PROTOCOL

TITLE: **PHASE I STUDY OF THE COMBINATION OF TRASTUZUMAB EMTANSINE (T-DM1) AND CAPECITABINE IN HER2-POSITIVE METASTATIC BREAST CANCER AND HER2-POSITIVE LOCALLY ADVANCED/METASTATIC GASTRIC CANCER PATIENTS, FOLLOWED BY A RANDOMIZED, OPEN-LABEL PHASE II STUDY OF TRASTUZUMAB EMTANSINE AND CAPECITABINE VERSUS TRASTUZUMAB EMTANSINE ALONE IN HER2-POSITIVE METASTATIC BREAST CANCER**

PROTOCOL NUMBER: MO28230 **VERSION NUMBER:** 4

EUDRACT NUMBER: 2012-001547-46

TEST PRODUCT: Trastuzumab emtansine (RO5304020)
Capecitabine (RO091978)

MEDICAL MONITOR: [redacted] MD

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Last date of signatures below

FINAL PROTOCOL APPROVAL

Name	Date and signature
[redacted]	22.3.16
[redacted] Statistician	23 March 2016
[redacted]	[redacted]

[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE: **PHASE I STUDY OF THE COMBINATION OF TRASTUZUMAB EMTANSINE (T-DM1) AND CAPECITABINE IN HER2-POSITIVE METASTATIC BREAST CANCER AND HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC GASTRIC CANCER PATIENTS, FOLLOWED BY A RANDOMIZED, OPEN-LABEL PHASE II STUDY OF TRASTUZUMAB EMTANSINE AND CAPECITABINE VERSUS TRASTUZUMAB EMTANSINE ALONE IN HER2-POSITIVE METASTATIC BREAST CANCER**

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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 the signed original of this form {as instructed by XX ***[e.g., your local study monitor, the CRO]***} ***[or]*** {to the contact provided below}. Please retain a copy for your study files.

{Name}
{Address}

PROTOCOL SYNOPSIS

TITLE: **PHASE I STUDY OF THE COMBINATION OF TRASTUZUMAB EMTANSINE (T-DM1) AND CAPECITABINE IN HER2-POSITIVE METASTATIC BREAST CANCER AND HER2-POSITIVE LOCALLY ADVANCED/METASTATIC GASTRIC CANCER PATIENTS, FOLLOWED BY A RANDOMIZED, OPEN-LABEL PHASE II STUDY OF TRASTUZUMAB EMTANSINE AND CAPECITABINE VERSUS TRASTUZUMAB EMTANSINE ALONE IN HER2-POSITIVE METASTATIC BREAST CANCER**

PROTOCOL NUMBER:	MO28230	**VERSION NUMBER:**	4
EUDRACT NUMBER:	2012-001547-46		
TEST PRODUCT:	Trastuzumab emtansine (RO5304020) Capecitabine (RO091978)		
PHASE:	I/II		
INDICATION:	HER2-positive metastatic breast cancer or HER2-positive locally advanced/metastatic gastric cancer		
SPONSOR:	F. Hoffmann-La Roche Ltd		

Objectives

Phase I: Maximum Tolerated Dose (MTD) Finding of Trastuzumab Emtansine (T-DM1) and Capecitabine in Metastatic Breast Cancer (mBC)

Primary Objective

- To determine the MTD of the combination of trastuzumab emtansine and capecitabine in patients with human epidermal growth factor receptor 2 (HER2)-positive mBC

Secondary Objectives

To assess the:

- Pharmacokinetics (PK) of trastuzumab emtansine, capecitabine, and their metabolites
- Safety of the combination of trastuzumab emtansine and capecitabine
- Overall response rate (ORR)

Randomized Phase II: Exploration of Efficacy and Safety in mBC

Primary Objective

- To explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in patients with HER2-positive mBC, as measured by ORR by Response Evaluation Criteria for Solid Tumors (RECIST) v.1.1 per investigator local assessment

Secondary Objectives

- To assess the safety profile of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone
- To explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in mBC patients, as measured by:
  - Time to response (TTR)

- Duration of response (DoR)
- Time to progression (TTP)
- Time to treatment failure (TTF)
- Progression-free survival (PFS)
- Clinical benefit rate (CBR)
- Overall survival (OS)

Phase I: MTD Finding of Trastuzumab Emtansine and Capecitabine in Locally Advanced/Metastatic Gastric Cancer (LA/mGC)

Primary Objective

- To determine the MTD of the combination of trastuzumab emtansine and capecitabine in patients with LA/mGC

Secondary Objectives

To assess the:

- PK of trastuzumab emtansine, capecitabine, and their metabolites
- Safety of the combination of trastuzumab emtansine and capecitabine
- ORR

Study Design

Description of Study

This is an international, multicenter study.

The study is designed to determine the MTD of capecitabine in combination with trastuzumab emtansine in patients with HER2-positive mBC or LA/mGC using a Phase I design, followed by a randomized, open-label Phase II study to explore the efficacy and safety of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in HER2-positive mBC. Results from the Phase I study in LA/mGC will be used as supporting information for future studies in the indication (see Figure 4 in the protocol).

Phase I: MTD Finding, Cohort 1: mBC

Cohort 1 used a 3 plus 3 classical design to determine the MTD of capecitabine in combination with trastuzumab emtansine. Initially the study had a dose escalation design, but following the occurrence of two DLTs at Dose Level 1 (750 mg/m^2 capecitabine bid + 3.6 mg/kg q3w trastuzumab emtansine), the study design was adapted and the dose de-escalated to 700 mg/m^2 capecitabine bid + 3.6 mg/kg q3w trastuzumab emtansine. At this Dose Level there were no DLTs and following review of the safety data, the Independent Data Monitoring Committee (IDMC) recommended that the study should proceed to explore this Dose Level further in the Randomized Phase II part of the study.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

Phase II will be conducted in mBC patients only. This part of the study will explore the efficacy and safety of the combination treatment of trastuzumab emtansine (T-DM1) and capecitabine, at 700 mg/m^2 bid (the recommended MTD), compared with trastuzumab emtansine alone in patients with mBC.

Approximately 160 additional patients with HER2-positive mBC will be randomized into the Phase II part of the study. Patients in the Phase I part of the study will not contribute to the Phase II part of the study; however, they will be followed up until end of study (EOS).

Phase I: MTD Finding, Cohort 2: LA/mGC

Cohort 2 will have a 3 plus 3 classical design and enroll patients with HER2-positive LA/mGC. Trastuzumab emtansine will be administered weekly at a dose of 2.4 mg/kg and capecitabine will start at dose level -1 (700 mg/m^2, the MTD defined in Cohort 1), with de-escalation if required as follows:

- If Dose Level -1 is well tolerated (DLT in ≤ 1/6 patients), this dose will be established as the MTD for LA/mGC
- If Dose Level -1 is not tolerated in Cohort 2 (DLT in > 1/6 patients), de-escalation will be to Dose Level -2.

- If Dose Level -2 is too toxic, the combination of capecitabine with trastuzumab emtansine 2.4 mg/kg every week may be considered unfeasible in LA/mGC, recruitment will be terminated and the LA/mGC part will be closed. However, this will have no impact on continuation of the Randomized Phase II mBC part.

Duration of treatment and follow-up

All patients will be treated until investigator-assessed disease progression, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor. In case of toxicities requiring the discontinuation of capecitabine, single agent trastuzumab emtansine may be continued. In case of toxicities requiring the discontinuation of trastuzumab emtansine, the patient will be followed up until EOS (treatment with capecitabine alone is not allowed).

All patients will be followed up until withdrawal of consent, death, or for up to a maximum of 2 years after the last patient was randomized in the Phase II part of the study, whichever occurs first.

Number of Patients

Phase I, Cohort 1: mBC

A minimum of 6 and up to 18 patients will be enrolled.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

Exploration of efficacy and safety in mBC will be based on approximately 160 randomized patients in total.

Phase I, Cohort 2: LA/mGC

A total of 6 to 12 patients will be enrolled.

Target Population

Phase I, Cohort 1: mBC

Patients with HER2-positive mBC will be enrolled.

The patient's HER2 status will be considered positive if the local institution or reference lab reported immunohistochemistry (IHC) 3+ staining intensity (on a scale of 0 to 3) or *in situ* hybridization (ISH) positive.

The HER2 status will be retrospectively confirmed by IHC and/or ISH in a central laboratory using archival paraffin-embedded tumor tissue. Retrospective central confirmation will not affect the treatment decisions or primary endpoint of Phase I and will be used to validate efficacy analyses in Phase I.

Before entering the study, patients must have received at least one prior treatment regimen for early or metastatic disease, which included a chemotherapy agent and trastuzumab either separately or in combination.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

Patients with HER2-positive mBC will be randomized to receive either the combination of trastuzumab emtansine with capecitabine or trastuzumab emtansine alone. Retrospective central confirmation will be used to categorize patients for subgroup analyses according to central HER2 testing.

Before entering the study, patients must have received at least one prior treatment regimen for early or metastatic disease, which included a chemotherapy agent and trastuzumab either separately or in combination.

Phase I, Cohort 2: LA/mGC

Patients with centrally confirmed HER2-positive LA/mGC will be enrolled.

Patients must not have received prior chemotherapy for advanced/metastatic disease.

Inclusion Criteria:

For mBC Patients:

1. Male or female.
2. Age ≥ 18 years old.
3. Signed informed consent before any study-specific procedure.

4. Able and willing to comply with the protocol.
5. 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 the medical history confirming that the patient is not of childbearing potential.
6. 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 or two effective forms of non-hormonal contraception and to continue its use for the duration of study treatment and for 7 months after the last dose of study treatment (see Section 5.2.4 in the protocol).
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
8. Blood:
   a) Platelet count > 100,000 cells/mm^3
   b) International normalized ratio (INR) < 1.5
   c) Absolute neutrophil count (ANC) > 1,500 cells/mm^3
   d) Hemoglobin > 9.0 g/dL. Patients are allowed to have received transfusion to achieve this level.
9. Liver function:
   a) Total bilirubin ≤ 1.5 × upper limit of normal (ULN) or direct bilirubin ≤ 1.5 × ULN in patients with documented Gilbert's syndrome.
   b) Serum glutamic oxaloacetic transaminase (SGOT)/aspartate transaminase (AST) and serum glutamic pyruvic transaminase (SGPT)/alanine transaminase (ALT) ≤ 2.5 × ULN.
   c) Alkaline phosphatase ≤ 2.5 × ULN. In patients with bone metastases: alkaline phosphatase ≤ 5 × ULN.
   d) Evidence of stable liver function during the month prior to enrollment with liver function test (LFT) fluctuations not exceeding 2.5 × ULN (for AST, ALT) and 1.5 × ULN (for total bilirubin).
10. Renal function:
    a) Serum creatinine of < 177 µmol/L or calculated creatinine clearance (CL) > 50 mL/min. If urine dipstick for proteinuria is ≥ 2+ at baseline, the patient must undergo 24-hour urine collection and demonstrate ≤ 1 g of protein/24 hours.
11. Cardiac function:
    a) Left ventricular ejection fraction (LVEF) ≥ 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan.
12. Life expectancy ≥12 weeks
13. Histologically or cytologically confirmed breast cancer.
14. HER2-positive disease, defined as IHC 3+ or ISH positive.
15. Tumor block or 8 slides available for retrospective central confirmation of HER2-positivity (central confirmation not necessary for enrollment).
16. mBC with at least one measurable lesion according to RECIST v.1.1.
17. Disease progression on at least one prior regimen containing trastuzumab and chemotherapy either separately or in combination. Patients may be eligible to receive study therapy in the first-line setting if trastuzumab and chemotherapy were given in the [neo]adjuvant setting.
18. Patients must have recovered from previous treatments

For LA/mGC Patients:

1. Male or female

2. Age ≥ 18 years old.
3. Signed informed consent before any study-specific procedure.
4. Able and willing to comply with the protocol.
5. 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 the medical history confirming that the patient is not of childbearing potential.
6. 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 or two effective forms of non-hormonal contraception and to continue its use for the duration of study treatment and for 7months after the last dose of study treatment (see Section 5.2.4 in the protocol).
7. ECOG performance status of 0, 1, or 2.
8. Blood:
   a) Platelet count > 100,000 cells/mm^3.
   b) INR < 1.5.
   c) ANC > 1,500 cells/mm^3.
   d) Hemoglobin > 9.0 g/dL. Patients are allowed to have received transfusion to achieve this level.
9. Liver function:
   a) Total bilirubin ≤ 1.5 × ULN or direct bilirubin ≤ 1.5 × ULN in patients with documented Gilbert's syndrome.
   b) SGOT/AST and SGPT/ALT ≤ 2.5 × ULN.
   c) Alkaline phosphatase ≤ 2.5 × ULN. In patients with bone metastases: alkaline phosphatase ≤ 5 × ULN.
   d) Evidence of stable liver function during the month prior to enrollment with LFT fluctuations not exceeding 2.5 × ULN (for AST, ALT) and 1.5 × ULN (for total bilirubin).
10. Renal function:
    a) Serum creatinine of < 177 µmol/L or calculated creatinine CL > 50 mL/min. If urine dipstick for proteinuria is ≥ 2+ at baseline, the patient must undergo 24-hour urine collection and demonstrate ≤ 1 g of protein/24 hours.
11. Cardiac function:
    a) LVEF ≥ 50% by ECHO or MUGA scan.
12. Life expectancy ≥ 2 weeks
13. Histologically or cytologically confirmed mGC or locally advanced GC.
14. HER2-positive tumor (primary tumor or metastatic lesion), defined as either IHC 3+ or IHC 2+ and ISH+, prospectively confirmed by a Sponsor-designated central laboratory prior to enrollment. ISH positivity is defined as a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of signals for CEP17.
    a) Archival tumor samples obtained from primary or metastatic sites are acceptable.
    b) Invasive tumor for central confirmation of HER2 status is required.
    c) A formalin-fixed paraffin-embedded (FFPE) tissue block with at least 5 mm of invasive tumor for central confirmation is preferred. If FFPE tissue blocks (or partial block) are unavailable due to country or site regulations, a minimum of 8 freshly cut unstained slides MUST be available for central review of HER2 status.
15. Inoperable LA/mGC.

