DM1, see Figure 1) is a novel antibody–drug conjugate (ADC) that is specifically designed for the treatment of HER2-positive malignancies. Trastuzumab emtansine is composed of trastuzumab (Herceptin®), a humanized monoclonal antibody directed against the extracellular region of HER2; an average of 3.5 molecules of DM1 (maytansinoid), an anti-microtubule agent derived from maytansine; and the thioether linker maleimidylmethyl cylcohexane-1-carboxylate (MCC), which is used to conjugate each molecule of DM1 to trastuzumab. DM1 is a highly potent drug synthesized from maytansinol that binds β–tubulin to inhibit tubulin polymerization. It binds to tubulin competitively with vinca alkaloids, but is 20–100 times more potent than vincristine in its cytotoxic effect against tumor cell lines. Its parent molecule, maytansine, has been studied in approximately 800 cancer patients in the 1970s and 1980s, with responses seen in patients with breast and lung cancer (Junttila et al. 2011; Issell and Crooke 1978). However, because of its narrow therapeutic index and the observed gastrointestinal toxicity of the free drug, it was not developed further as a therapeutic option (Cassady et al. 2004; Cabanillas et al. 1979).

Trastuzumab emtansine and trastuzumab recognize the same epitope on HER2 and are binding with a similar affinity. Following antigen specific binding of trastuzumab emtansine to HER2, it is hypothesized that the complex of receptor and ADC is internalized, where upon DM1-containing catabolites are released into the cytosol following proteolytic cleavage of the antibody in lysosomes (Erickson et al. 2006). Binding of these DM1-containing species to β-tubulin inhibits tubulin polymerization resulting in cell death (Cassady et al. 2004).

In addition to targeting delivery of DM1 to HER2-overexpressing tumor cells, trastuzumab emtansine retains the anti-tumor activities of trastuzumab, including suppression of HER2 signaling pathways that confer a proliferative and survival advantage to cells, and the flagging of cells for destruction through antibody-dependent cell cytotoxicity (Junttila et al. 2011).

Completed and ongoing Phase I and II single arm studies of trastuzumab emtansine have demonstrated clinical activity. The randomized Phase II study BO21976 described in Section 1.2.1.4 showed a significant improvement in PFS with a HR 0.59 p=0.0353 and a favorable safety profile compared with the standard of care trastuzumab and taxane combination. A Phase III study BO21977 (see Section 1.2.1.6) is underway comparing trastuzumab emtansine to standard of care HER2-targeted combination therapy (capecitabine and lapatinib) for patients with mBC who had received prior trastuzumab and taxane therapies. This trial has met its co-primary endpoint of improving PFS (by an independent review committee [IRC]) in patients who received trastuzumab emtansine compared with those who received the combination of lapatinib and capecitabine.

Figure 1 Molecular Structure of Trastuzumab Emtansine



	DM1 (derivative of maytansine)	Linker	Trastuzumab
MW:	**738**	**238**	**~150,000**
Ratio:	**3.5**	**3.5**	**1**

DM1 = Derivative of Maytansine, a microtubule destabilizing agent
MW = Molecular weight

The safety profile of trastuzumab emtansine is based on completed studies with single-agent treatment in 273 patients (from studies TDM4258g, TDM4374g, TDM4688g, and TDM4529g) and combined treatment with pertuzumab in 87 patients (from studies TDM4373g/BO22495 and TDM4688g). The most common adverse events (AEs) of fatigue, nausea, headache, pyrexia, and epistaxis were mostly Grade 1 or Grade 2 in intensity. Thrombocytopenia was the primary dose-limiting toxicity (DLT) in the Phase 1 study, and was the most common Grade ≥ 3 event in completed Phase II studies. AEs of particular clinical relevance include thrombocytopenia, hepatotoxicity, infusion reactions, cardiac dysfunction, and interstitial lung disease.

Preliminary safety data from a study comparing trastuzumab emtansine monotherapy with trastuzumab plus docetaxel (TDM4450g/BO21976) showed that the incidences of Grade ≥ 3 events and serious AEs (SAEs) were lower in the trastuzumab emtansine group. Thrombocytopenia and increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred more frequently in the trastuzumab emtansine group while alopecia, peripheral edema and neutropenia were greatly reduced compared with the trastuzumab plus docetaxel group.

Data from clinical trials of trastuzumab emtansine that are relevant to the design of the current trial are summarized below. Please refer to the trastuzumab emtansine Investigator's Brochure for further information on all of the completed and ongoing trastuzumab emtansine studies

1.2.1.1 Study TDM3569g

Study TDM3569g was a Phase I, dose-escalation study that evaluated the safety and efficacy of trastuzumab emtansine as a single agent in 52 patients with HER2-positive mBC, whose disease progressed on a trastuzumab-containing chemotherapy regimen. The study was completed on 11 June 2009, with a total of 52 patients treated; 24 patients received trastuzumab emtansine every 3 weeks (q3w); 28 patients received trastuzumab emtansine on a weekly schedule.

On the q3w dosing schedule, DLTs of Grade 4 thrombocytopenia were seen in 2 of 3 patients treated at 4.8 mg/kg. Therefore, 3.6 mg/kg was determined to be the maximum tolerated dose (MTD) of trastuzumab emtansine given q3w, and the cohort was expanded to 15 patients. On the basis of these data, the recommended dose schedule for the Phase II studies was 3.6 mg/kg q3w. Treatment with trastuzumab emtansine was well tolerated, and toxicity was generally mild, reversible, and non-cumulative. No drug-related cardiac toxicity was noted.

Trastuzumab emtansine administration demonstrated considerable activity in this Phase I study. The confirmed overall response rate (ORR) in patients with measurable disease at the 3.6 mg/kg q3w schedule was 44% (4 of 9 patients), as assessed by investigators. The median PFS among the 15 patients receiving 3.6 mg/kg q3w was 10.4 months.

1.2.1.2 Study TDM4258g

Study TDM4258g was a Phase II study that evaluated the safety and efficacy of trastuzumab emtansine administered at a dose of 3.6 mg/kg (intravenous [IV]) q3w in patients with HER2-positive mBC who had progressed on previous HER2 directed therapy and conventional chemotherapy.

The primary objectives for this study were: 1) to assess the ORR (by independent radiologic review) associated with trastuzumab emtansine 3.6 mg/kg IV q3w, and 2) to characterize the safety and tolerability of trastuzumab emtansine at this dose.

The study was activated on 20 July 2007, and enrollment was completed (n = 112) on 31 July 2008. The final analysis of ORR was performed with a data cut-off date of 25 June 2009, 11 months after the last patient was enrolled. The reported ORR in all patients was 37.5% (95% confidence interval [CI], 28.6%, 46.6%) by investigator assessment and 25.9% (95% CI, 18.4%, 34.4%) by IRC. The clinical benefit rate ([CBR] defined as complete response [CR], partial response [PR], or stable disease for >6 months) was 46.3% by investigator assessment and 39.3% by independent review. The median PFS was 4.6 months as assessed by both the investigators and the IRC. In the subset of patients whose archival primary tumors were retrospectively confirmed to be HER2-positive (74 of 95 patients with submitted tumor samples), the ORR was 33.8% by independent review and 47.3% based on investigator assessment.

The most common AEs (occurring in ≥20% of patients) were fatigue (65.2%), nausea (50.9%), headache (40.2%), epistaxis (35.7%), pyrexia (34.8%), constipation (30.4%), cough (27.7%), hypokalemia (26.8%), diarrhea (25.9%), vomiting (24.1%), arthralgia (22.3%), pain in extremity (22.3%), anemia (20.5%), and dyspnea (20.5%). Most of these AEs were Grade 1–2. The three most common Grade 3–4 AEs observed in this trial were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). There was one reported Grade 5 event in a patient who died of respiratory failure attributed by the investigator to underlying disease. No Grade ≥3 left ventricular systolic dysfunction events (symptomatic congestive heart failure [CHF] and/or left ventricular ejection fraction [LVEF] of <40%) were observed.

1.2.1.3 Study TDM4374g

Study TDM4374g was a Phase II, single arm study of trastuzumab emtansine administered at 3.6 mg/kg by IV infusion q3w to patients with HER2-positive mBC. Patients must have received an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine given in the neo-adjuvant, adjuvant, or metastatic setting or as treatment for locally advanced disease. Patients must have been treated with two HER2-directed therapies in the metastatic or locally advanced setting and have progressed on their most recent treatment.

The primary objectives of this study were: 1) to assess the ORR as assessed by an independent review using the modified Response Evaluation Criteria for Solid Tumors (RECIST; v. 1.0, and 2) to characterize the safety and tolerability of this trastuzumab emtansine regimen in the aforementioned patient population. The study was activated on 2 May 2008, and enrollment was complete on 2 April 2009. A total of 110 patients were enrolled and treated in the study.

An efficacy analysis (data cut-off date: 21 June 2010) with a median follow-up of 17.4 months demonstrated an ORR (complete and PR of 34.5% (95% CI: 26.1–43.9%; 38 of 110 patients) by Independent Review Facility and 32.7% (95% CI: 24.1–42.1%; 36 patients) by investigator assessment. The CBR was 48.2% by independent review and 46.4% by investigator assessment. The median duration of response (DoR) and PFS by independent review were 7.2 months and 6.9 months, respectively. In the subset of patients whose archival primary tumors were retrospectively confirmed to be HER2-positive (80 of 95 patients with submitted tumor samples), the ORR was 41.3% by independent review and 40.0% based on investigator assessment.

The most common AEs (occurring in ≥20% of patients) were fatigue (61.8%), thrombocytopenia (38.2%), nausea (37.3%), increased AST (26.4%), constipation (23.6%), pyrexia (22.7%), epistaxis (22.7%), headache (21.8%), hypokalemia (20.9%), decreased appetite (20.9%), dry mouth (20.0%), and anemia (20.0%). Most of these AEs were Grade 1–2. Fifty-two patients (47.3%) experienced at least one Grade ≥3 AE, the most common being thrombocytopenia (9.1%) and fatigue (4.5%). SAEs were recorded by 28 patients (25.5%), the most common being cellulitis (3.6%), pyrexia (2.7%), and pneumonia (2.7%). One patient recorded a Grade 5 AE of hepatic dysfunction, which was recorded as possibly related to trastuzumab

emtansine. The patient had pre-existing non-alcoholic fatty liver disease as well as multiple other co-morbidities, including renal insufficiency.

1.2.1.4 Study BO21976

This was a randomized, multicenter, Phase II study of the efficacy and safety of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with metastatic HER2-positive BC who had not received prior chemotherapy for metastatic disease. This study completed enrollment in December 2009 (n = 137). The primary objectives were to assess the efficacy of trastuzumab emtansine compared with the combination of trastuzumab and docetaxel, as measured by PFS based on investigator tumor assessments, and to characterize the safety of trastuzumab emtansine compared with the combination of trastuzumab and docetaxel in this population. Secondary endpoints included ORR, survival, and DoR.

The data cut-off date was 15 November 2010. Seventy patients were randomized to the control arm and 67 patients to the trastuzumab emtansine arm. The median duration of follow-up was 13.5 months for the control arm and 13.8 months for the trastuzumab emtansine arm.

PFS was 14.2 months in the trastuzumab emtansine arm versus 9.2 months in the trastuzumab plus docetaxel arm. The hazard ratio (HR) for PFS was 0.594 (95% CI: 0.364–0.968; p = 0.0353). The ORR in the trastuzumab emtansine arm was 64.2% (95% CI: 51.8–74.8%) compared with 58.0% (95% CI: 45.5–69.2%) in the control arm (based on 69 evaluable patients). The CBR was 74.6% (95% CI: 63.2–84.2%) in the trastuzumab emtansine arm versus 81.2% (95% CI: 70.7–89.1%) in the trastuzumab plus docetaxel arm (based on 69 evaluable patients). Based on safety data analyzed at the data cut-off date, single-agent trastuzumab emtansine appears to have a favorable overall safety profile compared with trastuzumab and docetaxel in first-line mBC. The incidence of Grade ≥3 AEs in the control arm (89.4%; n = 66) was nearly twice that of trastuzumab emtansine (46.4%; n = 69). The rates of SAEs for both arms were similar (control arm 25.8% versus trastuzumab emtansine 18.8%). One patient in the trastuzumab emtansine group died as a result of an AE (sudden death). This patient was randomized to receive trastuzumab plus docetaxel but mistakenly received a single dose of 6 mg/kg trastuzumab emtansine instead of 6 mg/kg trastuzumab. One patient in the trastuzumab plus docetaxel group died due to cardiopulmonary failure. With respect to cardiotoxicity, based on local assessments of LVEF, trastuzumab emtansine was not associated with an increase in cardiotoxicity compared with trastuzumab plus docetaxel.

1.2.1.5 Study TDM4688g

The effect of trastuzumab emtansine (3.6 mg/kg q3w) on the QT interval in patients with HER2-positive recurrent locally advanced BC or mBC was evaluated in Study TDM4688g. Trastuzumab emtansine had no meaningful effect on the corrected QT interval in these patients. At Cycle 1, Day 1, 15 minutes post-infusion, the baseline-adjusted mean heart rate-corrected QT interval using the Fridericia formula (QTcF) increased by 1.2 ms. By 60

minutes post-infusion, the baseline-adjusted mean QTcF interval decreased by 1.0 ms, and by Day 8 of Cycle 1, the baseline-adjusted mean QTcF interval decreased by 4.0 ms. By Cycle 3 Day 1, prior to trastuzumab emtansine infusion, the mean QTcF interval had reverted back to baseline. Following the third infusion of trastuzumab emtansine, the baseline-adjusted average QTcF interval at both the 15-minute and the 60-minute post-infusion time points was increased by an average of 4.7 ms. No patient exhibited an average change in QTcF interval from baseline exceeding 30 ms at any of the protocol-specified time points.

The relationship between trastuzumab emtansine pharmacokinetic (PK) and electrocardiogram (ECG) data was also assessed. While there appears to be a trend between trastuzumab emtansine drug concentration and its effect on QT interval, at the observed concentration ranges of trastuzumab emtansine, DM1, and total trastuzumab, there is reasonable assurance that the true increase in mean baseline-adjusted average QTcF does not exceed 5 ms. Moreover, because trastuzumab emtansine, total trastuzumab, and DM1 achieve steady-state levels by Cycle 3, the likelihood of progressively longer QTcF with repeated trastuzumab emtansine dosing is low.

In this study, ORR of 25.5% (95% CI: 15.2–38.5%) was assessed by the investigator; no independent review was performed in this study. The CBR was 39.2% (95% CI: 25.8–53.1%), and the median PFS was 4.3 months (95% CI: 4.0–6.7).

1.2.1.6 Study BO21977 (EMILIA)

Roche has conducted a randomized, open-label Phase III trial (BO21977) of single-agent trastuzumab emtansine versus lapatinib and capecitabine in HER2-positive locally advanced unresectable BC or mBC patients who have received a prior taxane and trastuzumab therapy and have documented disease progression. 991 patients have been enrolled.

Patients were randomized in a 1:1 ratio to trastuzumab emtansine or capecitabine plus lapatinib.

Trastuzumab emtansine was administered at 3.6 mg/kg IV every 3 weeks. The control arm treatment is capecitabine at 1,000 mg/m^2 as oral doses twice daily on Days 1–14 of a 21-day cycle plus oral lapatinib 1,250 mg/day given as continuous dosing. Study treatment was discontinued based on disease progression (as assessed by the investigator), unmanageable toxicity or study termination by the Sponsor.

This study of trastuzumab emtansine met both primary efficacy endpoints of PFS by independent review and OS in patients with mBC previously treated with a taxane and trastuzumab (Herceptin).

PFS and OS were investigated as co-primary endpoints in this study with PFS based on modified RECIST (Therasse et al. 2000) and conducted by the IRC. An additional tumor assessment of PFS was performed after investigator-documented disease progression. Furthermore ORR, DoR, and CBR were

included, on the basis of both investigator and independent review of tumor assessments, as key secondary endpoints.

Patients in the trastuzumab emtansine arm had a median PFS of 9.6 months vs. 6.4 months for patients in the control arm of lapatinib + capecitabine (HR=0.65; 95% CI: 0.55–0.77; $P < 0.001$). A consistent PFS benefit with T-DM1 vs. lapatinib + capecitabine was seen in all clinically relevant subgroups. Patients in the trastuzumab emtansine arm had a median OS of 30.9 months vs. 25.1 months for patients in the control arm of lapatinib + capecitabine (HR=0.68; 95% CI: 0.55–0.85; $P < 0.001$).

Based on safety data analyzed at the data cutoff date, single-agent trastuzumab emtansine appears to have a favorable overall safety profile compared with lapatinib and capecitabine in mBC. The incidence of Grade ≥3 AEs in the control arm (56.9%; n = 488) was 278 compared with that of trastuzumab emtansine (40.8%; n = 490), which was 200. No new safety signals were seen with trastuzumab emtansine.

It was concluded that overall trastuzumab emtansine demonstrated improved efficacy over capecitabine and lapatinib and that there is no concern regarding the clinical safety of trastuzumab emtansine based on the currently available data (Verma et al. 2012).

1.2.1.7 Study BO25734 (TH3RESA)

Preliminary results from a randomized, two-arm, open-label Phase III study of trastuzumab emtansine compared with treatment of physician's choice in patients with mBC or unresectable local advanced/recurrent HER2-positive BC have shown that treatment with trastuzumab emtansine resulted in a statistically significant improvement in PFS and fewer AEs of Grade 3 or higher severity in patients who had previously been treated with at least two HER2-directed regimens. The median PFS, as of the cutoff of 11 February 2013, was 6.2 months for patients treated with trastuzumab emtansine vs. 3.3 months (HR: 0.528 [0.422, 0.661]; p < 0.001) for patients who received treatment of physician's choice (Wildiers et al. 2013).

1.2.1.8 Pharmacokinetics

The PK of trastuzumab emtansine and its analytes (total trastuzumab and DM1) were characterized in one Phase I study (TDM3569g) and three Phase II studies (TDM4258g, TDM4374g, and TDM4688g).

For study TDM3569g, the final PK parameter estimates based on non-compartmental PK analysis for q3w and weekly regimens of trastuzumab emtansine administration are presented in Table 1.

Table 1 Cycle 1 Mean (SD) Pharmacokinetic Parameters for Trastuzumab Emtansine Following Trastuzumab Emtansine Administration Every Three Weeks and Weekly in Study TDM3569g

Dose (mg/kg)	No. of Patients	C_{max} (µg/mL)	AUC_{inf} (day µg/mL)	$t_{1/2}$ (day)	V (mL/kg)	CL (mL/day/kg)
Every 3 Week Dosing						
0.3	3	9.6 (1.7)	14.5 (3.4)	1.3 (0.2)	35.7 (7.5)	21.1 (4.5)
0.6	1	13.3	24.5	1.3	43.8	24.5
1.2	1	20.3	42.9	1.3	51.8	27.8
2.4	1	76.3	330.0	2.2	30.7	7.2
3.6	15	76.2 (19.1)	300.3 (65.8)	3.1 (0.7)	58.4 (12.4)	12.7 (3.6)
4.8	3	130.3 (7.8)	673.0 (12.2)	4.1 (0.7)	41.2 (6.2)	7.1 (0.1)
Weekly Dosing						
1.2	3	29.6 (5.7)	76.2 (10.4)	2.3 (0.6)	47.5 (6.0)	15.9 (2.4)
1.6	3	34.3 (4.8)	130.3 (39.7)	3.4 (0.8)	59.8 (16.6)	13.0 (3.4)
2.0	3	48.0 (9.6)	175.0 (41.0)	3.1 (0.3)	51.0 (8.1)	11.8 (2.4)
2.4	16	54.8 (12.6)	198.5 (54.5)	3.3 (1.1)	55.4 (13.0)	13.1 (4.1)
2.9	3	78.1 (33.9)	212.0 (39.0)	2.9 (0.5)	57.7 (2.2)	14.0 (2.6)

AUC_{inf} = area under the serum concentration-time curve from time 0 extrapolated to infinity; C_{max} = maximum serum concentration; CL = clearance; $t_{1/2}$ = terminal half-life; V = volume of distribution; SD = standard deviation.

Trastuzumab emtansine was administered from 0.3–4.8 mg/kg once q3w (n = 25) and from 1.2–2.9 mg/kg once weekly ([qw], n = 28) in the Phase I study TDM3569g, which enrolled patients with mBC (Krop et al. 2010; Beeram et al. 2012). The MTD of trastuzumab emtansine were 3.6 mg/kg q3w and 2.4 mg/kg qw. The ORR among women with HER2-positive mBC was similar with either 3.6 mg/kg q3w or 2.4 mg/kg qw. Dose intensity, defined as percentage of the planned trastuzumab emtansine dose that was actually received, was higher with the 3.6 mg/kg q3w regimen (median 99.7%, range 88%–106%) than with the 2.4 mg/kg qw schedule (median 82%, range 54%–101%). However, since the PK of trastuzumab emtansine is linear at doses ≥2.4 mg/kg, an almost 2-fold higher cumulative dose can be administered within a 21 day cycle with a 2.4 mg/kg qw regimen compared with 3.6 mg/kg q3w.

Based on a population PK analysis, trastuzumab emtansine has a consistent PK profile with low inter-individual variability (21–48%) in PK parameters among patients with mBC. Greater baseline tumor burden and lower serum albumin levels, potential indicators of disease severity, resulted in small increases (< 13%) in trastuzumab emtansine clearance (CL). However, trastuzumab emtansine PK was not affected by baseline residual trastuzumab (from prior treatment) or by differences in serum concentrations of HER2 extracellular domain (Gupta et al. 2011, Girish et al. 2012). The population PK

results will be updated following the availability of data from study BO21977, and other studies.

To date, no significant correlations have been observed between efficacy (as measured by overall response; RECIST, v1.0) and trastuzumab emtansine exposure (area under the concentration time-curve [AUC], maximum concentration [C_{max}]) after 3.6 mg/kg q3w trastuzumab emtansine dosing across the Phase II studies (TDM4258g and TDM4374g). Trastuzumab emtansine exposures were similar among patients with an objective tumor response, stable disease, or PD. This effect appears to be consistent regardless of Caucasian or Asian heritage (Girish et al. 2012). Similarly, no obvious relationships were observed between trastuzumab emtansine exposure and platelet count or serum concentrations of ALT or AST during the course of trastuzumab emtansine treatment across the studies at the dose of 3.6 mg/kg q3w (to be updated following the availability of data from study BO21977).

An aggregate PK assessment of trastuzumab emtansine was done with samples from studies TDM3569g, TDM4258g, TDM4374g, and TDM4688g (Girish et al. 2012). PK parameters for trastuzumab emtansine, total trastuzumab, and DM1 were consistent across the four studies at Cycle 1 and steady state. Trastuzumab emtansine PK was not affected by residual trastuzumab from prior therapy or circulating extracellular domain of HER2. No significant correlations were observed between trastuzumab emtansine exposure and efficacy, thrombocytopenia, or increased concentrations of transaminases. Across the four studies, the incidence of anti-therapeutic antibodies to trastuzumab emtansine was low and detected in 4.5% (13/286) of evaluable patients receiving trastuzumab emtansine q3w.

The PK profile (i.e., C_{max}, AUC, terminal half-life [$t_{½}$], apparent volume of distribution at steady state [V_{ss}], and CL) of single-agent trastuzumab emtansine (3.6 mg/kg q3w) is predictable, well characterized, and unaffected by circulating levels of HER2 extracellular domain or residual trastuzumab. Trastuzumab emtansine exposure does not correlate with clinical responses or key AEs.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

At present, mBC remains an incurable disease. The primary goals of treatment are maximizing the patient's survival and preserving quality of life. Treatment options for patients with mBC have become more numerous, with the option to use sequential single agents or combination regimens. Additional considerations to use therapies directed to specific molecular subtypes of BC also serve to maximize the benefit for an individual patient.

Trastuzumab emtansine is a novel agent that has demonstrated efficacy in the treatment of HER2-positive mBC.

In study TDM4450g/BO21976, trastuzumab emtansine has shown a significant difference in PFS in favor of trastuzumab emtansine versus the

current standard of care of trastuzumab and taxane (see Section 1.2.1.4) with a favorable safety profile.

Study TDM4370g/BO21977 met its co-primary endpoint of improving PFS in patients who received trastuzumab emtansine (by IRC) and OS compared with those who received the combination of lapatinib and capecitabine. The safety profile of trastuzumab emtansine was consistent with that seen in previous studies (see Section 1.2.1.6).

An integrated safety analysis of trials TDM4370g/BO21977, TDM4450g/BO21976, TDM4373g/BO22495, TDM4374g, TDM4258g, TDM4688g, TDM3569g and TDM4529g/BO25430 demonstrated that in 884 patients who received trastuzumab emtansine, the most commonly reported AEs (i.e. fatigue [46.3%], nausea [42.9%], thrombocytopenia [29.3%], headache [29.2%], and constipation [26.4%]) and the most common Grade 3–4 AEs (i.e. thrombocytopenia [11.7%] and increased aspartate aminotransferase serum concentration [4.3%]) were typically asymptomatic and manageable (see the Investigator's Brochure).

In this new study, the safety and tolerability of trastuzumab emtansine will be explored further to gain better understanding of the safety profile of trastuzumab emtansine.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the safety and tolerability of trastuzumab emtansine.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Overall Response Rate (ORR) = partial response (PR) + complete response (CR)
- Clinical Benefit Rate (CBR)
- Duration of Response (DoR)
- Time to Response (TTR)

2.3 PHARMACOECONOMICS OUTCOME OBJECTIVE

The pharmacoeconomics outcome objective for this study is as follows:

- To evaluate the resource expenditures, while on study treatment, due to hospitalizations that are not study-defined evaluations. The number of hospital visits, number of days admitted, and type of visits (emergency department versus inpatient care) will be recorded

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 OVERVIEW

This study is a two-cohort, open-label, international, multicenter Phase IIIb study to evaluate the safety and tolerability of trastuzumab emtansine.

This study will enroll patients with HER2-positive, unresectable, locally advanced BC (LABC) or mBC who have previously received prior anti-HER2 and chemotherapy treatment and have progressed on or after the most recent treatment for LABC or mBC, or within 6 months of completing adjuvant therapy.

Approximately 2220 patients will be enrolled into the study.