Exclusion Criteria:

For mBC Patients:

1. Prior treatments before first study treatment:
   a) Investigational therapy within ≤ 28 days or five half-lives, whichever is longer.
   b) Hormonal therapy within 14 days.
   c) Trastuzumab within 21 days.
2. Prior treatment with trastuzumab emtansine or prior enrollment in a trastuzumab emtansine-containing study, regardless of whether the patient received trastuzumab emtansine.
3. Prior treatment with capecitabine.
4. History of severe or unexpected reactions to fluoropyrimidine or known hypersensitivity to fluorouracil.
5. Related capecitabine contraindications:
   a) Treatment with sorivudine or its chemically-related analogs, such as brivudine.
   b) Rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
   c) Known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.
6. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product.
7. History of exposure to the following cumulative doses of anthracyclines:
   a) Doxorubicin or liposomal doxorubicin > 500 mg/m^2.
   b) Epirubicin > 900 mg/m^2.
   c) Mitoxantrone > 120 mg/m^2
   d) 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.
8. Brain metastases that are symptomatic, or require any radiation, surgery, or steroid therapy to control symptoms within 28 days before first study drug administration.
9. Current peripheral neuropathy of Grade ≥ 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0.
10. History of other malignancy within the last 5 years, except for appropriately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned above.
11. Current unstable ventricular arrhythmia requiring treatment.
12. History of symptomatic congestive heart failure (CHF) (New York Heart Association [NYHA] Classes II−IV).
13. History of myocardial infarction or unstable angina within 6 months prior to first study drug administration.
14. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment.
15. Severe dyspnea at rest due to complications of advanced malignancy or currently requiring continuous oxygen therapy.
16. Clinically significant malabsorption syndrome or inability to take oral medication.
17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease).
18. Major surgical procedure or significant traumatic injury within 28 days before enrollment or anticipation of the need for major surgery during the course of study treatment.
19. Current pregnancy or lactation.

20. Current known active infection with human immunodeficiency virus (HIV), hepatitis B, and/or hepatitis C virus (HBV/HCV).
    a) For patients who are known carriers of HBV, active hepatitis B infection must be ruled out based on negative serologic testing and/or determination of HBV deoxyribonucleic acid (DNA) viral load per local guidelines.
21. Lapatinib ≤ 14 days before first study drug administration.
22. Previous radiotherapy for the treatment of mBC is not allowed if:
    a) The last fraction of radiotherapy has been administered within 14 days prior to first study drug administration (28 days for patients with radiotherapy to control symptoms of brain metastases, see exclusion criterion 8).
    b) More than 25% of marrow-bearing bone has been irradiated.
    c) Any acute toxicity has not resolved to Grade ≤ 1 before first study drug administration.

For LA/mGC Patients:

1. Prior treatments before first study treatment:
    a) Investigational therapy within ≤ 28 days or 5 half-lives, whichever is longer.
    b) Hormonal therapy within 14 days.
    c) Trastuzumab within 21 days.
2. Prior treatment with trastuzumab emtansine or prior enrollment in a trastuzumab emtansine-containing study, regardless of whether the patient received trastuzumab emtansine.
3. Prior treatment with capecitabine.
4. History of severe or unexpected reactions to fluoropyrimidine or known hypersensitivity to fluorouracil.
5. Related capecitabine contraindications:
    a) Treatment with sorivudine or its chemically-related analogs, such as brivudine.
    b) Rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.
    c) Known complete absence of DPD activity.
6. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product.
7. History of exposure to the following cumulative doses of anthracyclines:
    a) Doxorubicin or liposomal doxorubicin > 500 mg/m^2.
    b) Epirubicin > 900 mg/m^2.
    c) Mitoxantrone > 120 mg/m^2.
    d) 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.
8. Brain metastases that are symptomatic, or require any radiation, surgery, or steroid therapy to control symptoms within 28 days before first study drug administration.
9. Current peripheral neuropathy of Grade ≥ 3 according to NCI CTCAE, v4.0.
10. History of other malignancy within the last 5 years, except for appropriately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned above.
11. Current unstable ventricular arrhythmia requiring treatment.
12. History of symptomatic CHF (NYHA Classes II−IV).
13. History of myocardial infarction or unstable angina within 6 months prior to first study drug administration.
14. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment.

15. Severe dyspnea at rest due to complications of advanced malignancy or currently requiring continuous oxygen therapy.
16. Clinically significant malabsorption syndrome or inability to take oral medication.
17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
18. Major surgical procedure or significant traumatic injury within 28 days before enrollment or anticipation of the need for major surgery during the course of study treatment
19. Current pregnancy or lactation.
20. Current known active infection with HIV, HBV, and/or HCV
    a) For patients who are known carriers of HBV, active hepatitis B infection must be ruled out based on negative serologic testing and/or determination of HBV DNA viral load per local guidelines
21. Previous chemotherapy for advanced/metastatic disease
    a) Prior adjuvant/neoadjuvant therapy is allowed if at least 6 months has elapsed between completion of adjuvant/neoadjuvant therapy and enrollment into the study
22. Lapatinib ≤ 14 days before first study drug administration

Length of Study

The duration of the study is estimated to be approximately 4 years. Recruitment is estimated to last 2 years in total (1 year for MTD Finding, 1 year for the Phase II Exploration of Efficacy and Safety in mBC).

End of Study

The study will end after the follow-up period has been completed as defined above. Last patient last visit (LPLV) is defined as the last data collection point, which can be either a clinic visit or a laboratory sample.

In case Dose Level -2 is too toxic in LA/mGC, the LA/mGC cohort may be terminated prematurely. Patients who, at that point, experience response according to RECIST v.1.1 will be offered the possibility to continue on trastuzumab emtansine as a single agent or with capecitabine, based on the risk-benefit balance and agreement with the SC.

Randomized Phase II Exploration of Efficacy and Safety in mBC: The primary analysis of best overall response (BOR) rate will be performed when 70% of the patients have experienced a PFS event or at the end of the trial, whichever occurs first. It is estimated that 70% of patients will have experienced a PFS event approximately 26 months after randomization of the first patient. The EOS analysis (approximately 24 months after the last patient is randomized) will include an updated analysis of BOR, which will be done in a purely exploratory manner.

Efficacy Outcome Measures

Efficacy will be evaluated according to RECIST v.1.1.

- BOR rate
- TTR
- DoR
- TTP
- TTF
- PFS
- CBR
- OS

Safety Outcome Measures

- DLT assessment/determination of the MTD of capecitabine when combined with trastuzumab emtansine (Phase I only)

- Incidence, nature, and severity by NCI CTCAE v4.0 of adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation from either component of the study treatment, and AEs of special interest (AESIs)
- Fatal AEs and their causes
- Events to monitor
- Laboratory parameters
- LVEF
- Treatment exposure
- Physical examinations
- ECOG performance status
- Premature withdrawal from study medication and/or study

Pharmacodynamic Outcome Measures

Hospital visit parameters.

Pharmacokinetic Outcome Measures

PK will be evaluated during Phase I for trastuzumab emtansine, capecitabine, and their metabolites (see Appendix 1, Schedule of Assessment in the protocol). In addition, PK samples may be taken *ad hoc*, in case of SAEs or unexpected toxicities, which may be suggestive of a potential drug-drug interaction.

Investigational Medicinal Products

For mBC Patients:

Trastuzumab emtansine will be administered q3w at a dose of 3.6 mg/kg intravenous (IV).

The total trastuzumab emtansine dose will be calculated based on the patient's weight on Day of each cycle (or up to 3 days before) with no upper limit.

Capecitabine will be administered orally bid for 14 days followed by a 7-day rest period at the Dose Levels described in the 'Trial Design' section.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Rounding of the capecitabine dose, based on 150 mg and 500 mg tablet strength, will be allowed to the nearest target dose based on the patient's body surface area (BSA).

For LA/mGC Patients:

Trastuzumab emtansine will be administered on Day 1 of each 1-week cycle at a dose of 2.4 mg/kg IV.

The total trastuzumab emtansine dose will be calculated based on the patient's weight on Day of each cycle (or up to 3 days before) with no upper limit.

Capecitabine will be administered orally bid for 14 days followed by a 7-day rest period at the Dose Levels -1 to -2 described in the 'Trial Design' section.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

The study will include 2 phases and 2 cohorts:

- Phase I, Cohort 1: mBC MTD-Finding Cohort
- Randomized Phase II: Exploration of Efficacy and Safety in mBC
- Phase I, Cohort 2: LA/mGC MTD-Finding Cohort

Corresponding analyses as described in the protocol will be performed when all data from both study phases are collected and cleaned.

Randomized Phase II: The primary analysis of BOR will be performed when 70% of the patients have experienced a PFS event or at the end of the trial, whichever occurs first. It is estimated that 70% of patients will have experienced a PFS event approximately 26 months after

randomization of the first patient. The EOS analysis (approximately 24 months after the last patient is randomized) will include an updated analysis of BOR, which will be done in a purely exploratory manner.

Analysis of primary and secondary endpoints:

Analysis Populations:

Phase I, Cohort 1: MTD-Finding: mBC Patients

The main analysis population for DLT assessment is the DLT-evaluable population, which is defined as all enrolled and treated patients who have not experienced any major protocol violations (including violations of the inclusion and exclusion criteria) and have completed Cycle 1.

The safety population (SP) will include all patients who received at least one dose of study medication (trastuzumab emtansine and/or capecitabine) during Phase I.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

The main analysis population for the efficacy analysis will be the intent-to-treat (ITT) population, which will include all patients randomized in the Phase II part of the study. The per-protocol (PP) population will include all ITT patients who have at least one post-baseline tumor assessment during the Phase II part of the study and no major protocol violations, which will be defined in the statistical analysis plan (SAP).

The SP will include all patients who received at least one dose of study medication during the Randomized Phase II part of the study.

Phase I, Cohort 2: MTD-Finding, LA/mGC Patients

The main analysis population for DLT assessment is the DLT-evaluable population, which is defined as all enrolled and treated patients who have not experienced any major protocol violation (including violation of the inclusion and exclusion criteria) and have completed Cycle 1.

The SP will include all patients who received at least one dose of study medication during Phase I.

Efficacy Endpoints:

Phase I, Cohort 1: MTD-Finding, mBC

The primary objectives are defining the MTD and establishing the safety profile of the combination regimen.

ORR, as a main efficacy endpoint, will be assessed via BOR rate. The BOR is defined as the best response recorded from the date of enrollment until disease progression, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first. The number of patients is very small in this part of the study. Therefore, all analyses will be descriptive.

Due to the small number of patients and the design of this part of the study, no secondary efficacy endpoints will be investigated.

Randomized Phase II: Exploration of Efficacy in mBC

The primary efficacy endpoint for the Phase II part of the study is the ORR, assessed via the BOR rate. BOR is defined as the best response recorded between randomization into the Phase II part of the study and disease progression, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first. To be assigned a status of partial response (PR) or complete response (CR), i.e., to be a responder, changes in tumor measurements must be confirmed by repeated assessments performed no less than 28 days after the response criteria are first met, i.e., patients need to have two consecutive assessments of PR or CR.

The primary hypothesis of interest when comparing ORR – as assessed via BOR - between the two treatment groups, combination of trastuzumab emtansine and capecitabine *versus* trastuzumab emtansine alone is:

- H0: $\pi_{\text{trastuzumab emtansine}} = \pi_{\text{trastuzumab emtansine + capecitabine}}$ where $\pi_{\text{trastuzumab emtansine}}$ is BOR in trastuzumab emtansine alone and $\pi_{\text{trastuzumab emtansine + capecitabine}}$ is BOR in trastuzumab emtansine + capecitabine
- H : trastuzumab emtansine trastuzumab emtansine + capecitabine

The number and proportions of responders and non-responders (based on BOR) together with the two-sided 90% Clopper-Pearson confidence intervals (CIs) will be presented for each treatment group. The difference in BOR between treatment groups will be displayed with associated 90% CIs using the Hauck-Anderson approach and p-value for the Fisher's exact test.

The secondary endpoints for the Phase II part of the study will be:

- TTR
- DoR
- TTP
- TTF
- PFS
- CBR
- OS

Estimates for the survivor function of both treatment groups for TTR, DoR, TTP, TTF, PFS and OS will be obtained by using the Kaplan-Meier method. Hazard ratios and associated 90% CIs will be estimated from non-stratified and stratified (based on the stratification factor) Cox regression models.

CBR will include patients whose best (confirmed) response was PR or CR, or stable disease (SD) that lasted at least 6 months. CBR will be summarized in a similar way to the primary efficacy endpoint, ORR, as assessed by BOR.

Phase I, Cohort 2: MTD-Finding: LA/mGC

The primary objectives are defining the MTD and establishing the safety profile of the combination regimen.

Efficacy endpoints will be analyzed in a similar way to that described for Phase I, Cohort 1 in mBC.

Safety Endpoints:

Phase I, Cohort 1: MTD-Finding: mBC

The number and proportion of patients with DLTs will be used as the primary measure for the MTD determination. The definition of DLTs is presented in Section 5.1.4. DLTs for this part of the study will be summarized by treatment dose.

Safety parameters for this study part will also be summarized by treatment dose. The summaries of AEs, SAEs, AEs that cause discontinuation from the study treatment, AESIs (as described in Section 5), and events to monitor will be analyzed in a similar way to AEs in Phase II. The summaries will include all patients who received at least one dose of study medication.

The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Patients who died will be listed together with the cause of death.

Laboratory parameters, hematology and biochemistry will be presented in shift tables of NCI CTCAE grade at baseline *versus* worst grade during treatment for Phase I, Cohort 1.

LVEF over time will be summarized as mean, median and range (minimum and maximum) and will be presented graphically.