- Cohort 1 (approximately 2000 patients)
- Cohort 2 (will include approximately 220 patients only of Asian race)

Overview of Cohort 1 and 2

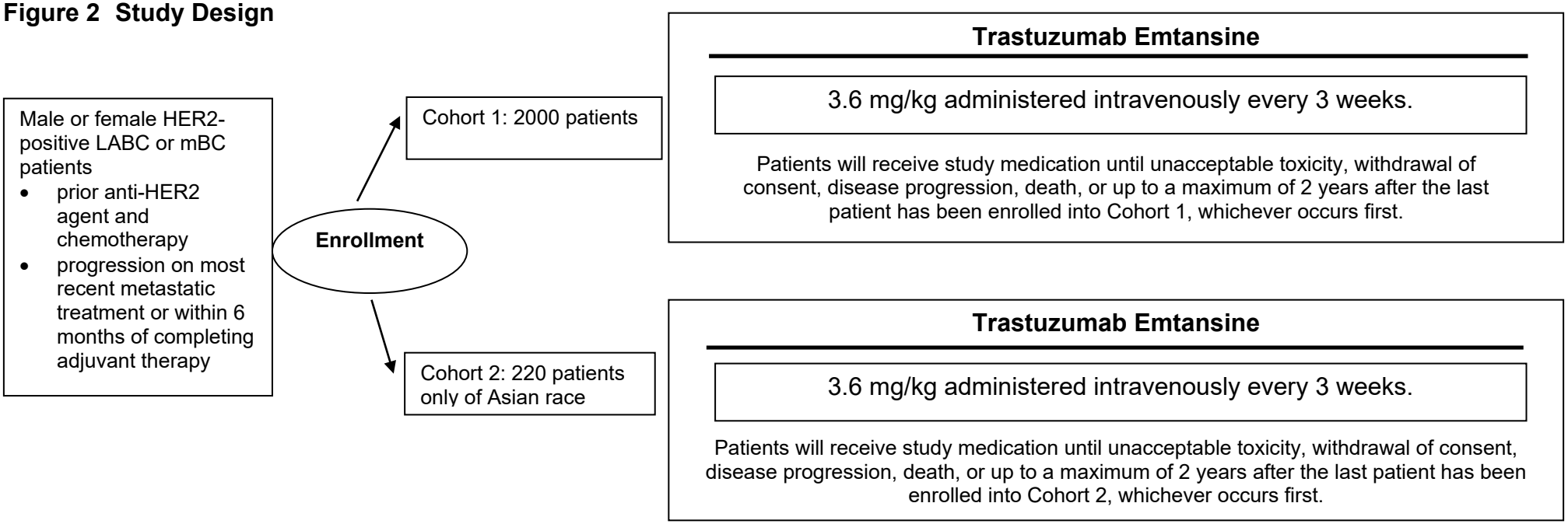
Enrollment into Cohort 2 will begin around the end of enrollment into Cohort 1. Therefore, the entire length of the study (covering enrollment and follow-up period) is estimated to be 6 years.

Patients who have not progressed at the end of the trial will be offered options to continue with trastuzumab emtansine treatment, see Section 4.2.4.

The study design is presented in Figure 2. The schedule of assessments is provided in Appendix 1.

All patients will be followed up for survival every 6 months (± 14 working days) until death, loss to follow-up or withdrawal of consent until study closure. Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 3-6 months until study closure.

Figure 2 Study Design



3.1.2 INDEPENDENT DATA MONITORING COMMITTEE

An independent data monitoring committee (iDMC) will review the safety data after approximately 50 patients have received at least one dose of study medication, with further review of accumulating safety data as required. Data will also be reviewed after each interim analysis (see Section 6.5). See the iDMC charter for further information.

3.1.3 STEERING COMMITTEE

A Steering Committee has been established for this study. It is composed of investigators participating in the study, and the Sponsor's representatives. See Steering Committee charter for further information.

3.2 END OF STUDY

The End of Study is defined as the date when the last patient, last visit (LPLV) occurs. This will be the last data collection point, which can be a clinic visit or a laboratory sample.

Cohort 1

LPLV for Cohort 1 will be approximately 4 years after enrollment of the first patient into Cohort 1. Enrollment is estimated to take 2 years and there will be 2 years of follow-up after the last patient has been enrolled into Cohort 1. Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after the last patient has been enrolled into Cohort 1, whichever occurs first.

Cohort 2

LPLV for Cohort 2 and global End of Study will be 4 years after enrollment of the first patient into Cohort 2. Enrollment is estimated to take 2 years and there will be 2 years of follow-up after the last patient has been enrolled into Cohort 2. Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after the last patient has been enrolled into Cohort 2, whichever occurs first. *Patients who are under trastuzumab emtansine treatment as of the date of version 6 of this protocol will continue under MO28231 protocol until 31 Dec 2019. After this date, or earlier if site activation in China allows, these patients will be transferred to and treated under the Kadcyla extension study protocol, BO25430.*

3.3 RATIONALE FOR STUDY DESIGN

In this two-cohort, open-label, multicenter study, the safety and tolerability of trastuzumab emtansine will be explored further to gain better understanding of the safety profile of trastuzumab emtansine.

The study design employs standard methods for Phase IIIb safety studies in patients with cancer.

The primary objective is to assess the safety and tolerability of trastuzumab emtansine in patients with HER2-positive mBC. Good efficacy and a manageable safety profile have been demonstrated in clinical trials of trastuzumab emtansine in this patient population. As this is a safety study, all patients will receive active treatment.

The ongoing study has been amended to add a second cohort to further explore the higher incidence of thrombocytopenia in the Asian population. The second cohort will enrich the total Asian population for the study. A two-cohort approach also allows for analysis of the initial population of the study before the end of the study.

Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure the safety of the patients at all times, as well as fulfilling international regulatory requirements.

3.3.1 RATIONALE FOR TEST PRODUCT DOSAGE

Trastuzumab emtansine will be administered intravenously q3w at a dose of 3.6 mg/kg over approximately 90 minutes for the first dose and 30 (±10) minutes for subsequent doses. The total trastuzumab emtansine dose will be calculated based on the patient's weight on Day 1 (or up to 28 days before) of each cycle with no upper limit.

In Study TDM3569g, the MTD of trastuzumab emtansine administered by IV infusion q3w was 3.6 mg/kg. As described in Section 1.2, clinical activity has been observed at a dose of 3.6 mg/kg q3w in two Phase II studies of single-agent trastuzumab emtansine in patients with advanced heavily pretreated HER2-positive mBC (protocols TDM4258g and TDM4374g) and in patients who had not received prior chemotherapy for metastatic disease (protocol TDM4450g and the Phase III study BO21977).

Thus, the trastuzumab emtansine dose of 3.6 mg/kg given every 3 weeks has been selected for testing in this study.

3.3.2 RATIONALE FOR CONTINUED DOSING

In the Phase I (TDM3569g) and Phase II (TDM4258g) studies of trastuzumab emtansine, 4 patients have received more than 12 months of treatment with trastuzumab emtansine at the MTD (3.6 mg/kg) on a q3w schedule, with 1 patient remaining on treatment for nearly 24 months. The reason for treatment discontinuation in these patients was due to disease progression and not toxicity. Patients who meet the criteria for ongoing clinical benefit will be allowed to continue study treatment in the absence of disease progression or unacceptable toxicity.

3.3.3 RATIONALE FOR PATIENT POPULATION

Nonclinical studies indicate that the sensitivity of cancer cells to trastuzumab emtansine requires HER2 overexpression, and measurement of such expression is a standard of care in determining eligibility for trastuzumab

therapy (see the Herceptin® Package Insert). Measurement of HER2 gene amplification has traditionally been performed using immunohistochemistry (IHC) measurement. HER2 gene amplification determined by in situ hybridization (ISH) has also proven to be a reliable method for demonstrating HER2-positive status (Press et al. 2005). Patients with incurable mBC whose tumors are positive for HER2 overexpression represent the patient population eligible for study enrollment. This study will explore the safety of trastuzumab emtansine using a two-cohort approach. The second cohort will only recruit patients who are of Asian race. A higher incidence of Grade ≥ 3 AEs has been observed in Asian patients treated with trastuzumab emtansine compared with Caucasian patients (63.6% versus 41.6%). These data were obtained from 99 Asian patients who were included in a pooled analysis of 884 patients with HER2-positive mBC who received treatment with trastuzumab emtansine 3.6 mg/kg as single agent every 3 weeks (see the Investigator's Brochure). The higher incidence of ≥ Grade 3 AEs observed was largely driven by the increased rates of Grade ≥ 3 thrombocytopenia in Asian patients. Enrollment into Cohort 2 will around the end of enrollment into Cohort 1.

3.4 OUTCOME MEASURES

3.4.1 SAFETY OUTCOME MEASURES

The primary objective of this study is to evaluate the safety and tolerability of trastuzumab emtansine.

The safety outcome measures for this study are as follows:

- Incidence, nature and severity by National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) version 4.0 of AEs and SAEs, including AEs Grade 3 or higher for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, and also all other AEs Grade 3 or higher related to trastuzumab emtansine. Pneumonitis of all grades will be analyzed.
- Incidence of congestive heart failure (CHF)
- Cases of drug-induced liver injury meeting Hy's law criteria
- Left ventricular ejection fraction (LVEF) decrease over the course of the study as measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
- Laboratory test abnormalities
- Premature withdrawal from study and study medication
- Exposure to study medication

3.4.2 EFFICACY OUTCOME MEASURES

A secondary objective of this study is to evaluate efficacy of trastuzumab emtansine treatment, assessed according to response evaluation criteria for solid tumors (RECIST) v1.1 as per investigator assessment.

The efficacy outcome measures for this study are as follows:

- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Overall Response Rate (ORR) = partial response (PR) + complete response (CR)
- Clinical Benefit Rate (CBR)
- Duration of Response (DoR)
- Time to Response (TTR)

3.4.3 PHARMACOECONOMICS OUTCOME MEASURES

The pharmacoeconomics outcomes defined in Section 2.3 will be measured.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with HER2-positive, unresectable, LABC or mBC who have previously received prior anti-HER2 and chemotherapy treatment and have progressed on or after the most recent treatment of LABC or mBC, or within 6 months of completing adjuvant therapy.

4.1.1 INCLUSION CRITERIA

1. HER2-positive disease determined locally i.e., IHC 3 + and/or gene-amplified by ISH as per institutional practice (however, both tests should be performed wherever possible and only one positive result is required for eligibility)
2. Histologically or cytologically confirmed invasive BC
3. Prior treatment for BC in the adjuvant, unresectable, locally advanced or metastatic setting must include both chemotherapy, alone or in combination with another agent, and an anti-HER2 agent, alone or in combination with another agent (complementary hormonal therapy is allowed)
4. Documented progression of incurable, unresectable, locally advanced, or mBC, defined by the investigator: progression must occur during or after most recent treatment for locally advanced/mBC or within 6 months of completing adjuvant therapy
5. Measurable and/or non-measurable disease
6. Signed written informed consent approved by the institution’s independent Ethics Committee (EC)

7. Age ≥ 18 years
8. LVEF ≥ 50% by either ECHO or MUGA
9. ECOG performance status of 0, 1 or 2
10. Adequate organ function:
    - Absolute neutrophil count > 1,500 cells/mm^3
    - Platelet count > 100,000 cells/mm^3
    - Hemoglobin > 9.0 g/dL. Patients are allowed to be transfused red blood cells to this level
    - Albumin ≥ 2.5 g/dL
    - Total bilirubin ≤ 1.5 × ULN) SGOT or AST, SGPT or ALT, and alkaline phosphatase ≤ 2.5 x ULN with the following exception: Patients with bone metastases: alkaline phosphatase ≤ 5 x ULN
    - Creatinine CL > 50 mL/min based on Cockroft-Gault glomerular filtration rate (GFR) estimation: (140 − Age) x (weight in kg) x (0.85 if female)/(72 x serum creatinine)
    - International normalized ratio (INR) < *1.5* (unless on therapeutic anti-coagulation)
11. For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception such as surgical sterilization or two effective forms of non-hormonal contraception (see Section 5.2.4)
12. Negative serum pregnancy test for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for all women not meeting the definition of postmenopausal (≥ 12 months of amenorrhea), and who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.2.4)
13. For Cohort 2, only patients of Asian race will be enrolled

4.1.2 EXCLUSION CRITERIA

1. History of treatment with trastuzumab emtansine
2. Prior enrollment into a clinical study containing trastuzumab emtansine regardless of having received trastuzumab emtansine or not
3. Peripheral neuropathy of Grade ≥ 3 per NCI CTCAE version 4.0
4. History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage 1 uterine cancer, synchronous or previously diagnosed HER2-positive BC
5. History of receiving any anti-cancer drug/biologic or investigational treatment within 21 days prior to first study treatment except hormone therapy, which can be given up to 7 days prior to first study treatment;

recovery of treatment-related toxicity consistent with other eligibility criteria

6. History of exposure to the following cumulative doses of anthracyclines:
   - Doxorubicin or liposomal doxorubicin > 500 mg/m^2
   - Epirubicin > 900 mg/m^2
   - Mitoxantrone > 120 mg/m^2
   - If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin
7. History of radiation therapy within 14 days of first study treatment. The patient must have recovered from any resulting acute toxicity (to Grade ≤ 1) prior to first study treatment
8. Metastatic central nervous system (CNS) disease only
9. Brain metastases which are symptomatic. NOTE: a 14 day window after end of radiotherapy must be observed. Patient must not be receiving steroids to control symptoms
10. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
11. History of symptomatic CHF (New York Heart Association [NYHA] Classes II−IV) or serious cardiac arrhythmia requiring treatment
12. History of myocardial infarction or unstable angina within 6 months of first study treatment
13. Current dyspnea at rest due to complications of advanced malignancy or requirement for continuous oxygen therapy
14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
15. Pregnancy or lactation
16. Currently known active infection with HIV, hepatitis B virus, or hepatitis C virus
17. History of intolerance (such as Grade 3−4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product
18. Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol throughout

4.2 STUDY TREATMENT

4.2.1 FORMULATION, PACKAGING, AND HANDLING

4.2.1.1 Trastuzumab Emtansine

Trastuzumab emtansine is provided as a single-use, lyophilized formulation in a colorless 20 mL Type I glass vial containing 160 mg of trastuzumab

emtansine closed by means of a FluroTec coated stopper and an overseal with flip-off cap. Upon receipt of trastuzumab emtansine, vials should be refrigerated at 2–8°C (36–46°F) until use. THE VIAL MUST NOT BE FROZEN OR SHAKEN. Trastuzumab emtansine must be stored in the original carton to protect it from light. Do not use the product beyond the expiration date provided by the manufacturer. The reconstituted product contains no preservative and is intended for single use only. Any remaining medication should be discarded.

All vials of trastuzumab emtansine should be handled by appropriately trained site staff wearing gloves and using appropriate procedures in place at the clinical site for preparation of chemotherapeutic drugs. Vials should be visually inspected upon receipt to ensure that they are intact without exterior contamination. Discard any cracked vials and report vials with surface contamination to the clinical site manager for assessment.

The lyophilized product should be reconstituted using Sterile Water for Injection (SWFI). Using a new syringe, 8 mL SWFI should be added to the vial and the vial swirled gently until the product is completely dissolved. The vial should not be shaken. The resulting product contains 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 60 mg/mL sucrose, and 0.02% (w/v) polysorbate 20. Each 20 mL vial contains enough trastuzumab emtansine to allow delivery of 160 mg trastuzumab emtansine. The reconstituted product contains no preservative and is intended for single use only.

The vial should be inspected to ensure the reconstituted product is a clear colorless solution, and is free of particulates before proceeding. Drug from any vial that appears abnormal upon inspection should not be administered to patients. Using a new syringe, the indicated volume of trastuzumab emtansine solution should be removed from the vial(s) and added to the IV bag containing at least 250 mL of 0.45% sodium chloride (preferred) or 0.9% sodium chloride injection and gently inverted to mix the solution. A 0.22 micron non-protein adsorptive polyethersulfone in-line filter is recommended when using 0.45% sodium chloride and required when using 0.9% sodium chloride injection. The solution of trastuzumab emtansine should not be shaken.

The solution of trastuzumab emtansine for infusion should be used immediately. If not used immediately, storage times should not be longer than 24 hours at 2–8°C (36–46°F) for solutions of trastuzumab emtansine diluted in polyvinyl chloride (PVC) or latex free PVC-free polyolefin, polypropylene, or polyethylene bags containing 0.45% or 0.9% Sodium Chloride for injection.

For additional details, please refer to the current version of the trastuzumab emtansine Investigator’s Brochure.

4.2.2 DOSAGE AND ADMINISTRATION

4.2.2.1 Trastuzumab Emtansine

Trastuzumab emtansine will be administered on Day 1 of a 3-week cycle q3w at a dose of 3.6 mg/kg IV unless dose reductions or dose delays are required. The total dose will be calculated based on the patient's weight up to 28 days before each cycle with no upper limit. If within these 28 days the patient experiences a severe weight loss, the dose should be recalculated accordingly.

If the timing of trastuzumab emtansine coincides with a holiday that precludes the procedure, the procedure should be performed within 3 working days of the scheduled date and, when possible, on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly.

The first infusion of trastuzumab emtansine will be administered over 90 minutes (±10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion associated symptoms. Vital signs must be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions), subsequent doses of trastuzumab emtansine may be administered over 30 minutes (±10 minutes), with a minimum 30 minutes observation period following infusion. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, death, or up to a maximum of 2 years after last patient has been enrolled into the trial, whichever occurs first. Patients who have not progressed at the end of the trial will be offered options to continue with trastuzumab emtansine treatment, see Section 4.2.4.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.8.

4.2.3 INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

The investigational medicinal product (IMP) required for completion of this study (trastuzumab emtansine) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, using the interactive voice/web recognition system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP 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 upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.2.4 POST-TRIAL ACCESS TO EXTENSION STUDY

The study will be concluded after the last patient has been followed up for 2 years after last patient has been enrolled.

Patients who have not progressed at the end of the trial will be offered the following options to continue with treatment:

- Patients in countries in which trastuzumab emtansine is approved and reimbursed for this indication at the study end, may continue treatment outside this study in accordance with local labeling and reimbursement.
- Patients in countries in which trastuzumab emtansine is not approved and/or not reimbursed for this indication or local regulations do not allow patients to receive continued treatment in this way, will be offered the possibility to continue treatment in an extension study *(BO25430)*.

*Since there is a delay in activation of sites in China for BO25430 as of the date of version 6 of this protocol, patients who are under trastuzumab emtansine treatment will continue under MO28231 protocol until 31 Dec 2019. After this date, or earlier if site activation allows, these patients will be transferred to and treated under the Kadcyla extension study protocol, BO25430.*In case a patient decides to withdraw from the study, no post-trial access will be granted. Currently, the Sponsor does not have any plans to provide other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.3 CONCOMITANT THERAPY

4.3.1 PERMITTED THERAPY

Concomitant therapy and premedication are defined as non-IMP.

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient between the 14 days preceding first treatment and the safety follow-up visit. Afterwards, only anti-cancer therapies will be recorded on the Concomitant Medications electronic Case Report Form (eCRF), as part of the survival follow-up period.

Premedication is allowed according to standard practice guidelines.

No premedication for the first infusion of trastuzumab emtansine is required; however, premedication is allowed at the investigator's discretion.

Concomitant use of erythropoiesis-stimulating agents is allowed if clinically indicated in accordance with local prescribing guidelines.

Palliative radiotherapy may be permitted to treat pre-existing bone metastases or to treat brain metastases (for patients who have disease control outside of the brain). Radiotherapy should be finished at least 7 days before resuming

administration of trastuzumab emtansine and all toxicities need to have resolved. If not, the cycle may be delayed for up to 42 days. Please contact the Medical Monitor for approval. If the Medical Monitor cannot be reached because of time zone differences, radiotherapy may be administered, but the Medical Monitor should still be informed.

Other medications considered necessary for the patient's safety and wellbeing may be given at the discretion of the investigator. Use of bisphosphonates or denosumab is permitted for the control of bone pain, prevention and/or treatment of bony metastases, and treatment of osteoporosis. If bisphosphonates are required for the treatment of symptomatic malignancy-associated hypercalcemia, tumor assessments should be performed to assess for potential disease progression. Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, antihistamines such as diphenhydramine, or corticosteroids) may also be given at the investigator's discretion.

Any Chinese traditional medicines that could potentially negatively impacting the liver functions are not permitted. However, any Chinese traditional medicines having a liver protective action would be considered acceptable, at the investigator's discretion. It will be the investigator's responsibility to verify whether a specific Chinese medication could potentially affect liver function.

4.3.2 PROHIBITED THERAPY

Use of the therapies described below is prohibited during the study prior to discontinuation of study treatment (collectively, these will be referred to as non-protocol therapy).

Any therapies intended for the treatment of cancer, other than trastuzumab emtansine, whether they are approved by national health authorities or experimental, including cytotoxic chemotherapy, immunotherapy, hormonal therapy (other than megestrol acetate), and biologic or targeted agents (other than granulocyte colony-stimulating factor and erythropoiesis-stimulating agents), are prohibited. *The use of Chinese traditional medicines in case when they have no anti-cancer activity are allowed at the investigator's discretion.*

Radiotherapy for unequivocal disease progression is not permitted while on study treatment, with the exception of new brain metastases or isolated progression of previously treated brain lesions. Patients who have disease control outside of the brain, defined as continued PR or CR of any duration, or stable disease for ≥ 4 months, but who have developed brain metastases that are treatable with radiation will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain that cannot be treated with additional radiation. Radiotherapy should be finished at least 7 days before resuming administration of trastuzumab emtansine and all toxicities need to have resolved. The Medical Monitor should be informed before a decision is made to resume study treatment after radiotherapy for brain metastases.

Patients with thrombocytopenia and on anti-coagulant treatment must be monitored closely during treatment with trastuzumab emtansine. Platelet counts will be monitored prior to each trastuzumab emtansine dose.

4.4 STUDY ASSESSMENTS

4.4.1 DESCRIPTION OF STUDY ASSESSMENTS

All patients will be closely monitored for safety and tolerability during all cycles of therapy and at the safety follow-up visit:

- Trastuzumab emtansine will be administered in 21-day cycles. Dose delays and dose reductions will be allowed for trastuzumab emtansine as outlined in Section 5.1.8
- Visits will be based on a 21-day cycle. Study assessments are outlined in this section and in Appendix 1.

4.4.1.1 Medical History and Demographic Data

Medical history includes previous clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to the screening visit.

Demographic data will include age, sex, and self-reported ethnicity.

4.4.1.2 Vital Signs

Abnormal or significant changes to vital signs (e.g., pulse rate, body temperature or blood pressure) from baseline should be recorded as AEs, if appropriate.

4.4.1.3 Physical Examinations

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

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

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

4.4.1.4 Tumor and Response Evaluations

Measurable and unmeasurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments with computed tomography (CT) or magnetic resonance imaging (MRI) scans with contrast of the chest, abdomen, and pelvis are to be performed as described in Appendix 1 (Schedule of Assessment). CT or MRI of the brain and baseline radioisotope bone scan must be obtained at screening. If an isotope-based scan was performed ≥ 28 days but ≤ 60 days prior to first treatment the bone scan does not need to be repeated and non-isotopic radiographic modalities should be utilized to document the extent of bony metastatic disease. Tumor assessments should include an evaluation of all known and/or suspected sites of disease, whenever possible. Patients should have lesions selected that can be evaluated at every tumor assessment. The same radiographic procedure used at screening must be used throughout the study for the same patient (e.g., the same contrast protocol for CT scans). Response assessments will be assessed by the investigator, based on physical examinations, CT or MRI scans, and bone scans using RECIST v. 1.1 (Appendix 2). In the event a positron emission tomography (PET)/CT scanner is used for tumor assessments, the CT portion of the PET/CT must meet criteria for diagnostic quality. For patients who continue study treatment after isolated brain progression, the frequency of follow-up scans is at the discretion of the investigator.

At the investigator's discretion, CT scans, MRI scans, and/or bone scans may be obtained at any time when clinically indicated or if PD is suspected. If a bone scan cannot be performed during the course of the study because of the unavailability of the Tc-99m isotope, the investigator may choose an alternative imaging modality (Appendix 3).

Radiographic imaging should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination. In applying RECIST, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

4.4.1.5 Scheduling of Tumor Assessments

Baseline total tumor burden must be assessed within a maximum of 28 days before first dose of study drug treatment. Post-baseline assessments are to be performed every 12 weeks, taking Day 1 of Cycle 1 as reference. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

After Cycle 1, Day 1, all tumor assessments should be performed ± 12 weeks +/- 5 working days of the scheduled visit, regardless of any delays in treatment or other assessments. If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. The schedule of assessments is provided in

Appendix 1 and is independent from drug administration (i.e., assessments should not be delayed in case of delayed drug administration).

After disease progression, assessments are no longer required to evaluate new lesions, non-target lesions, and target lesions.

4.4.1.6 LVEF Assessment

LVEF assessments will be performed within 28 days of enrollment, on Day 21 (or -7 days) of the cycle for Cycle 1, on Day 21 (or -7 days) of Cycle 3 and every third cycle thereafter, by either ECHO or MUGA scan (with ECHO as the preferred method). Patients will be reassessed with the same technique used for baseline cardiac evaluation throughout the study and, to the extent possible, will be obtained at the same institution for an individual patient. If treatment is delayed for any reason, LVEF assessments can be postponed to allow them to be performed within 7 days prior to the next treatment administration.

ECHO is the preferred modality because of the global technetium (Tc-99m) shortage (see Section 4.4.1.4 and Appendix 3). The same method used at screening should be used throughout the study.

4.4.1.7 ECOG Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 4).

It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study.

Performance status will be assessed according to the schedule of assessments (see Appendix 1).

4.4.1.8 Laboratory Assessments

Samples for HER2 testing, hematology, biochemistry, urinalysis, and INR assessments, coagulation, and pregnancy testing will be analyzed at the study site's local laboratory.

Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, red blood cell count, platelet count, white blood cell count with differential [including neutrophils, lymphocytes, monocytes, eosinophils and basophils])
- Serum chemistry (sodium, potassium, chloride, calcium, magnesium, glucose, blood urea nitrogen [BUN], creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT [SGPT], AST [SGOT], gamma-glutamyl transferase, lactate dehydrogenase, total bilirubin and direct bilirubin where total bilirubin > ULN)
- INR
- Urinalysis (includes specific gravity, pH, protein, glucose, blood, ketones, and bilirubin)

- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Testing should be performed at a local laboratory within 7 days prior to the first administration of study medication (Cycle 1, Day 1). For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. Urine pregnancy test in women of childbearing potential must be performed every 3 cycles and at 3- and 6- months after the safety follow-up visit. All positive urine pregnancy tests must be confirmed by a serum β-HCG test.

4.4.1.9 Electrocardiograms

A 12-lead ECG should be obtained at baseline and be printed and kept with the patient's record.

4.4.1.10 Pharmacoeconomics Evaluation

To evaluate pharmacoeconomics outcomes (see in Sections 2.3 and 3.4.3), the number of hospital visits, number of days admitted, and type of visits (emergency department versus inpatient care) will be entered in the eCRF.