Other safety variables, such as exposure to study medication, concomitant medications, and physical examinations, will be analyzed in a similar way. Exposure to study medication will be summarized by frequency tables.

ECOG performance status will be summarized over time and the percentage of patients in each category will be presented by bar charts at different time points.

Randomized Phase II: Exploration of Safety in mBC

Safety endpoints will be summarized by treatment group.

Safety endpoints during the Randomized Phase II part of the study will be assessed via: total AEs, Grade ≥ 3 AEs, SAEs, premature withdrawal from study medication, AESIs, events to monitor, laboratory parameters, LVEF, exposure to study medication, concomitant medications, ECOG performance status, and physical examination.

The incidence of AEs and SAEs will be summarized according to the primary SOC and within each SOC, by MedDRA preferred term. Time to onset of the first episode of AESI will also be summarized via Kaplan-Meier method. Patients who died will be listed together with the cause of death.

Laboratory parameters, hematology, and biochemistry will be presented in shift tables of NCI CTCAE grade at baseline *versus* worst grade during treatment in the Randomized Phase II part of the study.

LVEF over time will be summarized as mean, median and range (minimum and maximum) and will be presented graphically.

Other safety variables, such as exposure to study medication, concomitant medications, and physical examinations, will be analyzed in a similar way. Exposure to study medication will be summarized by frequency tables.

ECOG performance status will be summarized over time and the percentage of patients in each category will be presented by bar charts at different time points.

Phase I, Cohort 2: MTD-Finding: mGC

The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination. The definition of DLTs is presented in Section 5.1.4. DLTs for this part of the study will be summarized by treatment dose.

Safety parameters will be summarized in a similar way to that described for Phase I, Cohort 1 in mBC.

Pharmacokinetic Analysis

The following PK parameters of trastuzumab emtansine and capecitabine (not limited to these listed) will be determined only in the Phase I part of the study in all patients who receive study treatment using either non-compartmental and/or population methods, if data allow:

- Serum concentrations of trastuzumab emtansine (conjugate) and total trastuzumab
- Plasma concentrations of DM1, capecitabine, and its active metabolite 5-fluorouracil (5-FU)
- Total exposure (area under the serum concentration-time curve [AUC])
- Maximum concentration (C_{max})
- CL
- Volume of distribution (V_d)
- Terminal half-life ($T_{1/2}$)

All PK parameters will be listed and tabulated by treatment dose and by Cohort. Descriptive summary statistics including arithmetic mean, geometric mean (e.g., AUC and C_{max}), median, range, standard deviation (s.d.), and coefficient of variation will be presented for each Cohort. Nonlinear mixed effects modeling will also be used; details will be presented in the SAP.

Exploratory Analyses

For all patients with mBC (Phase I, cohort 1; Phase II Exploration of Efficacy and Safety in mBC), a retrospective central confirmation of the HER2 status will be done. Further exploratory analyses will be done according to centrally confirmed HER2 status for selected endpoints, e.g. BOR and safety (AEs, SAEs, Grade ≥ 3 AEs, and AESIs).

Subgroup analysis for BOR, safety (AEs, SAEs, AEs with Grade ≥ 3, and AESIs) in the Randomized Phase II part of the study will be presented for both treatment groups with respect to: elderly *versus* younger patients; patients with ECOG 0–1 *versus* ECOG 2; and patients with

≤1 *versus* >1 prior treatment line for metastatic disease. More details will be presented in the SAP.

Pharmacoeconomic Endpoint

The number of hospital visits, number of days admitted, and type of visits (emergency department *versus* inpatient care) will be collected and compared. The reason for admission (disease progression *versus* AE) will also be assessed.

Determination of Sample Size

Sample Size for Phase I: MTD-Finding: mBC

This part will be based on a classical 3 plus 3 Phase I design. A minimum of 6 and up to 18 patients will be enrolled in Cohort 1. There is no formal sample size estimation for this part.

Sample Size for Randomized Phase II: Exploration of Efficacy and Safety in mBC

The sample size for the primary endpoint BOR is based on a Fisher's exact test with an alpha level of 5% (one-sided), power of 70% and the clinical assumption of a BOR rate of 43% with trastuzumab emtansine alone and 62.5% with the combination of trastuzumab emtansine and capecitabine. Approximately 160 patients (approximately 80 patients in each treatment group), including a 15% withdrawal rate, will be randomized with a 1:1 ratio to either trastuzumab emtansine alone or the combination of trastuzumab emtansine and capecitabine.

Stratification Factors

The following stratification factor will be implemented in the Randomized Phase II part of the study:

- Number of prior lines of treatment for metastatic disease (≤1 or >1; excluding single-agent hormones).

A treatment line is defined as any treatment regimen given to a patient from treatment initiation until confirmed disease progression.

Sample Size for Phase I, Cohort 2: MTD-Finding: LA/mGC

This part will be based on a classical 3 plus 3 Phase I design. Between 3 and 12 patients might be enrolled in Cohort 2. There is no formal sample size estimation for this part.

Interim analysis

There is no formal interim analysis of efficacy.

An independent data monitoring committee (IDMC) will recommend whether the Randomized Phase II part of the study can commence.

The IDMC will also monitor safety outcomes after 25, 75, and 150 patients have received at least 3 cycles of treatment (Cycle 3 Day 21) in the Randomized Phase II part of the study. Afterwards, the IDMC will monitor accumulating patient safety data every 6 months during the Randomized Phase II part of the study or as requested.

Efficacy data will be provided only if required by the IDMC to estimate the risk-benefit balance for the patients. Further details on the function and logistics of the IDMC will be provided in the IDMC Charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	activities of daily living
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
AUC	area under the serum concentration-time curve
BC	breast cancer
bid	twice daily
BML	below measurable limit
BOR	best overall response
BSA	body surface area
BUN	blood urea nitrogen
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DM1	derivative of maytansine
DoR	duration of response
DPD	dihydropyrimidine dehydrogenase
DPYD	dihydropyrimidine dehydrogenase gene
5-DFUR	5'-deoxy-5-fluorouridine
5-FU	5-fluorouracil
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
EOS	end of study
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence *in situ* hybridization
GC	gastric cancer
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
HBV	hepatitis B virus
HCV	hepatitis C virus
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IgG	immunoglobulin
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
ISH	*in situ* hybridization
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous
IxRS	interactive voice/web recognition system
LA/mGC	locally advanced/metastatic gastric cancer
LC-MS/MS	liquid chromatography electrospray tandem mass spectrometry
LFT	liver function test
LPLV	last patient last visit

LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
mGC	metastatic gastric cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
N	number of patients
NCI	National Cancer Institute
NE	not evaluable
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
PP	per-protocol
PR	partial response
PVC	polyvinyl chloride
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
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SC	Steering Committee
s.d.	standard deviation
SD	stable disease
SDV	source data verification
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SOC	system-organ class
SP	safety population
SWFI	sterile water for injection
$T_{1/2}$	terminal half-life

TTF	time to treatment failure
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
V_d	volume of distribution
V_{ss}	volume of distribution at steady state
WBC	white blood cells
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

1.1.1 HER2-POSITIVE BREAST CANCER

Breast cancer (BC) is the most common cancer in women worldwide, both in the developed and the developing world[1], with an estimated 1.67 million new cases diagnosed in 2012. It is also the leading cause of cancer death in females in less developed regions, accounting for 324,000 deaths (14.3% of all cancer deaths) in 2012, and the second most common cause of cancer death in women in more developed regions (198,000 deaths, 15.4%) after lung cancer.[1] Metastatic breast cancer (mBC) is incurable, with the primary goal of treatment to extend life and palliate symptoms while preserving quality of life.

Human epidermal growth factor receptor 2 (HER2) is an important prognostic factor in BC and is a key factor influence treatment strategies. The human epidermal growth factor receptor (HER) tyrosine kinase receptor family comprises four receptors: HER1, HER2, HER3, and HER4. These receptors are important mediators of cell growth, survival, and differentiation.[2] 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.[3] 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 overall response rate (ORR), response duration, and progression-free survival (PFS) were associated with a 5-month overall survival (OS) advantage when trastuzumab was given in the first-line metastatic setting, as demonstrated in the initial Phase III trial.[4]

For patients with HER2-positive mBC, the combination of anti-HER2 therapy and a taxane is a globally accepted first-line treatment, based on the OS advantage demonstrated in three large pivotal trials.[4–6]

However, disease progresses in almost all patients with HER2-positive mBC and these patients require additional therapies. Importantly, such tumors continue to express high levels of HER2,[7] and neither the process of internalization nor the level of surface expression is altered when HER2 is bound by trastuzumab.[8]

After progression, the standard strategy is further HER2-directed therapy, either continuing trastuzumab with a different chemotherapy agent (eg trastuzumab plus capecitabine), or changing to a different HER2-directed regimen (eg lapatinib plus capecitabine). In a randomized Phase III trial, GBG26, in patients

whose disease had progressed on previous trastuzumab-containing therapy, the combination of trastuzumab and capecitabine was associated with significantly improved time to progression (TTP) (hazard ratio [HR] 0.69, median 8.2 *versus* 5.6 months, respectively) and ORR (48% *versus* 27%) compared with capecitabine alone.[9] In another 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 ORR (24% *versus* 14%) and TTP (median 6.2 months *versus* 4.3 months) compared with capecitabine alone.[9]

1.1.2 HER2-POSITIVE LOCALLY ADVANCED/METASTATIC GASTRIC CANCER

Gastric cancer (GC) remains one of the most common malignancies in the world with an estimated 952,000 new cases in 2012.[1] GC also continues to be a deadly disease; it is the third leading cause of cancer-related death, accounting for 723,000 deaths (8.8% of all cancer deaths) worldwide in 2012. The only potentially curative treatment for GC is complete resection of localized disease. The overall 5-year survival for all cases, regardless of initial stage at diagnosis, is less than 25%.[11-14] Among patients with localized disease who undergo curative surgery, approximately 40–60% will have disease recurrence. Patients with unresectable disease due to locally advanced growth or metastatic spread have the poorest prognosis, with an overall 5-year survival rate in the range of 3% to 15%.[11,13,14]

Whereas HER2 overexpression is associated with a poor prognosis in BC, the prognostic significance of HER2 overexpression in GC is not fully defined. Studies of HER2 positivity rates in GC have shown a broad variation of HER2 positivity ranging from 6.8% to 34.0% for immunohistochemistry (IHC) and 7.1% to 42.6% for fluorescence *in situ* hybridization (FISH) techniques.[15,16] In a recent study, HER2 positivity was shown in 17% of resected esophageal adenocarcinomas and was significantly associated with lower tumor grade, less invasiveness, fewer malignant nodes, and the presence of adjacent Barrett's esophagus.[17]

In the ToGA trial (study BO18255), a global, Phase III study of trastuzumab plus chemotherapy as first-line treatment for advanced HER2-positive GC,[18] an overall HER2-positivity rate of 22.1% was observed (810/3667 evaluable samples), which is similar to BC. A higher HER2 positivity rate was seen in adenocarcinoma of the gastroesophageal junction (GEJ) than in the stomach (33.2% *versus* 20.9%), and intestinal type GCs showed a significantly higher HER2 positivity rate than diffuse or mixed-type tumors (intestinal: 32.2%, diffuse: 6.1%, mixed: 20.4%).[19]

In the ToGA trial, the addition of trastuzumab to chemotherapy (capecitabine or fluorouracil combined with cisplatin) for the treatment of patients with HER2-positive (defined as IHC 3+ or FISH positive), inoperable, locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or GEJ resulted in

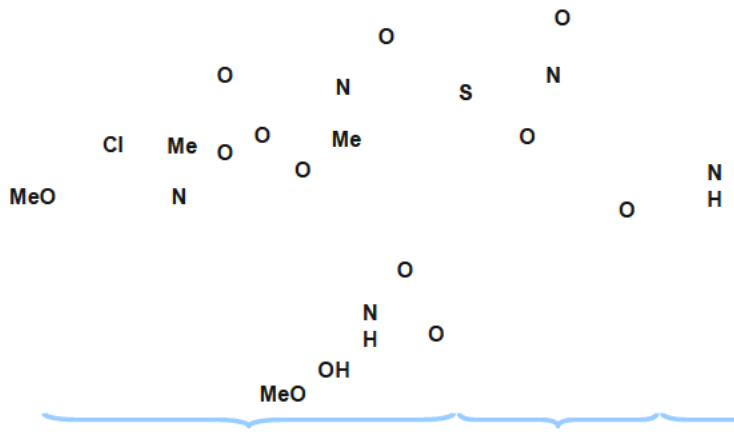
an increase in OS (median 13.8 months *versus* 11.1 months, HR 0.74, p = 0.0046), ORR (47% *versus* 35%), PFS (median 6.7 *versus* 5.5 months), and TTP (median 7.1 *versus* 5.6 months) compared with chemotherapy alone.[18]

1.2 BACKGROUND ON STUDY DRUGS

1.2.1 TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (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, a humanized monoclonal antibody directed against the extracellular region of HER2; an average of 3.5 molecules of derivative of maytansine (DM1; maytansinoid), an anti-microtubule agent; and the thioether linker maleimidylmethyl cylcohexane-1-carboxylate, 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, was studied in approximately 800 cancer patients in the 1970s and 1980s, with responses seen in patients with breast and lung cancers.[20,21] 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.[22,23]

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

Similar to trastuzumab, trastuzumab emtansine recognizes an epitope in the extracellular domain of HER2 and binds to HER2 with a similar affinity. Following antigen-specific binding of trastuzumab emtansine to HER2, the complex of receptor and ADC is internalized, whereupon DM1-containing catabolites are released into the cytosol following proteolytic cleavage of the antibody in lysosomes.[24] Binding of these DM1-containing species to β-tubulin inhibits tubulin polymerization, resulting in cell death.[22]

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.[20]

Phase I single-arm studies were conducted to identify the most appropriate dosing regimen for further clinical development, and assess the safety of trastuzumab emtansine. Low levels of DM1 in systemic circulation supported the stability of the linker.[25] The studies also provided an indication of clinical activity and led to randomized evaluation of single-agent trastuzumab emtansine versus other HER2-directed therapy in combination with chemotherapy. These trials demonstrated significantly superior PFS and OS with trastuzumab emtansine.[26–28]

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.[29,30] 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 (qw) schedule.