4.4.2 TIMING OF STUDY ASSESSMENTS

4.4.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Once the patient has signed the informed consent form, the investigator (or his designee) will call the IxRS to obtain the screening number for the patient prior to Cycle 1, Day 1. Informed consent forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. The IxRS will be available, 24 hours a day, 7 days a week. Detailed instructions regarding the IxRS will be provided to each study center. The screening numbers are to be allocated according to the specification document agreed with the IxRS provider.

Screening tests and evaluations will be performed according to the schedule of assessments (see Appendix 1) prior to first administration of study medication (dosing), after confirmation of other eligibility criteria, unless the procedures have already been conducted during the defined time period (see Appendix 1) as part of the patient's routine clinical care. Patient must have stable liver tests prior to the first dose of study drug.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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.

HER2-positive status on fixed blocks from the primary tumor (and/or metastatic site, if primary tumor not available) will be assessed locally by IHC

and/or ISH according to institutional criteria. These two different tests should be performed wherever possible.

Results from archival tissue are acceptable.

See Appendix 1 for the schedule of screening assessments.

4.4.2.2 Assessments during Treatment

During the treatment period, a window of ± 3 working days will apply to all visits and assessments, unless otherwise specified (see Appendix 1). This window of ± 3 working days also applies for the study treatment administration at each cycle. Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the Schedule of Assessments.

Please see Section 4.4.1.5 (Scheduling of Tumor Assessment) and Appendix 1 for the schedule of assessments performed during the treatment period.

4.4.2.3 Assessments at Safety Follow-up Visit

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first.

All patients will continue to be followed up every 6 months (± 14 working days, except for pregnancy test, which is at 3 and 6 months after safety follow-up visit) for 2 years after the last patient is enrolled, unless they have been lost to follow-up, withdrawn consent, *or* died (whichever occurs first).

Patients who discontinue from study treatment will be asked to return to the clinic 28-42 days after the last dose of study drug for the safety follow-up visit. The visit at which response assessment shows PD may be used as the safety follow-up visit.

See Appendix 1 for the schedule of assessments performed at the safety follow-up visit.

4.4.2.4 Follow-Up Assessments

After the safety follow-up visit, AEs should be followed as outlined in Sections 5.5 and 5.6.

All patients will be followed up for survival every 6 months (± 14 working days; except for pregnancy test, which is at 3 and 6 months after the safety follow-up visit) until death, loss to follow-up, or withdrawal of consent *or* study closure. Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 3-6 months *until disease progression occurs*. If assessments cannot be done at survival visits, the study site is permitted to collect survival information by phone call. After disease progression, patients will be followed up for survival every 6 months (± 14 working days) until death, loss to follow-up, withdrawal of consent, *or study closure* (whichever occurs first). Assessments are no

longer required to evaluate new lesions, non-target lesions, and target lesions. However a visit to collect survival information is still required. If a visit cannot be done, the study site is permitted to collect survival information by phone call.

See Appendix 1 for the schedule of follow-up assessments.

4.4.2.5 Assessments at Unplanned Visits

In case unplanned visits are required, eCRF pages will be available to report the information collected during those visits.

4.5 PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 PATIENT DISCONTINUATION

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or 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
- Noncompliance
- Disease progression

Patients who discontinue from study treatment prematurely for any of the above reasons except withdrawal of consent will continue to be followed according to Section 4.4.2.4 "Follow-Up assessments". The primary reason for discontinuation must be recorded on the appropriate eCRF page.

4.5.1.1 Discontinuation from Study Drug

Details of discontinuation due to toxicity are given in Section 5.1.

Patients who discontinue study drug prematurely will be asked to return to the clinic for a safety follow-up visit (see Section 5.5), and may undergo follow-up assessments (see Section 5.6). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.5.1.2 Withdrawal from Study

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs, treatment failure after a prescribed procedure, protocol violation, cure, administrative reasons, or for other reasons.

Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an AE, the principal specific event will be recorded on the Adverse Event eCRF.

In the case that the patient decides to prematurely discontinue study treatment ("refuses treatment"), he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in the medical records.

4.5.2 STUDY AND SITE DISCONTINUATION

The global End of Study is considered as the date of LPLV, this is defined as the last data collection point, which can be a clinic visit or a laboratory sample.

The last clinic visit is defined as the safety follow-up for the last mBC patient, which will happen, at the latest, 2 years after the last patient has been enrolled into Cohort 2 of the trial.

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 AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing 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 Harmonization (ICH) guidelines for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Overall safety will be assessed on an ongoing basis during the conduct of the study. The iDMC will monitor cumulative safety data as required (see iDMC charter) and Section 3.1.2. In addition, data on SAEs and deaths will be also

monitored by the Steering Committee (see Steering Committee charter and Section 3.1.3).

The safety plan for patients having trastuzumab emtansine treatment is based on nonclinical toxicities of trastuzumab emtansine, clinical experience with this molecule in completed and ongoing studies, and clinical toxicities related to its components (trastuzumab and maytansine, the parent drug of DM1). Some of the important safety risks anticipated with this treatment as well as measures intended to avoid or minimize such toxicities are outlined below. Please refer to the trastuzumab emtansine Investigator's Brochure for the most recent comprehensive information on the safety profile of trastuzumab emtansine.

Trastuzumab emtansine dose modifications are described in Section 5.1.8.

5.1.1 CARDIOTOXICITY

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) $<$ 40% has been observed in patients treated with trastuzumab emtansine. Patients without significant cardiac history and with an LVEF ≥ 50% determined by ECHO or MUGA scan are eligible for study participation. LVEF will be monitored at screening and regularly throughout the study until the assessment at the safety follow-up visit. Patients with symptomatic cardiac dysfunction will be discontinued from study treatment. Asymptomatic LVEF declines will be handled as per the algorithm shown in Figure 3. Treatment with trastuzumab emtansine has not been studied in patients with LVEF $<$ 50%.

5.1.2 HEMATOLOGIC TOXICITY (THROMBOCYTOPENIA)

Thrombocytopenia, or decreased platelet counts, was reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (≥ 50,000/mm^3), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (≥ 75,000/mm^3) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

Severe cases of both non-fatal and fatal hemorrhagic events, including CNS hemorrhage, have been reported in clinical trials with trastuzumab emtansine; these events were independent of the patients' ethnicity. In some of the observed cases, the patients were also receiving anti-coagulation therapy. There was no clear correlation between the severity of thrombocytopenia and severe hemorrhagic events. The need for platelet transfusions has been reported.

Patients with thrombocytopenia and on anti-coagulant treatment have to be monitored closely during treatment with trastuzumab emtansine. Platelet counts will be monitored prior to each trastuzumab emtansine dose.

Use of erythropoiesis-stimulating agents will be allowed as consistent with prescribing guidelines. Transfusion of red blood cells and/or platelets will be allowed according to and at the discretion of the treating physician.

5.1.3 HEPATOTOXICITY

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1 – 4 transaminitis), has been observed in patients while on treatment with trastuzumab emtansine in clinical trials. Transaminase elevations were generally transient. The incidence of increased AST was substantially higher than that for ALT. The proportion of patients with Grade 1 or 2 increases in transaminases increased with successive cycles, suggesting a modest cumulative effect of trastuzumab emtansine on transaminases; however, no increase over time in the proportion of Grade 3 abnormalities was observed. Patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine in the majority of the patients.

Rare cases of severe hepatotoxicity, including death due to drug-induced liver injury and associated hepatic encephalopathy, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases of acute liver injury may have been confounded by concomitant medications with known hepatotoxic potential and/or underlying conditions. An acute severe liver injury (Hy's law) case has the following components:

- Aminotransferase enzymes (ALT/AST) greater than 3 × ULN with concurrent elevation of serum total bilirubin to > 2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and serum total bilirubin, such as viral Hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed injury.
- The finding should be serious as shown by gross jaundice, clinical disability, need for hospital care, and be at least probably drug-induced (by trastuzumab emtansine)

Trastuzumab emtansine treatment in patients with serum transaminases $> 3 \times$ ULN and concomitant total bilirubin $> 2 \times$ ULN should be permanently discontinued

Patients must have adequate and stable liver function: hepatic transaminases (AST/ALT) and total bilirubin must be within acceptable range, as defined in the protocol, within 4 weeks prior to the first dose of trastuzumab emtansine. Liver function will be monitored prior to each trastuzumab emtansine dose. Trastuzumab emtansine is currently being studied in patients with HER2-positive mBC with serum transaminases $> 2.5 \times$ ULN or total bilirubin $> 1.5 \times$ ULN prior to initiation of treatment (Study BO25499).

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine and presenting with signs and symptoms of portal hypertension. NRH was also observed in one fatal case of hepatic failure. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can only be confirmed by histopathology.

NRH should be considered in patients who develop clinical symptoms of portal hypertension and/or a cirrhosis-like pattern seen on CT scan of the liver but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with trastuzumab emtansine. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.

5.1.4 PULMONARY TOXICITY

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome, have been reported in clinical trials with trastuzumab emtansine. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. Treatment has included administration of steroids and oxygen, and study drug discontinuation. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events.

Treatment with trastuzumab emtansine has to be permanently discontinued in patients who are diagnosed with ILD or pneumonitis.

5.1.5 INFUSION-RELATED REACTIONS/HYPERSENSITIVITY

Infusion-related reactions characterized by one or more of the following symptoms, flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia may occur with the administration of monoclonal antibodies and have been reported with trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Patients should be observed closely for infusion-related reactions, especially during the first infusion.

Patients should be observed closely for hypersensitivity. Serious, allergic/anaphylactic-like reactions have been observed in clinical trials with treatment of trastuzumab emtansine. Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients will be observed closely for infusion-related/hypersensitivity during and after each trastuzumab emtansine infusion for a minimum of 90 minutes after the first infusion and for a minimum of 30 minutes after subsequent infusions in the absence of infusion-related AEs. Premedication is allowed according to standard practice guidelines. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued. Patients who experience a Grade $\geq$ 3 allergic reaction or acute respiratory distress syndrome will be discontinued from study treatment.

5.1.6 NEUROTOXICITY

DM1, an anti-microtubule agent, can potentially cause peripheral neuropathy. Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine. Treatment with trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until symptoms resolve or improve to ≤ Grade 2. Patients should be examined for signs of peripheral neuropathy prior to each dose of trastuzumab emtansine. Patients who experience Grade ≥ 3 neurotoxicity in the form of peripheral neuropathy that does not resolve to Grade ≤ 2 within 42 days after last dose received will be discontinued from study treatment.

5.1.7 EXTRAVASATION

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Rare reports of more severe events such as cellulitis, pain (tenderness and burning sensation), and skin irritation have been received as part of the continuing surveillance of trastuzumab emtansine safety. These reactions have been observed more frequently within 24 hours of infusion. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

5.1.8 TRASTUZUMAB EMTANSINE DOSE MODIFICATION

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable.

Dose delays and reductions are designed to maximize treatment for those who derive clinical benefit from treatment while ensuring patient safety. Dose delays for trastuzumab emtansine–related toxicity other than the ones specified below (i.e., infusion reactions, hematologic toxicity, hepatotoxicity, neurotoxicity, cardiotoxicity, and ILD or pneumonitis) are as follows:

- If significant trastuzumab emtansine–related toxicities (other than infusion reactions, thrombocytopenia, hepatotoxicity, neurotoxicity, cardiotoxicity, and ILD or pneumonitis) have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days from the last dose received. *"*Significant*"* and *"*related*"* will be based on the judgment of the investigator (in consultation with the Sponsor's Medical Monitor or designee when appropriate). For example, alopecia even if considered related would most likely not be considered to be significant. Fatigue may or may not be considered either related or significant.
- In general, when the significant and related toxicity (or any other toxicity that the investigator chooses to delay dosing for) resolves to Grade 1 or baseline, the patient may resume trastuzumab emtansine if the delay has not exceeded 42 days from the last received dose. Patients should be re-evaluated weekly during the delay, whenever possible. If dosing

resumes, the patient may receive trastuzumab emtansine either at the same dose level as before or at one dose level lower (see Table 2), at the discretion of the investigator. Subsequent cycles should remain q3w, and patients should be assessed for toxicity.

- If a patient requires a dose reduction, dosing will be reduced by one dose level, per Table 2. No dose re-escalation will be allowed.
- If a toxicity does not resolve within 42 days from the last dose received, the patient will be discontinued from study treatment and will be followed for disease progression and survival outcome as described in Section 5.5.
- Patients who experience a Grade 3 or 4 hematologic event should be checked at least weekly for recovery. If values do not recover to baseline or Grade ≤ 1 within 42 days from the last dose received, the patient will be discontinued from study treatment.

Table 2 Dose Reduction for Trastuzumab Emtansine

Dose Level	Dose
0	3.6 mg/kg
−1	3.0 mg/kg
−2	2.4 mg/kg
Indication for further dose reduction	Off study

Protocol requirements for specific toxicities are outlined below.

5.1.8.1 Trastuzumab Emtansine Dose Modification for Thrombocytopenia

Platelet counts should be obtained no less frequently than weekly to evaluate recovery whenever any of the events listed below occurs. If platelet counts do not recover to Grade ≤ 1 within 42 days from the last dose received, the patient will be discontinued from study treatment.

No re-escalation of the trastuzumab emtansine dose is allowed.

Note: although complete blood counts with platelets are required within 72 hours prior to study treatment administration at each cycle, the investigator may monitor platelet counts (or any other laboratory test) more frequently as clinically indicated.

In the event of decreased platelet count to Grade 3 ($< 50{,}000/mm^3$), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq 75{,}000/mm^3$) then treat at the same dose level.

Patients receiving trastuzumab emtansine who experience a first Grade 4 thrombocytopenia event may, after adequate recovery to a platelet count of Grade ≤ 1 or baseline, continue treatment with trastuzumab emtansine at a dose of 3 mg/kg in subsequent treatment cycles. Patients at the 3 mg/kg dose level who experience a Grade 4 thrombocytopenia event may, after adequate recovery as defined above, continue treatment with trastuzumab emtansine at a dose of 2.4 mg/kg in subsequent treatment cycles. Patients who experience

a Grade 4 thrombocytopenia event at the 2.4 mg/kg dose level will be discontinued from study treatment. A dose delay of up to 42 days from the patient's last dose received is permitted.

5.1.8.2 Trastuzumab Emtansine Dose Modification for Hepatotoxicity

5.1.8.2.1 Concurrent elevations of ALT/AST and Bilirubin Meeting Hy's Law laboratory Criteria

Regardless of dose level, trastuzumab emtansine must be permanently discontinued in patients with ALT and/or AST > 3 × ULN and concurrent increase of total bilirubin to > 2 × ULN. All relevant hepatic laboratory tests performed (including AST, ALT, total bilirubin, alkaline phosphatase, INR, and albumin) will be entered into the clinical database.

5.1.8.2.2 Nodular Regenerative Hyperplasia (NRH)

Trastuzumab emtansine must be permanently discontinued in patients who are diagnosed with NRH.

5.1.8.2.3 Transaminase Elevations or Bilirubin Elevation Requiring Dose Adjustment

Liver function should be stable before the first dose of trastuzumab emtansine and monitored at least prior to each infusion. Patients who experience a Grade 3 elevation of liver function should be checked twice weekly for the recovery of total bilirubin and/or transaminases. If a patient's transaminases and/or total bilirubin do not recover as per Table 3 and Table 4, within 42 days from the patient's last dose received, the patient will be discontinued from study treatment.
No re-escalation of the trastuzumab emtansine dose is allowed.

Table 3 and Table 4 describe the dose modification guidelines for increases in serum bilirubin and transaminases, respectively.

Table 3 Trastuzumab Emtansine Dose Modification: Total Serum Bilirubin

Grade 2 (> 1.5 to ≤ 3 × the ULN)	Grade 3 (> 3 to ≤ 10 × the ULN)	Grade 4 (> 10 × the ULN)
Do not administer T-DM1 until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level.	Do not administer T-DM1 until total bilirubin recovers to Grade ≤ 1 and then reduce one dose level.	Discontinue T-DM1.

T-DM1 = trastuzumab emtansine; ULN = upper limit of normal.

Note: A maximum of two trastuzumab emtansine dose reductions is allowed. A patient requiring more than two dose reductions must discontinue study treatment.

Table 4 Trastuzumab Emtansine Dose Modification: Serum ALT or AST

Grade 2 (> 3 to ≤ 5 × the ULN)	Grade 3 (> 5 to ≤ 20 × the ULN)	Grade 4 (> 20 × the ULN)
Treat at the same dose level.	Do not administer T-DM1 until AST/ALT recovers to Grade ≤ 1, and then reduce one dose level.	Discontinue T-DM1.

ALT = alanine transaminase; AST = aspartate transaminase; T-DM1 = trastuzumab emtansine; ULN = upper limit of normal.

Note: A maximum of two trastuzumab emtansine dose reductions is allowed. A patient requiring more than two dose reductions must discontinue study treatment.

5.1.8.3 Trastuzumab Emtansine Dose Modification for Neurotoxicity

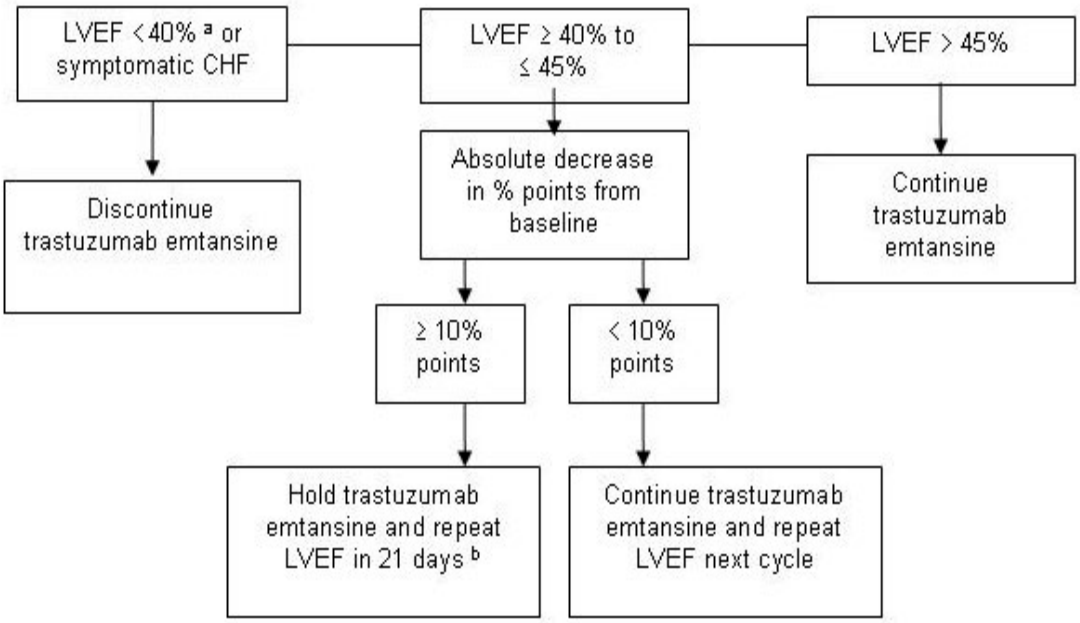
Patients receiving trastuzumab emtansine who experience Grade 3 or 4 peripheral neuropathy that does not resolve to Grade ≤ 2 within 42 days after the last dose received will be discontinued from study treatment.

5.1.8.4 Trastuzumab Emtansine Dose Modification for Cardiotoxicity

Patients without significant cardiac history and with a baseline LVEF ≥ 50% as determined by ECHO or MUGA scan are eligible for study participation. LVEF will be monitored on Day 21 of the cycle for Cycle 1, Cycle 3 and every third cycle thereafter until the assessment at the safety follow-up visit.

Figure 3 summarizes the management of trastuzumab emtansine on the basis of measured LVEF and changes in LVEF from baseline in patients. If the LVEF is reported as a range, the median of the range should be taken. If an investigator is concerned that an AE may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any patient who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

Figure 3 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Based on Left Ventricular Ejection Fraction Assessments in Patients



LVEF = left ventricular ejection fraction.

Note: LVEF assessment results must be reviewed before the next scheduled trastuzumab emtansine infusion.

[a] LVEF can be repeated within 21 days, and trastuzumab emtansine should be discontinued if LVEF < 40% is confirmed. Trastuzumab emtansine should be held while the repeat LVEF is obtained.

[b] After a second consecutive confirmatory result, trastuzumab emtansine should be discontinued if the LVEF is confirmed to be ≥ 10% points below baseline or if medical management was required to correct the LVEF.

The decision to stop or continue trastuzumab emtansine should be based on the algorithm shown in Figure 3. Trastuzumab emtansine must be discontinued in all patients for whom a confirmed drop of LVEF to below 40% is documented (with a repeat assessment within 21 days). For patients whose LVEF drops to values between 40% and 45% with an absolute decrease in LVEF of ≥ 10% points from baseline, trastuzumab emtansine should be held. For these patients, the LVEF should be repeated in 21 days, and trastuzumab emtansine should be discontinued if the LVEF has not recovered to within 10% absolute difference below baseline. If clinically significant cardiac dysfunction or cardiac failure develops or persists or if significant medical management is required to maintain ejection fraction, the patient should be discontinued from study treatment.

5.1.8.5 Trastuzumab Emtansine Dose Modification for Infusion-Related Reactions, Hypersensitivity Reactions

Trastuzumab emtansine treatment should be interrupted in patients with severe infusion-related reactions. Trastuzumab emtansine treatment should

be permanently discontinued in the event of life-threatening infusion-related reactions.

Infusion of trastuzumab emtansine should be interrupted for patients who develop dyspnea or clinically significant hypotension.

The infusion should be slowed to ≤ 50% or interrupted for patients who experience any other infusion-related symptoms. When the patient's symptoms have completely resolved, the infusion may be continued at ≤ 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate during the next cycle.

Patients who experience trastuzumab emtansine infusion-related temperature elevations to > 38.5°C and/or other infusion-related symptoms may be treated symptomatically with acetaminophen and/or diphenhydramine hydrochloride. Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive care such as oxygen, beta agonists, antihistamines, antipyretics, or corticosteroids at the investigator's discretion. Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent infusions of trastuzumab emtansine at the investigator's discretion. Patients should be monitored until complete resolution of symptoms. Patients who experience a Grade ≥ 3 hypersensitivity reaction or acute respiratory distress syndrome will be discontinued from the study.

Patients who experience a severe delayed infusion reaction will be discontinued from study treatment.

5.1.8.6 Trastuzumab Emtansine Dose Modification for Pulmonary Toxicity

Cases of ILD including pneumonitis (including severe, life-threatening cases) and some leading to acute respiratory distress syndrome or fatal outcome has been rarely reported with trastuzumab emtansine. Treatment with trastuzumab emtansine has to be permanently discontinued in patients who are diagnosed with ILD or pneumonitis.

5.1.8.7 Trastuzumab Emtansine Dose Modification for Extravasation

During clinical development of T-DM1, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised of erythema, tenderness, skin irritation, pain or swelling at the infusion site. Although T-DM1 is not considered as a vesicant, close monitoring of the infusion site for possible subcutaneous infiltration during drug administration is recommended.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (AESIs; see Section 5.2.3 for details); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 5.4.

5.2.1 ADVERSE EVENTS

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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 5.3.5.7
- 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
- AEs 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 SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that had occurred in a more severe form or had been allowed to continue and might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.8)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)

- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); 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 AE recorded on the eCRF.

SAEs 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 5.4.2 for reporting instructions).

5.2.3 PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST/NON-SERIOUS EXPEDITED ADVERSE EVENTS

Non-serious AESIs 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 5.4.2 for reporting instructions).

AESIs for this study include the following:

- Potential drug-induced liver injury
- Suspected transmission of an infectious agent by the study drug

Potential drug-induced liver injury:

Any potential case of drug-induced liver injury as assessed by laboratory criteria for Hy’s law will be considered as a protocol-defined event of special interest and will need to be reported to the Sponsor expeditiously. The following laboratory abnormalities define potential Hy’s law cases:

- AST and/or ALT elevations that are > 3 × ULN
- Concurrent elevation of total bilirubin > 2 × ULN (or clinical jaundice if total bilirubin measures are not available), except in patients with documented Gilbert’s syndrome. For patients with Gilbert’s syndrome, elevation of direct bilirubin > 2 × ULN should be used instead.

Suspected transmission of an infectious agent by the study drug:

- 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 indicating an infection in a patient exposed to a medicinal product. This term ONLY

applies when a contamination of the study drug is suspected, NOT for infections supported by the mode of action, e.g., immunosuppression.

5.2.4 PREGNANCY AND CONTRACEPTION

ICH M3 guidance requires precautions to be taken to minimize risk to fetus or embryo when including women of childbearing potential in clinical studies. These precautions include the use of highly effective contraceptive measures, excluding pregnancy at baseline (serum test), continued pregnancy monitoring, and continued pregnancy testing for up to 6 months after the safety follow-up visit (follow-up period based on PK considerations).

Trastuzumab, a component of trastuzumab emtansine, can cause fetal harm when administered to a pregnant woman; post-marketing case reports indicate that its use during pregnancy increases the risk for oligohydramnios during the second and third trimester. Trastuzumab has also been associated with fetal pulmonary hypoplasia, skeletal abnormalities, and neonatal death (see the Herceptin® Package Insert). There are no clinical studies of trastuzumab in pregnant women. Immunoglobulin G (IgG) is known to cross the placental barrier.

Therefore, trastuzumab emtansine should be not used during pregnancy. Women of childbearing potential (who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy) and men with partners of childbearing potential must agree to use a highly effective non-hormonal form of contraception or two effective forms of non-hormonal contraception by the patient and/or partner.

Methods of birth control which result in a low failure rate (i.e., < 1% per year) when used consistently and correctly are considered highly effective forms of contraception. The use of the following non-hormonal methods of contraception is acceptable:

- True abstinence, when this is the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, and symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception
- Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner

Alternatively, use of two of the following effective forms of contraception is acceptable:

- Placement of intrauterine device (IUD) or intrauterine system (IUS). Consideration should be given to the type of device being used, as there are higher failure rates for certain types (e.g., steel or copper wire)
- Condom with spermicidal foam/gel/film/cream/suppository
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection
- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone

It should be noted that two forms of effective contraception are required. A double barrier method, defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, is acceptable.

Contraception is not a requirement in the case of any of the following:

- The female patient or female partner of a male patient is considered not to be of childbearing potential: if she is postmenopausal, defined by amenorrhea of ≥ 12 months duration in a woman > 45 years old; or is ≥ 40 years of age and has had amenorrhea of ≥ 24 months duration; or has undergone surgical sterilization (hysterectomy and/or bilateral oophorectomy*)*
- The male patient or male partner of a female patient is surgically sterilized

For male patients with a female partner of childbearing potential, cooperation of female partner is required (i.e., use of two forms of contraception as stated above) during the study and for at least 7 months following the last dose of study treatment when a highly effective form of contraception is not appropriate.