On the q3w dosing schedule, dose-limiting toxicities (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. On the qw schedule, 2.4 mg/kg was identified as the MTD.

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 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 whose disease had progressed on previous HER2-directed therapy and conventional chemotherapy.[31]

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 independent review. The clinical benefit rate (CBR; defined as complete response [CR], partial response [PR], or stable disease [SD] 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 independent review. 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 adverse events (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.[32] Patients must have received an anthracycline, trastuzumab, a taxane, lapatinib, and capecitabine given in the neoadjuvant, 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 experienced progressive disease (PD) on their most recent treatment.

The primary objectives of this study were: 1) to assess the ORR as determined 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 (CR or PR) of 34.5% (95% CI: 26.1%–43.9%; 38 of 110 patients) by independent review 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 median PFS by independent review was 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 aspartate transaminase (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%). Serious AEs (SAEs) were recorded in 28 patients (25.5%), the most common being cellulitis (3.6%), pyrexia (2.7%), and pneumonia (2.7%). There was one Grade 5 AE (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 comorbidities, including renal insufficiency.

1.2.1.4 Study TDM4450g

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.[26] This study completed enrollment in December 2009 (n = 137). The co-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, OS, 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.

As of 15 November 2010, the median PFS was 14.2 months in the trastuzumab emtansine arm *versus* 9.2 months in the trastuzumab plus docetaxel arm. The 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 as first-line therapy for 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.[33] No meaningful effect of trastuzumab emtansine on the corrected QT interval was seen 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 to baseline. Following the third infusion of trastuzumab emtansine, the baseline-adjusted mean QTcF interval at both the 15-minute and the 60-minute post-infusion time points was increased by 4.7 ms. No patient exhibited a mean 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, the ORR was 25.5% (95% CI: 15.2%–38.5%) as assessed by the investigator; no independent review was performed. 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 Phase III Study TDM4370g

A randomized, open-label Phase III trial (TDM4370g; EMILIA) compared single-agent trastuzumab emtansine *versus* lapatinib and capecitabine in patients with HER2-positive locally advanced unresectable BC or mBC who had received a prior taxane and trastuzumab therapy and had documented PD.[27]

Patients were randomized in a 1:1 ratio to trastuzumab emtansine 3.6 mg/kg IV q3w or the combination of oral capecitabine 1,000 mg/m^2 twice daily (bid) on

Days 1–14 q3w plus oral lapatinib 1,250 mg/day given as continuous dosing. Treatment was continued until PD (as assessed by the investigator), unmanageable toxicity, or study termination. PFS and OS were co-primary endpoints, with PFS based on modified RECIST[34] and assessed by independent review. Key secondary endpoints were ORR, DoR, and CBR, determined both by the investigator and by independent review.

The study demonstrated statistically significant and clinically meaningful improvements in both PFS and OS for trastuzumab emtansine compared with lapatinib plus capecitabine. Median PFS was 9.6 months in the trastuzumab emtansine arm *versus* 6.4 months in the control arm (HR = 0.65; 95% CI: 0.55–0.77; p < 0.001, log-rank test). Median OS was 30.9 months *versus* 25.1 months, respectively (HR = 0.68; 95% CI: 0.55–0.85; p < 0.001, log-rank test).

This benefit was supported by consistent improvements in all secondary efficacy endpoints, including investigator-assessed PFS, ORR, time to treatment failure (TTF), and the patient-reported outcome of time to symptom progression. The ORR in the trastuzumab emtansine arm was 43.6% (95% CI: 38.6%–48.6%) compared with 30.8% (95% CI: 26.3%–35.7%) in the control arm (based on 786 evaluable patients). 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; that of trastuzumab emtansine (40.8%; n = 490) was 200. The rates of SAEs for both arms were similar (control arm 18% *versus* trastuzumab emtansine 15.5%).

Based on the results of this phase III trial, both the Food and Drug Administration (FDA) in the US and the European Commission in Europe approved trastuzumab emtansine for the treatment of HER2-positive mBC previously treated with trastuzumab and a taxane.

1.2.1.7 Phase III study TDM4997g

A second open-label randomized Phase III trial (TDM4997g; TH3RESA) compared single-agent trastuzumab emtansine *versus* the investigator's choice of therapy in patients with HER2-positive advanced BC who had previously received two or more HER2-directed regimens in the advanced setting, including trastuzumab and lapatinib, and previous taxane therapy in any setting.[28] A total of 602 patients were randomized in a 2:1 ratio (404 to trastuzumab emtansine and 8 to physician's choice).

After median follow-up of approximately 7 months in both arms, 219 patients (54%) in the trastuzumab emtansine group and 2 (65) in the physician's choice group had experienced PFS events. PFS was significantly improved with trastuzumab emtansine compared with physician's choice (HR 0.528, p<0.0001; median PFS 6.2 months with trastuzumab emtansine *versus* 3.3 months in the control arm. The HR for OS at the interim analysis was 0.552 (95% CI 0.369–0.826) but the stopping boundary was not crossed.

Grade ≥3 AEs occurred less frequently with trastuzumab emtansine than with physician's choice (32 of patients vs 43). Grade ≥3 neutropenia, diarrhea, and febrile neutropenia were less common with trastuzumab emtansine than physician's choice, whereas grade ≥3 thrombocytopenia (5% *vs* 2%) was more common with trastuzumab emtansine.

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 qw regimens of trastuzumab emtansine administration are presented in Table 1.

Table 1 Cycle 1 Mean (s.d.) Pharmacokinetic Parameters for Trastuzumab Emtansine Following Trastuzumab Emtansine Administration q3w and qw in Study TDM3569g

Dose (mg/kg)	No. of Patients	C_{max} (µg/mL)	AUC_{inf} (day µg/mL)	$T_{1/2}$ (day)	V_d (mL/kg)	CL (mL/day/kg)
q3w 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)
qw 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; s.d. = standard deviation; $T_{1/2}$ = terminal half-life; V_d = volume of distribution.

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 q3w cycle with a 2.4 mg/kg qw regimen compared with 3.6 mg/kg q3w.[29,30]

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.[35]

An aggregate PK assessment of trastuzumab emtansine was performed with samples from studies TDM3569g, TDM4258g, TDM4374g, and TDM4688g.[36,37] 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., maximum concentration [C_{max}], area under the serum concentration-time curve [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. Weekly administration of trastuzumab emtansine in study TDM3568g at a dose of 2.4 mg/kg showed consistent PK data with the q3w dosing schedule.[29]

1.2.2 CAPECITABINE

Capecitabine (Xeloda®) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), which is converted to 5-fluorouracil (5-FU) in the tumor, where it inhibits DNA synthesis and slows down tumor tissue growth. It is approved in combination with docetaxel and as monotherapy in mBC. Please see the national Xeloda® prescribing information or Investigator brochure for more information.

The activity of capecitabine as single-agent chemotherapy was initially demonstrated in two multicenter Phase II clinical trials (before testing of HER2 status was standard) in patients with locally advanced or mBC after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy was not indicated.[38,39] In these trials, a total of 236 patients were treated with capecitabine (1,250 mg/m^2 bid for 2 weeks followed by 1-week rest period). The ORRs (investigator assessment) were 20% (first trial)

and 25% (second trial). The median TTP was 3.1 months and 3.2 months, respectively. Median OS was 12.6 months and 12.3 months, respectively.

The combination of capecitabine and docetaxel was studied as treatment for locally advanced or mBC after failure of anthracycline-containing chemotherapy in a multicenter randomized controlled Phase III clinical trial (SO14999).[40] In this trial, 255 patients were randomized to treatment with capecitabine (1,250 mg/m^2 bid for 2 weeks followed by a 1-week rest period) and docetaxel (75 mg/m^2 as a 1-hour IV infusion q3w) and 256 patients were randomized to treatment with docetaxel alone (100 mg/m^2 as a 1-hour IV infusion q3w). OS was superior in the capecitabine plus docetaxel combination arm (HR 0.775; p = 0.0126). Median OS was 14.5 months (capecitabine plus docetaxel) *versus* 11.5 months (docetaxel alone). The ORR in the all-randomized population (investigator assessment) was 41.6% (capecitabine plus docetaxel) *versus* 29.7% (docetaxel alone; p = 0.0058). TTP was superior in the capecitabine plus docetaxel combination arm (HR 0.652; p < 0.0001). The median TTP was 6.1 months (capecitabine plus docetaxel) *versus* 4.2 months (docetaxel alone).

This trial led to the randomized Phase II CHAT trial evaluating the addition of capecitabine to first-line trastuzumab and docetaxel for locally advanced or metastatic HER2-positive mBC.[41] PFS was significantly improved with the addition of capecitabine (HR 0.72; median 17.9 months *versus* 12.8 months in patients receiving docetaxel and trastuzumab without capecitabine), although there was no difference in ORR (71% *versus* 73%, respectively).

1.2.2.1 Study BO18255: Capecitabine and Trastuzumab in LA/mGC

A global Phase III study (ToGA trial, BO18255) of trastuzumab plus chemotherapy as first-line treatment for advanced HER2-positive GC was conducted in 584 patients previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or GEJ. Patients received either capecitabine or fluorouracil combined with cisplatin or the same chemotherapy in combination with trastuzumab. The primary study endpoint was OS, defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182/290 patients (62.8%) in the control arm and 167/294 patients (56.8%) in the trastuzumab-containing arm. The majority of the deaths were due to events related to the underlying cancer.[18]

Most patients enrolled in the study were male (76%); 52.9% were Asian and 37.7% were white. The primary tumor site was the stomach for 81.8% of patients, with the others having GEJ tumors. The addition of trastuzumab to chemotherapy resulted in an increase in median OS from 11.1 months to 13.8 months (HR 0.74, p = 0.0046). ORR (47% *versus* 35%), PFS (median 6.7 *versus* 5.5 months), and TTP (median 7.1 *versus* 5.6 months) were also significantly increased with the addition of trastuzumab to chemotherapy compared with chemotherapy alone.

With regard to OS, a treatment effect could not be excluded in any predefined subgroup, including primary tumor site, histologic subtype, method of determining HER2-positivity, performance status, chemotherapy regimen, age, gender, and region of enrollment. A multivariate analysis for OS showed a consistent result, with an adjusted HR of 0.72 (p = 0.0036); variables found to influence primary outcome included Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 *versus* 2), prior gastrectomy, and Asian region of enrollment (data on file). A multivariate analysis of OS for patients enrolled in Japan, from which the bulk of Asian patients were enrolled, demonstrated a HR of 0.68. This was consistent with the overall study results.[42]

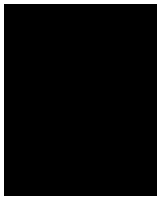
A pre-planned subgroup analysis by IHC score indicated that positive treatment effects were greater in tumors with higher levels of HER2 expression. Among patients whose tumors had these higher levels of HER2 expression, the median OS was 11.8 months *versus* 16 months (HR = 0.65; 95% CI: 0.51–0.83) and median PFS was 5.5 months *versus* 7.6 months (HR = 0.64; 95 % CI: 0.51–0.79) for chemotherapy *versus* chemotherapy plus trastuzumab respectively. For OS, the HR was 0.75 (95% CI: 0.51–1.11) in the IHC 2+/FISH+ group and 0.58 (95% CI: 0.41–0.81) in the IHC 3+/FISH+ group.[18]

The addition of trastuzumab to chemotherapy did not result in an increased incidence of severe (Grade 3/4) or fatal AEs. There were no additional significant safety issues with trastuzumab used in the treatment of advanced GC over and above those observed when it was used in BC. Taken together, the results of the ToGA trial (BO18255) not only demonstrate the role of HER2 suppression in the treatment of HER2-positive GC but also show that HER2-directed therapies can be added to conventional chemotherapy regimens without substantial increases in side effects.

1.2.3 PRECLINICAL DATA OF THE COMBINATION OF TRASTUZUMAB EMTANSINE AND A FLUOROPYRIMIDINE

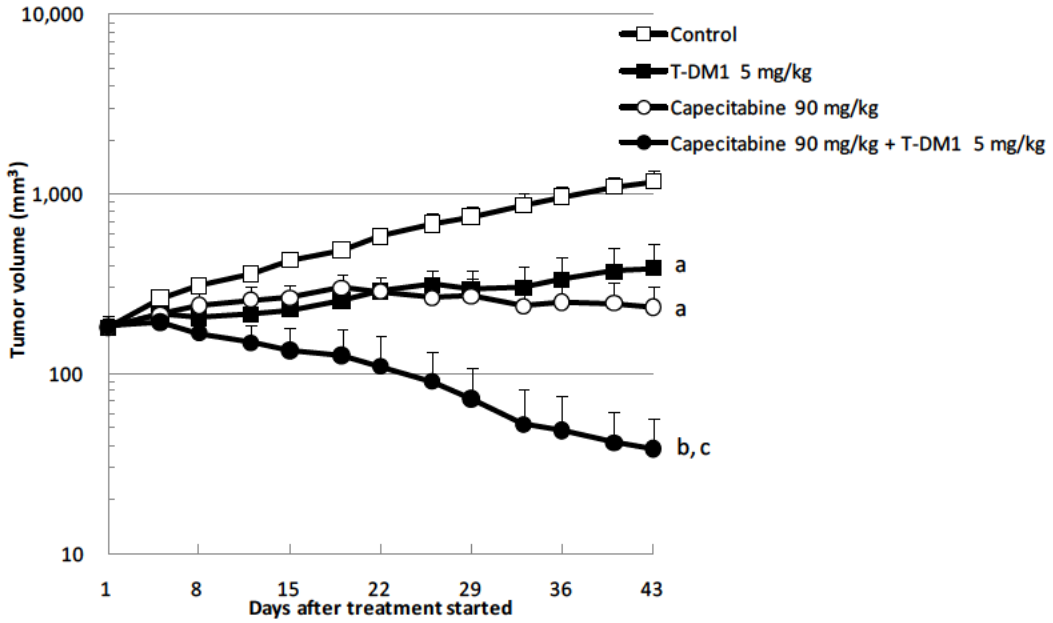
In preclinical BC models, additive anti-tumor activity was observed with combinations of trastuzumab emtansine and 5-FU (seeFigure 2).[43] In GC models a similar additive effect was observed with trastuzumab emtansine and capecitabine (see Figure 3 [data on file]).