Based on PK considerations, contraception must continue for the duration of study treatment and for at least 7 months after the last dose of study treatment.

A female patient who becomes pregnant during the study must be instructed to stop taking the study medication and immediately inform the investigator. The investigator should report all pregnancies within 24 hours to the Sponsor including the partners of male patients. The investigator should counsel the patient/partner, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient/partner should continue until conclusion of the pregnancy. Pregnancies occurring up to 7 months after the completion of study medication must also be reported to the investigator. Please refer to Section 5.4.3 for reporting procedures.

It is not known whether trastuzumab or trastuzumab emtansine are excreted in human milk. Maternal IgG is excreted in milk and any of these monoclonal antibodies could harm infant growth and development; therefore, women should be advised to discontinue nursing during trastuzumab emtansine therapy and not to breastfeed for at least 7 months following the last dose of either study drug.

Experimental studies have reported that IgGs are present in both the pre-ejaculate and the seminal plasma (Moldoveanu et al. 2005). To date, there have been no clinical studies to assess the IgG profile in the pre-ejaculate and seminal plasma in male patients receiving trastuzumab or trastuzumab emtansine. Therefore, as a precaution male patients with female partners of childbearing potential are required to use highly effective form of contraception or use two forms of contraception as outlined above. Similarly, vaginal absorption of trastuzumab emtansine is unknown and therefore male patients with pregnant partners are required to use condoms for the duration of the pregnancy, and then revert to contraceptive methods as outlined above. This is to ensure that the fetus is not exposed to the study medication through vaginal absorption. In addition, sperm or blood donation should not occur for at least 7 months after the last dose of study treatment.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 ADVERSE EVENT REPORTING PERIOD

Investigators will seek information on AEs at each patient contact. All AEs, 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 SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. After this period, the investigator is not required to actively monitor patients for AEs; however, the Sponsor should be notified if the investigator becomes aware of any poststudy SAEs or non-serious AESIs (see Section 5.6).

5.3.2 ELICITING ADVERSE EVENT INFORMATION

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation time points. 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 AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity Table 5.

Table 5 Adverse Event Severity Grading Scale

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 NCI CTCAE (v4.0), which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[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 one's self, 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 SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2).

[d] Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2).

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 AE is considered to be related to study drugs, indicating "yes" or "no" accordingly. To ensure consistency of causality assessments, investigators should apply the general guidelines outlined in Table 6.

Table 6 Guidance for Causal Attribution of Adverse Event/Serious Adverse Event

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge. **Investigators should apply facts, evidence, or rationales based on scientific principles and clinical judgment to support a causal/contributory association with an investigational product.**
NO	**AEs will be considered related, unless they fulfill the criteria as specified below.** Evidence exists that the AE has an etiology other than the investigational product (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug). Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities. **Attribution of SAEs will be reviewed on an ongoing basis, and may be changed as additional clinical data emerges (e.g., reversibility of AE, new clinical findings in patient with AE, effects of retreatment, AEs in other patients)**.

In addition to assessing causality with respect to study drugs, investigators should also assess whether other factors (e.g., disease under study, concurrent illness, concomitant medication, or study procedure) may have caused the event, using similar guidance.

The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

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 AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

AEs that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For AEs other than infusion-related reactions, 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 AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.)

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the AE eCRF.

Any potential case of Drug-Induced Liver Damage as assessed by laboratory criteria for Hy's Law should be reported to the Sponsor expeditiously (see Section 5.4 for reporting instructions), irrespective of regulatory seriousness criteria or causality. The Medical Monitor should be contacted in the event of a potential case of Hy's Law as assessed by laboratory criteria before continuing study treatment.

The following laboratory abnormalities define potential Hy's Law cases:

- AST or ALT increases that are > 3 × ULN
- Concurrent increases of total bilirubin > 2 × ULN (or clinical jaundice if total bilirubin measures are not available), except in patients with documented Gilbert syndrome. For patients with Gilbert's syndrome, elevation of direct bilirubin > 2 × the ULN should be used instead.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. 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 not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness or etiology changes.

5.3.5.5 Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of BC 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 5.4.2). The iDMC will monitor the frequency of deaths from all causes.

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 only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of 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 post-study survival follow-up (i.e., follow-up post-progression or post-AEs requiring discontinuation until study site closure or loss to follow-up), deaths attributed to progression of BC should be recorded only on the Survival eCRF.

5.3.5.6 Pre-existing Medical Conditions

A pre-existing 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 pre-existing medical condition should be recorded as an AE 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 pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.7 Lack of Efficacy or Worsening of Breast Cancer

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

5.3.5.8 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

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:

- SAEs
- Non-serious AESIs
- Pregnancies

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 SAEs to the local health authority and Institutional Review Board/Ethics Committee (IRB/EC).

5.4.1 EMERGENCY MEDICAL CONTACTS

MEDICAL MONITOR (THE SPONSOR MEDICAL RESPONSIBLE) CONTACT INFORMATION

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Sponsor Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Sponsor Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information and List of Investigators").

5.4.2 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

For reports of SAEs and non-serious AESIs, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report expeditiously via the electronic data capture (EDC) system. An expedited report will be generated and sent to the Sponsor Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper SAE/Non-Serious AE of Special Interest CRF and Fax Coversheet should be completed and faxed to the Sponsor Safety Risk Management or its designee within 24 hours after learning of the event, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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 within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to the Sponsor Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should have the patient discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. *Sponsor will collect additional follow-up information using the dedicated Pregnancy Report Form at the end of the second trimester, after delivery, and at 3, 6, and 12 months of the infant's life on all pregnancy reports received by the Sponsor from any source (clinical study and spontaneous reports) or identified in the literature by the Sponsor. Also, Sponsor may send follow-up queries asking for further information, if required for a comprehensive assessment of the case.*

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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 within 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 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 INVESTIGATOR FOLLOW-UP

The investigator should follow each AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded 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 5.4.3.1.

5.5.2 SPONSOR FOLLOW-UP

For SAEs, non-serious AESIs, 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 SAE that occurs after the end of the AE reporting period (defined as 28 days [see Section 5.3.1] 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 Roche or its designee using the eCRF, if still available. If the eCRF is no longer available, then these events should be reported by either faxing or 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

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the trastuzumab emtansine 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.

The Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final analysis will be performed when all patients have been followed up for safety and efficacy for up to a period of 2 years after the last patient has been enrolled in Cohort 2 of the trial (i.e., after LPLV as in Section 3.2).

There are no formal statistical hypothesis tests to be performed. There are no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Analysis populations: Cohort 1 data will be analyzed after 2 years follow-up after last patient is enrolled and prior to Cohort 2.

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 2000 patients is planned for Cohort 1. For the purpose of the estimation of sample size, the incidence of AEs of Grade 3 or higher related to trastuzumab emtansine was chosen as a safety endpoint of primary interest.

If the observed incidence of AEs Grade ≥ 3 related to trastuzumab emtansine e.g., hepatic events, pneumonitis, thrombocytopenia or allergic reactions is between 5% and 10% (Study TDM4450g/BO21976), the precision for the estimation of the incidence of AE is presented in the table below by 95% Clopper-Pearson CIs.

Table 7 Cohort 1: Clopper-Pearson 95% Confidence Intervals for the incidence of AEs Grade ≥ 3 based on 2000 patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
20 (1%)	0.6% - 1.5%
40 (2%)	1.4% - 2.7%
60 (3%)	2.3% - 3.8%
80 (4%)	3.2% - 5%
100 (5%)	4.1% - 6%
120 (6%)	5% - 7.1%
140 (7%)	5.9% - 8.2%
160 (8%)	6.8% - 9.3%
180 (9%)	7.8% - 10.3%
200 (10%)	8.7% - 11.4%

For the purpose of the sample size estimate of Cohort 2, the incidence of Grade ≥ 3 thrombocytopenia in Asian patients was chosen as a safety endpoint of primary interest.

This is based on the pooled analysis of trials TDM4370g/BO21977, TDM4450g/BO21976, TDM4373g/BO22495, TDM4374g, TDM4258g, TDM4688g, TDM3569g and TDM4529g/BO25430, and the results of a subset of 99 Asian patients (see the trastuzumab emtansine Investigator's Brochure).

If the observed incidence of Grade ≥ 3 thrombocytopenia in Asian patients is between 30% and 55%, the precision for the estimation of the incidence of AEs is presented in the table below by 95% Clopper-Pearson CIs.

Table 8 Cohort 2: Clopper-Pearson 95% Confidence Intervals for the incidence Grade ≥ 3 thrombocytopenia based on 220 Asian patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CIs
2 (1%)	0.1% - 3.6%
10 (5%)	2.4% - 9%
20 (10%)	6.2% - 15%
60 (30%)	23.7% - 36.9%
70 (35%)	28.4% - 42%
80 (40%)	33.2% - 47.1%
90 (45%)	38% - 52.2%
100 (50%)	42.9% - 57.1%
110 (55%)	47.8% - 62%

The sample size of approximately 2220 patients is planned for the pooled analysis of Cohorts 1 and 2.

Table 9 Clopper-Pearson 95% Confidence Intervals for the incidence of Grade ≥ 3 AEs based on 2220 patients

Number of AEs/observed AE incidence	95% Clopper-Pearson CI
22 (1%)	0.6% - 1.5%
44 (2%)	1.5% - 2.7%
66 (3%)	2.3% - 3.8%
88 (4%)	3.2% - 4.9%
110 (5%)	4.1% - 6%
132 (6%)	5% - 7.1%
154 (7%)	6% - 8.1%
176 (8%)	6.9% - 9.2%
198 (9%)	7.8% - 10.3%
220 (10%)	8.8% - 11.3%

Summaries of Conduct

This is a safety study with the safety populations being the main analysis populations. Per-protocol (PP) population will not be defined; however major protocol violations will be summarized and defined. A median time to treatment and median time to follow-up/study will be estimated.

Two Safety populations will be defined; Safety population 1 and Safety population 2, which will be used to summarize safety variables.

Safety population 1 will include all patients who have received at least one dose of study medication in Cohort 1 while Safety population 2 will include all patients who received at least one dose of study medication in Cohort 2.

Pooled analysis for safety will be performed on the Safety population that includes all patients in Safety population 1 and Safety population 2.

6.2 SUMMARIES OF TREATMENT GROUP COMPARABILITY

This study includes only one treatment arm, hence treatment comparability is not applicable.

All safety and efficacy summaries will be presented for each cohort separately, and for the pooled analysis of Cohorts 1 and 2. The pooled analysis of Cohorts 1 and 2 will be conducted in parallel to the final analysis of Cohort 2.

Baseline and disease characteristics such as demographics, medical history, etc. will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation [SD], and 25th-75th quartiles for the continuous variables).

6.2.1 PRIMARY EFFICACY ENDPOINT

This is a safety study; therefore the primary objective of this study is the safety parameters.

6.2.2 SECONDARY EFFICACY ENDPOINTS

The efficacy variables will be summarized for the intent-to-treat (ITT) population 1 and ITT population 2. ITT1 will include all patients enrolled in Cohort 1, while ITT2 will include all patients in Cohort 2.

Pooled analysis for efficacy will be performed on the ITT population that includes ITT1 and ITT2.

PFS is defined as the time from the date of enrollment until the first documented progression of disease or death from any cause, whichever occurs first. Patients with no PFS events will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of enrollment plus one day.

OS is defined as the time from the date of enrollment until the date of death, regardless of the cause of death. Patients who were alive at the time of the final analysis will be censored at the date of the last follow-up assessment.

The overall response will be estimated via best (confirmed) overall response (BOR) as assessed by investigators. The BOR is defined as the best response recorded from the start of this study (date of enrollment) until disease progression/recurrence or death from any cause. To be assigned a status of PR or CR, i.e., to be a responder, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to

have two consecutive assessments of PR or CR. This status will be assessed only for patients with measurable disease at baseline. Patients with non-measurable disease at baseline will be assessed for the time-to-event endpoints (e.g., PFS, OS, etc).

Logistic analysis will be performed for BOR rate to assess the influence of baseline covariates, e.g., age (> 65, ≤ 65), ECOG 0 – 1 versus ECOG 2 in an exploratory manner.

In addition to these predictor factors, for the pooled analysis of Cohort 1 and 2, a further factor will be added: region (Asian versus non-Asian regions).

CBR includes patients whose best (confirmed) response was PR or CR or stable disease that lasts at least 6 months.

DoR is defined as the period from the date of initial confirmed PR or CR until the date of PD or death from any cause. Patients with no documented progression after CR or PR will be censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS. Only patients with BOR of CR or PR (i.e., responders) will be included in the analysis of DoR.

TTR: time from enrolment to first documentation of confirmed PR or CR (whichever occurs first). Patients who do not have a confirmed response are censored at the date of the last tumor assessment.

The number and proportions of responders and non-responders together with two-sided, 95% Clopper-Pearson CIs will be presented.

The analysis of ORR is based on the BOR. The BOR will be assessed by the number and proportion of responders and non-responders, together with two-sided 95% CIs. Patients without a post-baseline tumor assessment will be considered to be non-responders. More details will be specified in the statistical analysis plan.

Estimates for the survivor function for PFS, OS, DoR and TTR will be obtained by the Kaplan-Meier (KM) approach.

6.3 SAFETY ANALYSES

Summaries for safety data described below will be performed for Cohort 1, Cohort 2, and the pooled analysis.