Figure 2 MMTV HER2 Fo5 Mammary Tumor Transplants



T-DM1 = trastuzumab emtansine; 5-FU = 5-fluorouracil

Figure 3 Anti-tumor Activity of Trastuzumab Emtansine in Combination with Capecitabine in NCI-N87



T-DM1 = trastuzumab emtansine; 5-FU = 5-fluorouracil

1.3 STUDY RATIONALE AND RISK-BENEFIT ASSESSMENT

1.3.1 FOR MBC

At present, mBC remains an incurable disease. The primary goal of treatment is maximizing the patient's survival and quality of life.

HER2-positive breast tumors have been shown to benefit from anti-HER2 therapy. Regimens using the combination of anti-HER2 agents and chemotherapy have demonstrated higher efficacy than single-agent therapy. As a consequence several different combination therapies have been approved for HER2-positive mBC treatment in most countries and are considered the current standard of care.

The combination of capecitabine with anti-HER2 therapies has been shown to be beneficial in patients with HER2-positive mBC. The combination of capecitabine and lapatinib was approved in the United States in March 2007 for the treatment of patients with HER2-positive mBC who have previously received an anthracycline, a taxane, and trastuzumab. In June 2008, the European Commission granted conditional marketing authorization for lapatinib in combination with capecitabine for the treatment of patients with HER2-positive advanced or mBC whose disease has progressed on an anthracycline, a taxane,

and trastuzumab in the metastatic setting. The combination of capecitabine and trastuzumab has demonstrated significant efficacy benefit when compared with capecitabine alone.[9]

The Phase III, TDM4370g trial met its co-primary endpoint of improving PFS (by independent review) and OS compared with the combination of lapatinib and capecitabine (see Section 1.2.1.6).

Based on the studies mentioned above, the combination of trastuzumab emtansine and capecitabine could provide the potential for enhanced anti-tumor efficacy in mBC compared with single-agent trastuzumab emtansine or trastuzumab in combination with chemotherapy. Furthermore, preclinical data suggest that the combination of trastuzumab emtansine and capecitabine has an additive effect (see Section 1.2.3).

Approximately 2,000 patients with BC have been treated in trastuzumab emtansine clinical trials with an acceptable safety profile and a positive risk-benefit ratio. A broad development program is in place to seek approval for indications for mBC. Capecitabine in combination with an anti-HER2 agent is a proven efficacious regimen with a well-established safety profile in mBC. Trastuzumab emtansine and capecitabine have no known significant overlapping toxicities. As part of the Phase I conduct, regular teleconference calls with the investigators will be held to discuss the study treatment risk-benefit profile for each patient. An Independent Data Monitoring Committee (IDMC) will be established with the main responsibility of assessing the risk-benefit for the Phase II part of the study. Therefore, exploring the benefit of combination therapy of trastuzumab emtansine and capecitabine in patients with mBC seems justified.

1.3.2 FOR MGC

As for mBC, the primary goal of treatment for metastatic gastric cancer (mGC) is to maximize patients' survival and quality of life.

In HER2-positive gastric tumors, anti-HER2 therapy has shown benefit. In the ToGA study (BO18255), the combination of chemotherapy and trastuzumab significantly improved OS versus chemotherapy alone (see Section 1.2.2.1) in this population. Fluoropyrimidine-based therapies (capecitabine, 5-FU) are the standard of care in mGC in general and were also the most frequent combination agents used in the ToGA trial (BO18255; see Section 1.2.2.1).

Furthermore, preclinical data suggest that the combination of trastuzumab emtansine and capecitabine has an additive effect (see Section 1.2.3).

A development program for trastuzumab emtansine is in place to seek approval for mGC indications. Capecitabine in combination with trastuzumab is a proven efficacious regimen with a well-established safety profile in mGC. Trastuzumab emtansine and capecitabine might have overlapping toxicities and therefore safety monitoring is in place to avoid exposing patients to harm. Therefore,

exploring the benefit of combination therapy of trastuzumab emtansine and capecitabine in patients with mGC seems justified.

In the ToGA study in LA/mGC, trastuzumab exposure was lower than that observed in breast cancer studies. Based on this observation, together with pharmacokinetic results and findings from a Phase I study in mBC, it was considered that a weekly trastuzumab emtansine regimen may provide higher cumulative trastuzumab emtansine exposure than the q3w schedule and was therefore chosen for the Phase I, Cohort 2 part of the present study in LA/mGC. This approach has subsequently been supported by findings from stage I of the adaptive phase II/III BO27952 trial in this setting (see Section 3.3.2.2). In October 2013, the IDMC for the BO27952 trial recommended selection of the weekly 2.4 mg/kg regimen for further evaluation in the phase III part of the trial based on pharmacokinetic, safety, and efficacy data available at the time.

Results from the Phase I part of the study in mGC will be used as supporting information for future studies in the indication.

2. OBJECTIVES

2.1 PHASE I: MTD-FINDING OF TRASTUZUMAB EMTANSINE AND CAPECITABINE IN MBC

2.1.1 PRIMARY OBJECTIVE

- To determine the MTD of the combination of trastuzumab emtansine and capecitabine in patients with HER2-positive mBC

2.1.2 SECONDARY OBJECTIVES

To assess the:

- PK of trastuzumab emtansine, capecitabine and their metabolites
- Safety of the combination of trastuzumab emtansine and capecitabine
- ORR

2.2 RANDOMIZED PHASE II: EXPLORATION OF EFFICACY AND SAFETY IN MBC

2.2.1 PRIMARY OBJECTIVE

To explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in patients with HER2-positive mBC, as measured by ORR by RECIST v.1.1 per investigator local assessment

2.2.2 SECONDARY OBJECTIVES

To assess the safety profile of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone

To explore the efficacy of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone in patients with HER2-positive mBC, as measured by:

- Time to response (TTR)
- DoR
- TTP
- TTF
- PFS
- CBR
- OS

2.3 PHASE I: MTD FINDING OF TRASTUZUMAB EMTANSINE AND CAPECITABINE IN LA/MGC

2.3.1 PRIMARY OBJECTIVE

To determine the MTD of the combination of trastuzumab emtansine and capecitabine in patients with LA/mGC

2.3.2 SECONDARY OBJECTIVES

To assess the:

- PK of trastuzumab emtansine, capecitabine, and their metabolites
- Safety of the combination of trastuzumab emtansine and capecitabine
- ORR

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is an international, multicenter Phase I/II dose-finding study of two dosing schedules of trastuzumab emtansine and capecitabine combination therapy in HER2-positive mBC and LA/mGC.

The study is designed to determine the MTD of capecitabine in combination with trastuzumab emtansine in Phase I studies in patients with HER2-positive mBC or LA/mGC.

The efficacy and safety of the combination in patients with mBC will also be explored in a randomized, open-label Phase II part of the study.

3.1.1 OVERVIEW OF STUDY DESIGN

Overview of Study Design

The study is designed to determine the MTD of capecitabine in combination with trastuzumab emtansine in patients with HER2-positive mBC or LA/mGC using a Phase I design, followed by a randomized, open-label Phase II part of the study to explore the efficacy and safety of the combination in patients with HER2-positive mBC. There will be no follow-on randomized exploration of efficacy in mGC. Results from the Phase I study in LA/mGC will be used as supporting information for future studies in the indication.

Cohort 1 for patients with mBC will open first and the MTD will be established. Once the MTD is defined, both the randomized Phase II trial for patients with HER2-positive mBC and the Phase I Cohort 2 for patients with LA/mGC will open.

An overview of the study design is depicted in Figure 4.

Duration of Treatment and Patient Follow-up

Duration of treatment: All patients will be treated until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor. In case of toxicities requiring the discontinuation of capecitabine, single agent trastuzumab emtansine may be continued. In case of toxicities requiring the discontinuation of trastuzumab emtansine, the patient will be followed up until EOS (treatment with capecitabine alone is not allowed).

If at the time of study closure there are patients whose disease has not progressed and who are still receiving study treatment, they will be offered the possibility to continue treatment by enrolling in an extension study at the discretion of the investigator.

Patient follow-up: All patients will be followed up until withdrawal of consent, death, or for up to a maximum of 2 years after the last patient was randomized in the Randomized Phase II part of the study, whichever occurs first.

Duration of Study, Database Closure and Data Reporting

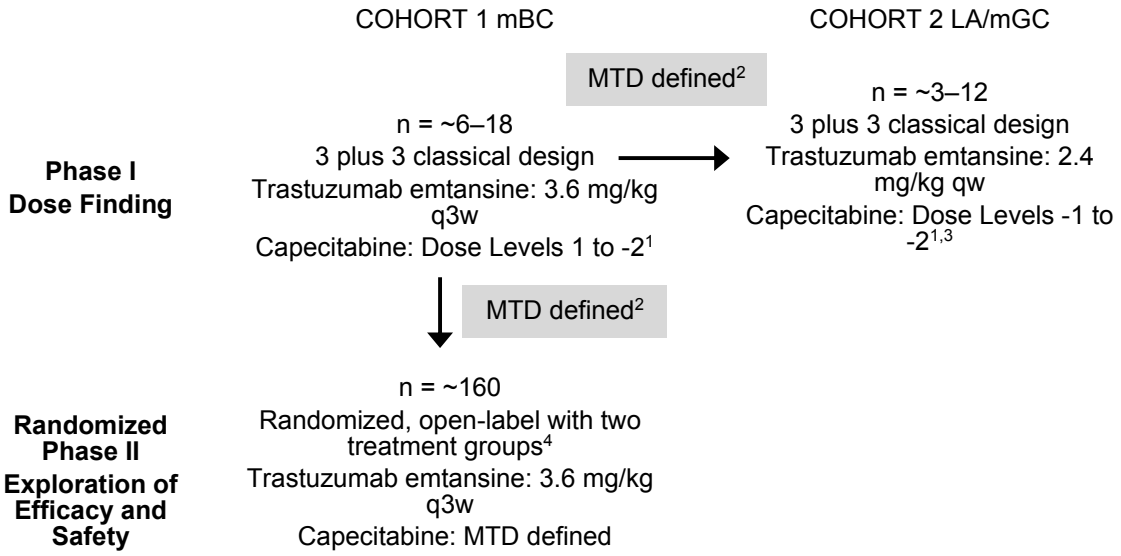
The duration of the study is estimated to be approximately 4 years. Recruitment is estimated to last 2 years in total (1 year for the MTD-Finding study in mBC and 1 year for the Phase II Exploration of Efficacy and Safety in mBC). See Section 3.2 for further details about EOS.

Specifically in Phase I, cohort 2, if dose level -2 is too toxic in LA/mGC, recruitment into the LA/mGC cohort will be closed. See Section 3.1.1.3 for details of treatment continuation if patients are still responding to treatment at this time.

Data may be published/presented publicly at the end of each cohort e.g., once the MTD for Cohort 1 for mBC has been defined and the dose for Phase II Exploration of Efficacy and Safety has been selected, and after the prespecified

analyses for the Randomized Phase II exploration of efficacy and safety in mBC. The Clinical Study Report (CSR) will be finalized/published within 1 year after EOS (LPLV).

Figure 4 Overview of Study Design



[1] Capecitabine doses are administered daily on Days 1–14 q3w

[2] The MTD defined in the mBC Phase I study will be implemented in the mBC Randomized Phase II and mGC Phase I studies

[3] Cohort 2 will open to recruit patients with LA/mGC using the MTD defined in Phase I for patients with mBC. Dose Level 1 will not be explored in Cohort 2 (see also Section 3.3.2.2)

[4] Stratification factor: Number of prior lines of treatment for metastatic disease (≤1 or >1; excluding single-agent hormones)

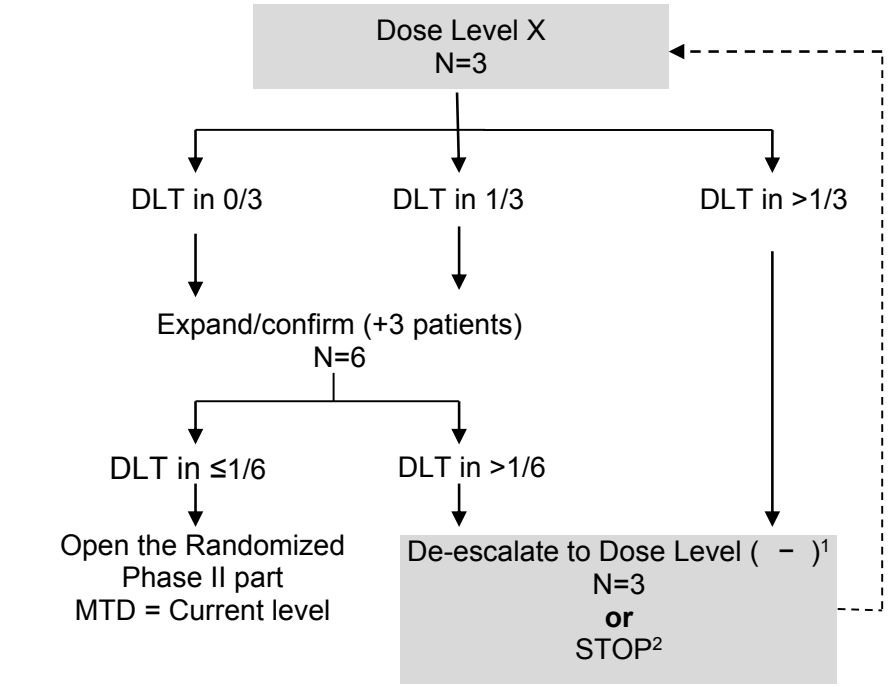
mBC = metastatic breast cancer; LA/mGC = locally advanced/metastatic gastric cancer; MTD = maximum tolerated dose; q3w = every 3 weeks; qw = weekly.