All AEs will be assessed according to the NCI CTCAE v 4.0 grading system. The analysis of AEs will focus on treatment-emergent AEs i.e., AEs occurring on the day of or after first administration of study drug. Non-treatment-emergent AEs (i.e., those occurring before commencement of study medication) will only be listed.

AEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Based on the safety profile of trastuzumab emtansine, time to onset of the first episode of each AE described in Section 5 will also be summarized via KM estimates. Additional summaries by

frequency tables will also be provided for these AEs. Pneumonitis events of all grades will be analyzed.

The primary endpoint in this study will be AEs Grade 3 or higher for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, also all other AEs Grade 3 or higher related to trastuzumab emtansine, and pneumonitis of all grades. AEs leading to treatment interruption and discontinuation, and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative study medication doses and duration of exposure.

LVEF over time will be analyzed using descriptive statistics for continuous variable and presented graphically over time with associated 95% CI.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI CTCAE version 4.0 grade at baseline versus worst grade during treatment period. The summary of laboratory parameters presented by means, SD, minimum, and maximum will also be presented. The selected laboratory parameters will be graphically presented over time.

Exploratory Analyses

The following subgroup analyses will be performed for both cohorts and pooled across cohorts:

- AST or ALT increases that are > 3 × ULN and total bilirubin > 2 × ULN except in patients with documented Gilbert's syndrome
- Country
- Race
- Region (Asian versus non-Asian regions)
- Age (> 65, ≤ 65)
- Age (>75, ≤75)
- ECOG 0–1 versus ECOG 2

6.4 PHARMACOECONOMICS ANALYSES

The resource expenditure due to hospitalizations that are not study-defined evaluations while on study treatment will be evaluated. The number of hospital visits, number of days admitted, and type of visits (emergency department versus inpatient care) will be collected (see Section 2.3). The reason for admission (disease progression versus AE) will also be assessed.

6.5 INTERIM ANALYSES

Cohort 1

In addition to the final analysis, there will be five safety interim analyses for review by the iDMC: after approximately 50 and 350 patients have completed Cycle 1, Day 1 and after approximately 1,000, 1,500, and 2,000 patients have completed the first cycle of study medication (Cycle 1, Day 21), with further review of accumulating safety data as required (see iDMC charter and Section 3.1.2).

Cohort 2

In addition to the final analysis, there will be one interim safety analysis for review by the iDMC after approximately 100 patients have completed Cycle 1 (Cycle 1, Day 21).

In addition to the above interim analyses, there may be additional interim analyses for Health Authority purposes (e.g., to support SFDA [China]) after 150 Chinese patients have been enrolled and completed Cycle 1 (Cycle 1, Day 21) or by January 2017, whichever occurs first.

Final Analysis

The final analysis will be performed when all patients have been followed up for safety and efficacy for a period of up to 2 years after the last patient has been enrolled in Cohort 2 of the trial (i.e., as in Section 3.2).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. The sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures 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 by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and a 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 (PROs), 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 7.5.

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 investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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 (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, the Sponsor's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

7.5 RETENTION OF RECORDS

U.S. FDA regulations (21 Code of Federal Regulations §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the ICH Guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

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

For studies conducted outside the United States under a U.S. Investigational New Drug application (IND), the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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. IND application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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 Sample Informed Consent Forms or any alternate consent

forms proposed by the site 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.

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.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study Monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to the Sponsor for regulatory purposes.

If the site uses a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/EC 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 enrollment 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 to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and

are unexpected. 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 regulatory requirements and with 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 only be disclosed to third parties 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, which includes an audit trail containing a complete record of all changes to data.

9.2 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.

9.3 ADMINISTRATIVE STRUCTURE

The study will have an iDMC, Steering Committee, IxRS, eCRF, and will be conducted by a contract research organization (CRO) together with the Sponsor. Assessment of laboratory test results will be performed locally.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. 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.

9.5 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

	Screening	Treatment Period (all visits within ± 3 days of scheduled treatment day)	Post-treatment Follow-up	
	Day -28 to Day 1	**Day 1 of each Treatment Cycle**	**Safety Follow-up Visit** (28–42 days after last dose)	**Follow-up until Study Closure[2]** (every *3*–6 months)
Informed Consent	X[a]			
HER2 Status	X[b]			
Medical History and Demographics	X			
Complete Physical Examination	X			
Limited Physical Examination[c]		X	X	
Height and Weight[d]	X	X	X	
Vital Signs[e]	X	X	X	
ECOG Performance Status	X	X	X	
Concomitant Medication Reporting	X[f]	Ongoing		X[f]
Adverse Event Reporting	X[g]	Ongoing		X[h]
12-lead ECG	X			
ECHO/MUGA[i]	X[i]	X[i]	X[i]	
Tumor Assessments[j]	X	Every 12 weeks	X	X
Brain CT or MRI[k]	X	At the discretion of the investigator, if clinically indicated, until disease progression		

Appendix 1 Schedule of Assessments (cont.)

	Screening	Treatment Period (all visits within ± 3 days of scheduled treatment day)	Post-treatment Follow-up	
	Day -28 to Day 1	**Day 1 of each Treatment Cycle**	**Safety Follow-up Visit** (28–42 days after last dose)	**Follow-up until Study Closure[2]** (every 3–6 months)
Bone Scan/Imaging[l]	X	As clinically indicated or to confirm a response, until disease progression		
Hematology[m]	X[1]	X[n]	X	
Biochemistry[o]	X[1]	X[n]	X	
Urinalysis[p]	X[1]	As clinically indicated	X	
INR	X[1]	As clinically indicated, e.g. for patients receiving anti-coagulation therapy	X	
Pregnancy Test[q]	X	Every 3 cycles	X	X[q]
Assessment of Patient Hospitalizations and/or Hospital Visits		X	X	
Administration of Trastuzumab Emtansine		X[r]		

Appendix 1 Schedule of Assessments (cont.)

AE = Adverse Event; CT = Computed Tomography; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; D = Day; HER2 = human epidermal growth factor receptor 2; INR = International Normalized Ratio; MRI = Magnetic Resonance Imaging; MUGA = Multiple-Gated Acquisition; PD = Progressive Disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = Serious Adverse Event.

1. NOTE: Local laboratory (hematology, biochemistry, urinalysis, and INR assessments) at Screening: to be performed within **14 days** prior to first study treatment. Screening laboratory assessments may be done on the day of first study treatment (Cycle 1, Day 1).
2. All patients will be followed up for survival every 6 months (± 14 working days; except for pregnancy test which is at 3 and 6 months after safety follow-up visit) until death, loss to follow-up, withdrawal of consent, *or* study closure . Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 3-6 months *until disease progression occurs*. If assessments cannot be done at survival visits, the study site is permitted to collect survival information by phone call. *After disease progression, patients will be followed up for survival every 6 months (± 14 working days) until death, loss to follow-up, withdrawal of consent, or study closure (whichever occurs first).*

a) Informed consent may be obtained at any time (including prior to the 28-day screening period) but must be obtained prior to the performance of any screening assessments. Results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within 28 days prior to first study treatment may be used rather than repeating required tests.

b) HER2 positivity is defined as IHC 3+ or gene amplification by ISH, it will be performed locally.

c) Defined as a directed physical rather than thorough examination of all body systems. For example if a patient presents with a symptom, there should be a more comprehensive assessment of the affected body system.

d) Height to be obtained at screening or at Cycle 1, Day 1 only.

e) Vital signs should be obtained and reviewed but are not required to be entered into the eCRF. Abnormal vital signs at any time during the course of study treatment should be recorded as AEs or SAEs.

f) Record all prior investigational, anti-cancer therapies and concomitant medications within 28 days prior to first study treatment. At follow-up, assessment of anti-cancer therapies only.

g) During screening, only SAEs considered related to protocol-mandated procedures will be collected.

h) Patients will be followed for new or worsening AEs for 28 days following the last infusion of study drug, until treatment-related AEs resolve or stabilize, or until the initiation of another anti-cancer therapy, whichever occurs first, and until disease progresses for tumor assessments. After 28 days following last study treatment administration, the investigator should continue to follow all unresolved study-related AEs and SAEs until their resolution or stabilization, the patient is lost to follow-up or until it is determined that the study treatment or participation is not the cause of the AE/SAE. Additionally, patients will be contacted regarding the occurrence of any new SAE considered to be treatment-related at 60 and 90 days following the last study treatment administration or until initiation of another anti-cancer therapy, whichever occurs first.

i) Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. Assessments will occur during the screening period, and on Day 21 (or -7 days) of the cycle for Cycle 1, Cycle 3 and every third cycle thereafter. ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed ≥ 28 days after last study treatment administration or if no post-treatment evaluation was performed. The same imaging technique should be used per patient throughout the study. Results must be reviewed and documented prior to administration of study treatment. If treatment is delayed for any reason, LVEF assessments can be postponed to allow them to be performed within 7 days prior to the next treatment administration.

j) From Cycle 1, Day 1 onwards, tumor assessments, including a CT or MRI with contrast of the chest, abdomen, and pelvis should be performed according to the indicated schedule (± 5 working days), regardless of any delays in treatment or other assessments. Tumor assessments obtained within 28 days prior to first study treatment may be used for screening purposes. Tumor response must be assessed through physical examination and imaged-based evaluation using RECIST version 1.1. Assessments should include an evaluation of all sites of disease. In cases where there is suspicion of progression before the next scheduled assessment, an unscheduled assessment should be performed. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study for the same patient, e.g. the same contrast protocol for CT scans. For patients who discontinue study treatment for reasons other than PD, continued tumor assessments according to the protocol every 3-6 months. After disease progression, assessments are no longer required to evaluate new lesions, non-target lesions, and target lesions.

k) Patients with isolated brain metastases may continue study treatment if they demonstrate clinical benefit (CR or PR of any duration or SD ≥ 4 months) as detailed in Section 4.4.1.4. A brain MRI or CT should be performed along with regularly scheduled tumor assessments in these instances.

l) An isotope bone scan and/or other radiographic modalities (as a consequence of the anticipated Tc-99 shortage), will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions. If an isotope-

based scan was performed >28 days but ≤ 60 days prior to first study treatment, non-isotopic radiographic modalities should be utilized to document the extent of bony metastatic disease. Refer to Appendix 3 for additional details.

m) Hematologic assessments include Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cells (WBC) with differential (including neutrophils, lymphocytes, monocytes, eosinophils and basophils).

n) Scheduled for Day 1 of Cycle 1 and beyond: to be performed within 72 hours preceding administration of study treatment; results must be reviewed and documented prior to administration of study treatment.

o) Biochemistry assessments include: sodium, potassium, chloride, calcium, magnesium, glucose, BUN, creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), gamma-glutamyl transferase, lactate dehydrogenase, total bilirubin (and direct bilirubin where total bilirubin > ULN).

p) Includes specific gravity, pH, protein, glucose, blood, ketones and bilirubin.

q) Serum β-HCG test must be performed during screening. Urine β-HCG test must be performed at subsequent time points for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for women not meeting the definition of postmenopausal (refer to Section 5.2.4). Testing should be performed at a local laboratory within 7 days prior to the first administration of study medication (Cycle 1, Day1). For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. Urine pregnancy test in women of childbearing potential must be performed every 3 cycles and at 3- and 6- months after the safety follow-up visit. All positive urine pregnancy tests must be confirmed by a serum β-HCG test. Contraception should be used for 7 months after the last dose of study medication.

r) The initial dose of trastuzumab emtansine will be administered over 90 minutes if well tolerated subsequent infusions may be administered over 30 (±10) min.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): 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 ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 ≥ 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 mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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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.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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 as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are 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.

<u>Target Lesions: Specifications by Methods of Measurements</u>

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as

possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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 only be considered measurable 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 including 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 based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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 if

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.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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.

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 if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT 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 × 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.

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

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

- 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: 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 BML (below measurable limit) 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 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. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- 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).
- 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 if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, 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. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

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 (for example, some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show 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 if it represents truly new disease.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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. Time point Response (Overall Response)

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point 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 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 1 Time point 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 Time point 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 all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can

be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and 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, as this equates with the case being not evaluable at that time point.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Time point	Overall Response at Subsequent Time point	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 time point, any disease seen at a subsequent time point, 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 time point. 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.

Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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 (i.e., 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 3 Instructions for Scans in the Event of Isotope Shortage

Two key suppliers of Tc-99m generators (Chalk River Reactor, Canada and High Flux Reactor, the Netherlands) are expected to close. Supplies from other reactor sources will be unable to meet the expected world-wide patient-care needs. As a result, significant shortages of Tc-99m are expected, and the instructions listed below should be followed:

- ECHO will be the preferred imaging modality over MUGA scans to evaluate cardiac function.
- Tc-99m bone scans should be obtained as part of the baseline tumor assessment in all patients and should be repeated to confirm a CR or if progression of existing bone lesions and/or the development of new bone lesions is clinically suspected.
- If a bone scan cannot be performed at baseline or if the investigator suspects that a bone scan may not be able to be repeated during the course of the study because of the Tc-99m shortage, the investigator may choose F-18 NaF or FDG-PET scan as an alternative.
- If bone lesions are selected as index non-target lesions, they must be apparent on baseline CT scans or other radiographic modalities (e.g., skeletal X-rays that can be repeated in subsequent tumor assessments). Additional scans may be obtained to follow clinically important bone lesions if not visualized on the chest, abdomen, or pelvic CT scan.

These measures are intended to ensure that the same method of assessment and the same imaging technique is used throughout the study for each patient. If there is a question regarding the choice of alternatives in the event that a standard bone scan cannot be obtained during screening and/or during the study, please contact the Medical Monitor.

Appendix 4 ECOG Performance Status

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