A schedule of assessments is provided in Appendix 1.

3.1.1.1 Overview of Phase I Design in Patients with mBC

An overview of the Phase I study design is depicted in **Figure 5**.

Figure 5 Overview of Phase I Dose Finding Study Design



[1] Repeat with the new dose level until the MTD is established

[2] If Dose Level -2 is too toxic (DLT in > 1/6 patients), the study will be terminated.

DLT = dose-limiting toxicity; MTD = maximum tolerated dose

Determination of the MTD in Patients with mBC

The trial will first investigate the feasibility of the combination of capecitabine and trastuzumab emtansine q3w in one cohort of up to 18 patients, by de-escalating the dose of capecitabine from 750 mg/m^2 bid to 650 mg/m^2 bid on Days 1 to 14 q3w with a 3 plus 3 classical Phase I design. Cohort 1 will open first and enroll patients with HER2-positive mBC.

Enrollment into Cohort 1

MTD-finding in patients with mBC (Phase I)

According to the 3 plus 3 classical study design, Cohort 1 will start with the enrollment of 3 patients at Dose Level 1. Patients will be evaluated for DLTs as specified in the DLT definition (see Section 5.1.4). The dose of trastuzumab emtansine is fixed at 3.6 mg/kg q3w. Three dose levels of capecitabine administered bid on Days 1 to 14 q3w will be tested.

The following doses will be explored in Cohort 1:

Dose Level 1: 750 mg/m^2 capecitabine bid plus 3.6 mg/kg q3w trastuzumab emtansine

Dose Level -1: 700 mg/m^2 capecitabine bid plus 3.6 mg/kg q3w trastuzumab emtansine

Dose Level -2: 650 mg/m^2 capecitabine bid plus 3.6 mg/kg q3w trastuzumab emtansine

The following MTD determining rules will be applied during the MTD-Finding treatment phase:

- Step 1: Three patients will be enrolled at Dose Level 1
- Step 2: The toxicity of Dose Level 1 will be monitored and the following actions taken:
  a) If none of these 3 patients (0/3) experiences a DLT, the MTD will be established as the current dose level and will need to be confirmed in 3 more patients (to achieve DLTs in ≤ 1/6 patients at that dose level)
  b) If 1 of the initial 3 patients (1/3) experiences a DLT, an additional 3 patients should be enrolled and treated at the same dose, i.e., Dose Level 1
  c) If no additional patients experience a DLT (1/6), the MTD will be established as the current dose level
  d) If 1 or more additional patients experience a DLT (> 1/6), the dose will be de-escalated to the next lowest dose level. If no more than 1 patient experiences a DLT (≤ 1/6) after dose de-escalation, the dose will be considered the MTD and, following IDMC recommendation, will be further explored in the Randomized Phase II part of the study. Dose re-escalation will not be allowed. If 2 or more patients experience a DLT (> 1/6) after dose de-escalation, de-escalation should continue to the next lowest dose level. Based on the DLT findings, the next dose level may be considered the MTD and, following IDMC recommendation, be further explored in the Randomized Phase II part of the study or the study may be terminated if DLTs occur in > 1/6 patients at Dose Level -2.

In order to define the dose for the Randomized Phase II Exploration of Efficacy and Safety part of the study, evaluation will include not only the DLTs during Cycle 1 but also all available safety information during the subsequent cycles. The dose level considered optimal will be the dose level selected to proceed to the Phase II and LA/mGC parts of the study.

Once the appropriate dose of study medication is established, the Randomized Phase II part of the study and Phase I, Cohort 2 will open as shown in Figure 4.

3.1.1.2 Overview of Phase II: Exploration of Efficacy and Safety in Patients with mBC

After review of safety data from Part 1, cohort 1, the IDMC recommended a regimen of capecitabine 700 mg/m^2 bid days 1–14 in combination with trastuzumab emtansine 3.6 mg/kg q3w for further evaluation. The Phase II part of the study will explore the efficacy and safety of this recommended regimen compared with trastuzumab emtansine alone in patients with HER2-positive mBC. See Section 3.1.1 for details of duration of treatment.

Approximately 160 additional patients with HER2-positive mBC will be randomized into the Phase II part of the study. Patients in the Phase I part of the study will not contribute to the Phase II part of the study; however, they will be followed-up until end of study (EOS).

3.1.1.3 Overview of Phase I Design in LA/mGC Patients

Determination of the MTD in Patients with LA/mGC

Cohort 2 will enroll patients with HER2-positive LA/mGC. Trastuzumab emtansine will be administered qw at a fixed dose of 2.4 mg/kg and capecitabine will be started at 700 mg/m^2 bid, the MTD defined for patients with mBC in Cohort 1.

Enrollment into Cohort 2

Cohort 2 will open with a 3 plus 3 classical design to investigate the feasibility of combination therapy of capecitabine and trastuzumab emtansine in up to 12 patients with LA/mGC. The capecitabine dose will be de-escalated from the starting dose of 700 mg/m^2 bid (the MTD recommended in Cohort 1).

The dose levels for de-escalation of capecitabine will be the same as described for Cohort 1, except for Dose Level 1, which will not be explored in patients with mGC (see also Section 3.3.2.2).

If Dose Level -1 (700 mg/m^2 bid, the MTD recommended in cohort 1) is well tolerated (DLT in ≤ 1/6), this dose will be established as the MTD for LA/mGC.

- If Dose Level -1 is not tolerated in Cohort 2 (DLT in > 1/3 or > 1/6 patients), de-escalation will be to Dose Level -2.
- If Dose Level -2 is not tolerated in Cohort 2 (DLT in > 1/6), the combination will be considered not feasible in LA/mGC and Cohort 2 will be terminated. Patients who, at that time, experience response according to RECIST v.1.1 will be offered the possibility to continue on trastuzumab emtansine as a single agent, or with the combination, based on risk-benefit balance and agreement with the Steering Committee (SC).

3.1.1.4 Number of Patients

Overall, it is anticipated that the maximum number of patients enrolled into the study will be approximately 190.

Phase I, Cohort 1: mBC

Between 6 and 18 patients will be enrolled into Cohort 1 to determine the MTD of capecitabine in combination with trastuzumab emtansine in patients with mBC.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

For this part of the study, a total of approximately 160 patients with mBC will be randomized.

Phase I, Cohort 2: mGC

After the MTD in Cohort 1 has been established, 3–12 patients will be enrolled into Cohort 2 to determine the MTD of capecitabine in combination with trastuzumab emtansine in patients with mGC.

3.1.1.5 Number of Centers

This is a multicenter, international study.

3.1.2 STEERING COMMITTEE

A SC has been established for this study. Initially, it is composed of the investigators participating in the Phase I, Cohort 1 part of the study and one medical representative and one statistician of the Sponsor. The study design and DLT definition have been developed by the SC. See the SC Charter for further information.

The SC will collectively review the status of the ongoing patients in Phase I on a regular basis. The SC will adjudicate in the event of DLTs that are not covered by the existing DLT criteria.

3.1.3 INDEPENDENT DATA MONITORING COMMITTEE

An IDMC will review the safety outcomes for patients enrolled in Phase I, Cohort 1 and recommend whether the Randomized Phase II part of the study can commence. The IDMC will also monitor safety outcomes after 25, 75, and 150 patients have received at least 3 cycles (Cycle 3 Day 21) of treatment in the Phase II part of the study. Afterwards, the IDMC will monitor accumulating patient safety data every 6 months during the Randomized Phase II part of the study or as requested.

3.2 END OF STUDY

EOS is defined as the last patient last visit (LPLV) at the end of the follow-up period, as defined in Section 3.1.1. This will be the last data collection point,

which can be a clinic visit or a laboratory sample. LPLV is expected to occur approximately 2 years after the last patient has been randomized into the Phase II part of the trial.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 RATIONALE FOR PATIENT GROUP SELECTION

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® national prescribing information). Measurement of HER2 gene amplification has traditionally been performed using IHC. HER2 gene amplification determined by ISH has also proven to be a reliable method for demonstrating HER2-positive status.[44]

This study will enroll patients diagnosed with HER2-positive mBC or LA/mGC. Capecitabine is an established chemotherapy for both diseases. In patients with HER2-positive mBC or LA/mGC, anti-HER2 therapy has demonstrated activity. Furthermore, the combination of anti-HER2 therapy and capecitabine has been shown to be efficacious in both mBC[9,10] and LA/mGC.[18] Eligible patients for this study will have incurable mBC or LA/mGC overexpressing HER2.

3.3.1.1 Rationale for Phase I

The 3 plus 3 design is a well-established and well-known method for Phase I studies. PK parameters will be collected and analyzed to investigate the PK interaction of the drugs under investigation.

The capecitabine dose evaluated in combination with trastuzumab and docetaxel in the CHAT trial was 950 mg/m^2 bid. However, retrospective evaluations and post hoc analyses of early dose reduction suggest that lower starting doses of capecitabine offer similar efficacy with better tolerability. Therefore the capecitabine starting dose selected in combination with trastuzumab emtansine for the MTD-Finding Phase I part of the present study was 750 mg/m^2 bid, taking into account the aim of maintaining the good tolerability of trastuzumab emtansine while benefitting from synergy observed between the two agents in nonclinical studies.

The combination of T-DM1 and capecitabine was evaluated with a de-escalation study design. Following the emergence of two DLTs (grade 3 vomiting, grade 3 elevated AST/ALT) at the starting dose of 750 mg/m^2 bid (days 1–14 q3w) in combination with trastuzumab emtansine 3.6 mg/kg q3w, a de-escalated dose cohort was opened to evaluate capecitabine 700 mg/m^2 bid combined with the same dose of trastuzumab emtansine. At this dose no DLTs were observed in the six patients treated, and of note, none of the patients had experienced grade ≥3 AEs in cycles delivered after the DLT evaluation period.[45] Following review of safety data from patients treated at these two dose levels, the IDMC

recommended the regimen of capecitabine 700 mg/m^2 bid combined with trastuzumab emtansine 3.6 mg/kg q3w for the phase II exploration of efficacy and safety.

In the ToGA study in LA/mGC, trastuzumab exposure was lower than that observed in breast cancer studies. A weekly trastuzumab emtansine regimen may provide higher cumulative trastuzumab emtansine exposure than the q3w schedule and was therefore chosen for the Phase I, Cohort 2 part of the present study in LA/mGC. This approach has subsequently been supported by findings from stage I of the adaptive phase II/III BO27952 trial in this setting (see Section 3.3.2.2).

3.3.1.2 Rationale for Randomized Phase II

The Randomized Phase II part of the study is designed to explore the efficacy and safety of the combination recommended following the Phase I MTD-Finding phase (trastuzumab emtansine 3.6 mg/kg in combination with capecitabine 700 mg/m^2) compared with trastuzumab emtansine alone.

3.3.2 RATIONALE FOR INVESTIGATIONAL MEDICINAL DOSE SELECTION

3.3.2.1 In Patients with mBC

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 heavily pre-treated HER2-positive mBC (protocol TDM4258g[31] and protocol TDM4374g[32]), in patients who had not received prior chemotherapy for metastatic disease (TDM4450g[26]), and subsequently in the randomized phase III trials.[27,28]

Capecitabine doses have been selected as being in the range of efficacious doses for single-agent or combination use. The doses selected are within the dosing range included in the Xeloda® Summary of Product Characteristics (SmPC) and therefore are considered to be efficacious.

3.3.2.2 In Patients with mGC

In the ToGA study (BO18255) evaluating trastuzumab in combination with chemotherapy for mGC, patients with higher drug exposure had a greater benefit than those with lower exposure.[46] As a consequence, an ongoing randomized, open-label, multicenter Phase IIIb study is comparing two trastuzumab dosing regimens, each in combination with cisplatin/capecitabine chemotherapy, as first-line therapy in patients with HER2-positive metastatic gastric or GEJ adenocarcinoma (Study BO27798).

In TDM3569g (see Section 1.2.1.1), the qw administration of 2.4 mg/kg of trastuzumab emtansine resulted in higher exposure than q3w dosing (see

Section 1.2.1.8).[29,30] Therefore, this dose may result in larger clinical benefit for patients with mGC.

In the ongoing randomized adaptive phase II/III BO27952 trial evaluating trastuzumab emtansine versus the investigator's choice of taxane therapy in unrectable LA/mGC, two trastuzumab emtansine regimens were evaluated in stage I: 3.6 mg/kg q3w and 2.4 mg/kg qw. In October 2013, the IDMC for the BO27952 trial recommended selection of the weekly 2.4 mg/kg regimen for further evaluation in the phase III part of the trial based on pharmacokinetic, safety, and efficacy data available at the time. This recommendation provides further support for using the weekly regimen in Phase I, Cohort 2 of the present trial.

In Cohort 2, the starting dose of capecitabine will be 700 mg/m^2 bid (the MTD from Cohort 1 in mBC) in order to minimize the exposure of patients to sub-optimal treatment. The dose of capecitabine can be de-escalated if needed.

3.3.2.3 Rationale for Duration of Treatment

Treatment will be given until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor (see Section 3.1.1 for full information). As of 1 January 2010, of 237 patients enrolled in studies TDM3569g, TDM4258g, and TDM4374g receiving trastuzumab emtansine at 3.6 mg/kg, approximately 30% have tolerated more than 12 cycles, with 14.8% having received more than 17 cycles. Twenty patients (8.4%) have discontinued trastuzumab emtansine due to AEs and 24 patients (10.1%) required dose reductions in trastuzumab emtansine because of AEs. In the absence of unacceptable toxicity, patients with mBC are generally treated until PD. Further support for treatment until PD comes from the EMILIA randomized phase III trial.[27] Among the 490 patients randomized to trastuzumab-emtansine, only 29 (5.9%) discontinued because of adverse events.

Capecitabine will be given until PD, in accordance with Xeloda® national prescribing information.

3.3.3 PHARMACOKINETIC SAMPLING RATIONALE

PK is studied only in the Phase I (MTD-Finding) parts (both cohorts 1 and 2). The PK sampling rationale is to characterize the PK of trastuzumab emtansine and capecitabine and their metabolites, to assess any potential drug-drug interaction when trastuzumab emtansine is given in combination with capecitabine, and to explore potential correlations between drug exposure and measures of both efficacy (ORR) and toxicity (alanine transaminase [ALT]/AST, platelets, etc.), if data allow.

3.4 OUTCOME MEASURES

3.4.1 PHASE I: MBC

3.4.1.1 Primary Outcome Measure

The main objective for Phase I is to determine the MTD of capecitabine when combined with trastuzumab emtansine.

3.4.1.2 Secondary Outcome Measure

The secondary outcome is ORR, based on best overall response (BOR) rate according to RECIST v.1.1, per investigator local assessment.

3.4.1.3 Primary Safety Outcome Measure

The primary safety outcome measure is to establish the MTD. The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination and will be summarized for each treatment dosage.

3.4.1.4 Secondary Safety Outcome Measures

Safety endpoints will be summarized for each treatment dosage:

- Incidence, nature, and severity of AEs, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.0
- Incidence, nature, and severity of SAEs, according to NCI CTCAE v. 4.0
- Incidence and nature of Grade ≥3 AEs
- Incidence, nature, and severity of AEs of special interest (AESIs), according to NCI CTCAE v. 4.0
- Fatal AEs and their causes
- Laboratory parameters
- LVEF
- Exposure to study medication
- Physical examination
- ECOG performance status
- Premature withdrawal from study medication and/or study

3.4.1.5 Pharmacokinetic Outcome Measures

The PK outcome measures to be assessed in patients receiving trastuzumab emtansine and capecitabine will include:

- Serum concentrations of trastuzumab emtansine (conjugated drug) and total trastuzumab (free and conjugated to DM1)

- Plasma concentration of DM1
- Plasma concentration of capecitabine and its active metabolite 5-FU
- Total exposure (e.g., AUC)
- C_{max}
- CL
- V_d
- $T_{1/2}$

3.4.2 RANDOMIZED PHASE II: EXPLORATION OF EFFICACY AND SAFETY IN MBC

The primary and secondary efficacy outcome measures will be presented for each treatment group.

3.4.2.1 Primary Efficacy Outcome Measure

The primary outcome measure is ORR by investigator assessment, based on BOR (defined as the best response recorded from randomization into the Phase II part of the study and until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first) according to RECIST v.1.1 (See Appendix 3).

3.4.2.2 Secondary Efficacy Outcome Measures

Secondary efficacy outcomes include:

- TTR
- DoR
- TTP
- TTF
- PFS
- CBR
- OS

3.4.2.3 Primary Safety Outcome Measure

A primary safety outcome is defined only for Phase I.

3.4.2.4 Secondary Safety Outcome Measures

The summary of safety endpoints will be presented for each treatment group:

- Incidence, nature, and severity of AEs, according to NCI CTCAE v. 4.0
- Incidence, nature, and severity of SAEs, according to NCI CTCAE v. 4.0

- Incidence and nature of Grade ≥3 AEs
- Incidence, nature, and severity of AESIs, according to NCI CTCAE v. 4.0
- Fatal AEs and their causes
- Events to monitor
- Laboratory parameters
- LVEF
- Exposure to study medication
- Physical examination
- ECOG performance status
- Premature withdrawal from study medication and/or study

3.4.2.5 Pharmacokinetic Outcome Measures

Not applicable for Phase II.

3.4.3 PHASE I: LA/MGC

3.4.3.1 Primary Outcome Measure

The main objective for Phase I is to determine the MTD of capecitabine when combined with trastuzumab emtansine. The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination and will be summarized for each treatment dosage.

3.4.3.2 Secondary Efficacy Outcome Measure

The secondary (efficacy) outcome is ORR, based on BOR rate according to RECIST v.1.1 according to investigator assessment.

3.4.3.3 Secondary Safety Outcome Measures

Safety endpoints will be summarized for each treatment dosage:

- Incidence, nature, and severity of AEs, according to NCI CTCAE v. 4.0
- Incidence, nature, and severity of SAEs, according to NCI CTCAE v. 4.0
- Incidence and nature of Grade ≥3 AEs
- Incidence, nature, and severity of AESIs, according to NCI CTCAE v. 4.0
- Fatal AEs and their causes
- Events to monitor
- Laboratory parameters
- LVEF

- Exposure to study medication
- Physical examination
- ECOG performance status
- Premature withdrawal from study medication and/or study

3.4.3.4 Pharmacokinetic Outcome Measures

The PK outcome measures to be assessed in patients receiving trastuzumab emtansine and capecitabine will include:

- Serum concentrations of trastuzumab emtansine (conjugated drug) and total trastuzumab (free and conjugated to DM1)
- Plasma concentration of DM1
- Plasma concentration of capecitabine and its active metabolite 5-FU
- Total exposure (e.g., AUC)
- C_{max}
- CL
- V_d
- $T_{1/2}$

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 PATIENTS WITH MBC

This study will enroll patients with HER2-positive BC with histologically or cytologically confirmed metastatic disease that is amenable to combination treatment with trastuzumab emtansine and capecitabine.

Patients with mBC must have received at least one prior treatment regimen for early or metastatic disease, which included a chemotherapy agent and trastuzumab either separately or in combination. In both study parts (Phase I and II), only patients whose HER2 tumor status was locally scored as IHC 3+ or in situ hybridization (ISH) positive will be eligible.

4.1.2 LA/MGC PATIENTS

This study will enroll patients with HER2-positive GC with histologically or cytologically confirmed inoperable LA/mGC that is amenable to combination treatment with trastuzumab emtansine and capecitabine.

Patients with mGC must not have received prior chemotherapy for advanced/metastatic disease, and only patients with HER2-positive primary

tumor or metastasis as assessed by the central laboratory will be allowed to enroll in the mGC part of the study.

4.1.3 INCLUSION CRITERIA

4.1.3.1 For Patients with mBC

Patients must meet the following criteria for study entry:

1. Male or female
2. Age ≥ 18 years old
3. Signed informed consent before any study-specific procedure
4. Able and willing to comply with the protocol
5. 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 the medical history confirming that the patient is not of childbearing potential.
6. 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 or two effective forms of non-hormonal contraception and to continue its use for the duration of study treatment and for 7 months after the last dose of study treatment (see Section 5.2.4).
7. ECOG performance status of 0, 1, or 2
8. Blood:
   a) Platelet count > 100,000 cells/mm^3
   b) International normalized ratio (INR) < 1.5
   c) Absolute neutrophil count (ANC) > 1,500 cells/mm^3
   d) Hemoglobin > 9.0 g/dL. Patients are allowed to have received transfusion to achieve this level.
9. Liver function:
   a) Total bilirubin ≤ 1.5 × upper limit of normal (ULN) or direct bilirubin ≤1.5 × ULN in patients with documented Gilbert's syndrome.
   b) Serum glutamic oxaloacetic transaminase (SGOT)/AST and serum glutamic pyruvic transaminase (SGPT)/ALT ≤ 2.5 × ULN
   c) Alkaline phosphatase ≤ 2.5 × ULN. In patients with bone metastases: alkaline phosphatase ≤ 5 × ULN
   d) Evidence of stable liver function during the month prior to enrollment with liver function test (LFT) fluctuations not exceeding 2.5 x ULN (for AST, ALT) and 1.5 x ULN (for total bilirubin).

10. Renal function:
    a) Serum creatinine of < 177 µmol/L or calculated creatinine CL > 50 mL/min. If urine dipstick for proteinuria is ≥ 2+ at baseline, the patient must undergo 24-hour urine collection and demonstrate ≤ 1 g of protein/24 hours
11. Cardiac function:
    a) LVEF ≥ 50% by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan
12. Life expectancy ≥ 2 weeks
13. Histologically or cytologically confirmed BC
14. HER2-positive disease, defined as IHC 3+ or ISH positive
15. Tumor block or 8 slides available for retrospective central confirmation of HER2-positivity (central confirmation not necessary for enrollment).
16. mBC with at least one measurable lesion according to RECIST v.1.1
17. Disease progression on at least one prior regimen containing trastuzumab and chemotherapy either separately or in combination. Patients may be eligible to receive study therapy in the first-line setting if trastuzumab and chemotherapy were given in the [neo]adjuvant setting.
18. Patients must have recovered from previous treatments

4.1.3.2 For Patients with LA/mGC

Patients must meet the following criteria for study entry:

1. Male or female
2. Age ≥ 18 years old
3. Signed informed consent before any study-specific procedure
4. Able and willing to comply with the protocol
5. 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 the medical history confirming that the patient is not of childbearing potential
6. 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 or two effective forms of non-hormonal contraception and to continue its use for the duration of study treatment and for 7 months after the last dose of study treatment (see Section 5.2.4)
7. ECOG performance status of 0, 1, or 2

8. Blood:
   a) Platelet count > 100,000 cells/mm^3
   b) INR < 1.5
   c) ANC > 1,500 cells/mm^3
   d) Hemoglobin > 9.0 g/dL. Patients are allowed to have received transfusion to achieve this level.
9. Liver function:
   a) Total bilirubin ≤ 1.5 × ULN or direct bilirubin ≤1.5 × ULN in patients with documented Gilbert's syndrome
   b) SGOT/AST and SGPT/ALT ≤ 2.5 × ULN
   c) Alkaline phosphatase ≤ 2.5 × ULN. In patients with bone metastases: alkaline phosphatase ≤ 5 × ULN
   d) Evidence of stable liver function in the month prior to enrollment with LFT fluctuations not exceeding 2.5 x ULN (for AST, ALT) and 1.5 x ULN (for total bilirubin).
10. Renal function:
    a) Serum creatinine of < 177 µmol/L or calculated creatinine CL > 50 mL/min. If urine dipstick for proteinuria is ≥ 2+ at baseline, the patient must undergo 24-hour urine collection and demonstrate ≤ 1 g of protein/24 hours
11. Cardiac function:
    a) LVEF ≥ 50% by ECHO or MUGA scan
12. Life expectancy ≥ 2 weeks
13. Histologically or cytologically confirmed mGC or locally advanced GC
14. HER2-positive tumor (primary tumor or metastatic lesion), defined as either IHC 3+ or IHC 2+ and ISH+, prospectively confirmed by a Sponsor-designated central laboratory prior to enrollment. ISH positivity is defined as a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of signals for CEP17.
    a) Archival tumor samples obtained from primary or metastatic sites are acceptable.
    b) Invasive tumor for central confirmation of HER2 status is required.
    c) A formalin-fixed paraffin-embedded (FFPE) tissue block with at least 5 mm of invasive tumor for central confirmation is preferred. If FFPE tissue blocks (or partial block) are unavailable due to country or site regulations, a minimum of 8 freshly cut unstained slides MUST be available for central review of HER2 status.
15. Inoperable LA/mGC

4.1.4 EXCLUSION CRITERIA

4.1.4.1 For Patients with mBC

1. Prior treatments before first study treatment:
   a) Investigational therapy within ≤ 28 days or 5 half-lives, whichever is longer
   b) Hormonal therapy within 14 days
   c) Trastuzumab within 21 days
2. Prior treatment with trastuzumab emtansine or prior enrollment in a trastuzumab emtansine-containing study, regardless of whether the patient received trastuzumab emtansine
3. Prior treatment with capecitabine
4. History of severe and unexpected reactions to fluoropyrimidine or known hypersensitivity to fluorouracil
5. Related capecitabine contraindications:
   a) Treatment with sorivudine or its chemically-related analogues, such as brivudine
   b) Rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
   c) Known complete absence of DPD activity.
6. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product
7. History of exposure to the following cumulative doses of anthracyclines:
   a) Doxorubicin or liposomal doxorubicin > 500 mg/m^2
   b) Epirubicin > 900 mg/m^2
   c) Mitoxantrone > 120 mg/m^2
   d) 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.
8. Brain metastases that are symptomatic, or require any radiation, surgery, or steroid therapy to control their symptoms within 28 days before first study drug administration
9. Current peripheral neuropathy of Grade ≥ 3 according to NCI CTCAE, v. 4.0
10. History of other malignancy within the last 5 years, except for appropriately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned above.
11. Current unstable ventricular arrhythmia requiring treatment

12. History of symptomatic CHF (New York Heart Association [NYHA] Classes II−IV)
13. History of myocardial infarction or unstable angina within 6 months prior to first study drug administration
14. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
15. Severe dyspnea at rest due to complications of advanced malignancy or currently requiring continuous oxygen therapy
16. Clinically significant malabsorption syndrome or inability to take oral medication
17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
18. Major surgical procedure or significant traumatic injury within 28 days before enrollment or anticipation of the need for major surgery during the course of study treatment
19. Current pregnancy or lactation
20. Current known active infection with human immunodeficiency virus (HIV), hepatitis B and/or hepatitis C virus (HBV/HCV)
    a) For patients who are known carriers of HBV, active hepatitis B infection must be ruled out based on negative serologic testing and/or determination of HBV DNA viral load per local guidelines
21. Lapatinib ≤ 14 days before first study drug administration
22. Previous radiotherapy for the treatment of mBC is not allowed if:
    a) The last fraction of radiotherapy has been administered within 14 days prior to first study drug administration (28 days for patients with radiotherapy to control symptoms of brain metastases, see exclusion criterion 8).
    b) More than 25% of marrow-bearing bone has been irradiated.
    c) Any acute toxicity has not resolved to Grade ≤ 1 before first study drug administration.

4.1.4.2 For Patients with LA/mGC

1. Prior treatments before first study treatment:
    a) Investigational therapy within ≤ 28 days or 5 half-lives, whichever is longer
    b) Hormonal therapy within 14 days
    c) Trastuzumab within 21 days
2. Prior treatment with trastuzumab emtansine or prior enrollment in a trastuzumab emtansine-containing study, regardless of whether the patient received prior trastuzumab emtansine

3. Prior treatment with capecitabine
4. History of severe or unexpected reactions to fluoropyrimidine or known hypersensitivity to fluorouracil
5. Related capecitabine contraindications:
   a) Treatment with sorivudine or its chemically-related analogs, such as brivudine
   b) Rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
   c) Known complete absence of DPD activity.
6. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins or any component of the product
7. History of exposure to the following cumulative doses of anthracyclines:
   a) Doxorubicin or liposomal doxorubicin > 500 mg/m^2
   b) Epirubicin > 900 mg/m^2
   c) Mitoxantrone > 120 mg/m^2
   d) 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.
8. Brain metastases that are symptomatic, or require any radiation, surgery, or steroid therapy to control symptoms within 28 days before first study drug administration
9. Current peripheral neuropathy of Grade ≥ 3 according to NCI CTCAE, v. 4.0
10. History of other malignancy within the last 5 years, except for appropriately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome as those mentioned above
11. Current unstable ventricular arrhythmia requiring treatment
12. History of symptomatic CHF (NYHA Classes II−IV)
13. History of myocardial infarction or unstable angina within 6 months prior to first study drug administration
14. History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
15. Severe dyspnea at rest due to complications of advanced malignancy or currently requiring continuous oxygen therapy
16. Clinically significant malabsorption syndrome or inability to take oral medication
17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)

18. Major surgical procedure or significant traumatic injury within 28 days before enrollment or anticipation of the need for major surgery during the course of study treatment
19. Current pregnancy or lactation
20. Current known active infection with HIV, HBV, and/or HCV
    a) For patients who are known carriers of HBV, active hepatitis B infection must be ruled out based on negative serologic testing and/or determination of HBV DNA viral load per local guidelines
21. Previous chemotherapy for advanced/metastatic disease
    a) Prior adjuvant/neoadjuvant therapy is allowed if at least 6 months has elapsed between completion of adjuvant/neoadjuvant therapy and enrollment into the study
22. Lapatinib ≤ 14 days before first study drug administration

4.1.5 PATIENT REPLACEMENT POLICY

None of the patients in the Phase I part of the study may be replaced unless approved by the entire SC. Phase II patients will not be replaced.

4.2 METHOD OF TREATMENT ASSIGNMENT

In the Randomized Phase II part of the study, patients will be randomized to receive either the combination of trastuzumab emtansine and capecitabine or trastuzumab emtansine alone. Patients are stratified according to the number of prior lines of treatment for metastatic disease (≤ or > , excluding single-agent therapy).

This is an open-label randomized study; therefore, no blinding will be used.

4.3 STUDY TREATMENT

4.3.1 FORMULATION, PACKAGING, AND HANDLING

4.3.1.1 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. 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.

4.3.1.2 Capecitabine

The following information has been obtained from the Xeloda® European Union (EU) SmPC and US Xeloda® Package Insert.

Capecitabine is available as biconvex, oblong, film-coated tablets, available as follows:

- 150 mg tablets: color, light peach; engraving, XELODA on one side, 150 on the other; packs of 60
- 500 mg tablets: color, peach; engraving, XELODA on one side, 500 on the other; packs of 120

Capecitabine tablets should not be stored above 30°C.

4.3.2 DOSAGE AND ADMINISTRATION

4.3.2.1 For Patients with mBC

Trastuzumab Emtansine

Trastuzumab emtansine will be administered on Day 1 q3w at a dose of 3.6 mg/kg IV (see Appendix 1). The total dose will be calculated based on the patient's weight on Day 1 of each cycle (or up to 3 days before) with no upper limit.

If the timing of trastuzumab emtansine coincides with a holiday that precludes the procedure, the procedure should be performed within 3 business 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-minute observation period following infusion. Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.

Pre-medication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, antihistamines such as diphenhydramine, or corticosteroids) may be given at the investigator's discretion.

Capecitabine

Capecitabine will be administered twice a day, orally for 14 days followed by a 7-day rest period at the Dose Levels described in Section 3.1.1. Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Capecitabine doses can be delayed for up to 4 hours, while keeping the minimal interval of 8 hours between the doses.

Rounding of the dose, based on 150 and 500 mg strength tablets, will be allowed to the nearest dose per patient body surface area (BSA).

If a dose is missed, the patient should skip that dose. The patient should not double the dose during the next administration.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.3.2.2 For Patients with LA/mGC

Trastuzumab Emtansine

Trastuzumab emtansine will be administered on Day 1 qw at a dose of 2.4 mg/kg IV (see Appendix 1). The total dose will be calculated based on the patient's weight on Day 1 of each cycle (or up to 3 days before) with no upper limit.

Administration time and observation period are described in Section 4.3.2.1 for trastuzumab emtansine.

Guidelines regarding timing delays and infusion times are the same as for patients with mBC, as is the accepted pre-medication.

Capecitabine

Capecitabine will be administered at a starting dose of 700 mg/m^2 bid, orally, for 14 days followed by a 7-day rest period (the dose level determined as the MTD in cohort 1, with de-escalation as described in section 3.1.1.3. Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Capecitabine doses can be delayed for up to 4 hours, while keeping the minimal interval of 8 hours between the doses.

If a dose is missed, the patient should skip that dose. The patient should not double the dose at the next administration.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.

4.3.3 INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

All investigational medicinal products (IMPs) required for completion of this study (trastuzumab emtansine and capecitabine) 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.

IMPs will be either 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.

4.3.4 POST-TRIAL ACCESS TO EXTENSION STUDY

Post-trial access to trastuzumab emtansine and capecitabine will be performed as described in Section 3.1.1, *Duration of Treatment and Patient Follow-Up*. If 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.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 PERMITTED THERAPY

Concomitant therapy and pre-medication are defined as non-IMPs.

Concomitant therapy includes any prescription medication, over-the-counter preparation, or herbal therapy between the 14 days preceding first treatment and the Study Treatment Discontinuation Visit. Afterwards, only anti-cancer therapies will be collected as part of the survival follow-up.

Pre-medication is allowed according to standard practice guidelines.

No pre-medication for the first infusion of trastuzumab emtansine is required; however, pre-medication 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 is permitted to treat pre-existing painful bone metastases or to treat brain metastases (for patients who have disease control outside of the brain). 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 well-being 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 PD.

4.4.2 PROHIBITED THERAPY

During the study, use of the therapies described below is prohibited until 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.

Radiotherapy for unequivocal PD 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 SD for ≥ 3 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. Patients must not miss more than one cycle of study treatment for the treatment of their brain metastases and must have an ECOG performance status of 0, 1, or 2 to continue on therapy. The Medical Monitor should be informed before a decision is made to resume study treatment after radiotherapy for brain metastases.

4.5 STUDY ASSESSMENTS

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

- Visits will be based on a q3w cycle for mBC
- Visits will be based on a qw cycle for mGC

Study assessments are outlined in this section and in Appendix 1.

4.5.1 DESCRIPTION OF STUDY ASSESSMENTS

All patients will be closely monitored for safety and tolerability during all cycles of therapy and at the Study Treatment Discontinuation Visit. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. Trastuzumab emtansine will be administered either in q3w cycles (patients with mBC) or qw cycles (patients with mGC) if no additional time is required for resolution of toxicity. Dose delays and dose reductions will be allowed for trastuzumab emtansine as outlined in Section 5.1.5.

If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that precludes the procedure within the allotted window, the procedure should be performed on the nearest following date (i.e., within 3 business days).

4.5.1.1 Medical History and Demographic Data

Medical history includes 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 race/ethnicity (unless not allowed per local regulations).

4.5.1.2 Vital Signs

Vital signs will include measurements of weight, respiratory rate, heart rate, blood pressure, and temperature. Abnormal or significant changes to vital signs from baseline should be recorded as AEs, if appropriate.

4.5.1.3 Physical Examinations

A complete physical examination should include the evaluation of head, eye, ear, nose, and throat; cardiovascular; dermatological; musculoskeletal; respiratory; gastrointestinal; and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

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

Limited physical examinations will be symptom-directed.

4.5.1.4 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 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 (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 (see Appendix 3). 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 (see Appendix 4).

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

4.5.1.5 Laboratory Assessments

For Patients with mBC:

Local Laboratory Assessments:

- Hematology, biochemistry, coagulation, urinalysis, and pregnancy testing
- Prospective or retrospective HER2 status. Patients will be enrolled based on local results.

Central Laboratory Assessments:

- Retrospective HER2 status. Retrospective central confirmation will not impact the treatment decisions or primary endpoint of Phase I, Cohort 1 and will be used to validate efficacy analyses in Phase I and to define subgroups for efficacy analyses in the Randomized Phase II part of the study
- PK assays:
  - Serum trastuzumab emtansine concentration and total trastuzumab using a validated immunoassay
  - Serum capecitabine and 5-FU PK samples
  - Plasma concentration of DM1 using a validated liquid chromatography electrospray tandem mass spectrometry (LC-MS/MS) method

For Patients with mGC:

Local Laboratory Assessments:

- Hematology, biochemistry, coagulation, urinalysis, and pregnancy testing

Central Laboratory Assessments:

- Prospective HER2 status. Patients will be enrolled based on the central testing results
- PK assays:
  - Serum trastuzumab emtansine concentration and total trastuzumab using a validated immunoassay
  - Serum capecitabine and 5-FU PK samples
  - Plasma concentration of DM1 using a validated LC-MS/MS method

4.5.1.6 Electrocardiograms

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

4.5.1.7 ECOG Performance Status

Performance status will be measured using the ECOG performance status scale (see Appendix 6).

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

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

4.5.1.8 ECHO/MUGA

ECHO is the preferred modality because of the global technetium (Tc-99m) shortage (see Appendix 4). The same method used at screening should be used throughout the study.

4.5.2 TIMING OF STUDY ASSESSMENTS

4.5.2.1 Screening and Pretreatment Assessments

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

Once the patient has signed the Informed Consent Form, the investigator (or his or her designee) will call the IxRS to obtain the screening number for the patient prior to Cycle 1, Day 1.

Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study start may be used; such tests do not need to be repeated for screening. Patients must have stable LFTs before the first dose of study drug.

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

Patients in Cohort 1 will not contribute to Phase II; however, they will be followed up until EOS. In the Randomized Phase II part, patients will be randomized in a 1:1 ratio to receive trastuzumab emtansine alone or the combination of trastuzumab emtansine and capecitabine prior to receiving the first dose of study medication.

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.

Please see Appendix 1 for the schedule of screening assessments.

4.5.2.2 Assessments during Treatment

For Patients with mBC

Scheduled study visits are based on a q3w cycle, with Cycle 1 beginning at Day 1. All visits must occur within ± 3 business days from the scheduled date, unless otherwise noted in the schedule of assessments. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration should be performed prior to study treatment administration unless otherwise noted. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend, it should be performed on the nearest following date (i.e., within 3 business days).

Local laboratory assessments scheduled for Day 1 of all cycles must be performed within 72 hours prior to study treatment administration unless otherwise specified. Results of local laboratory assessments must be reviewed and the review documented prior to study treatment administration.

Please see Appendix 1 for the schedule of treatment period assessments.

For Patients with mGC

Scheduled study visits are based on a qw cycle, with Cycle 1 beginning at Day 1. All visits must occur within ± 3 business days from the scheduled date, unless otherwise noted in the schedule of assessments. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration should be performed prior to study treatment administration unless otherwise noted. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend, it should be performed on the nearest following date (i.e., within 3 business days).

Local laboratory assessments scheduled for Day 1 of all cycles must be performed within 72 hours prior to study treatment administration unless otherwise specified. Results of local laboratory assessments must be reviewed and the review documented prior to study treatment administration.

Please see Appendix 1 for the schedule of treatment period assessments.

4.5.2.3 Assessments at Study Completion/Early Termination Visit

Patients may remain on study treatment until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor. Patients who discontinue study treatment will be followed up until EOS and will be asked to return to the clinic approximately 28–42 days after the last study treatment administration for the safety follow-up visit.

Please see Appendix 1 for assessments to be performed at the safety follow-up visit.

4.5.2.4 Follow-up Assessments

After the Study Treatment Discontinuation Visit, all patients (regardless of reason for discontinuation) will have survival status and anti-cancer therapies recorded and will be followed for all unresolved study-related AEs and SAEs until their resolution or stabilization, the patient is lost to follow-up or dies, 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.

Patients who discontinue study drugs for any reason other than PD or withdrawal of consent (e.g., an AE) will continue to be followed according to the tumor assessment schedule until withdrawal of consent, death, or EOS, whichever occurs first.

After the study treatment completion/early termination visit, AEs should be followed as outlined in Section 5.5 and 5.6.

Please see Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

In case unplanned visits are required, electronic Case Report Form (eCRF) pages will be available to report the information collected during those visits.

4.6 PATIENT AND STUDY DISCONTINUATION

4.6.1 PATIENT DISCONTINUATION

Patients have the right to withdraw from the study at any time for any reason. The investigator has the right to discontinue a patient from study treatment or from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of non-compliance (e.g., missed doses, visits), if the patient becomes pregnant, or if the investigator determines it is in the best interest of the patient.

Patients must be withdrawn from study treatment if they become pregnant or experience PD defined using RECIST v. 1.1 (Appendix 3). The exception to this is patients who develop isolated progression in the brain as described in Appendix 3.

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

Patients who discontinue from study treatment prematurely for any of the above reasons will continue to be followed according to Section 4.5.2.4 “Follow-Up Assessments”. The primary reason for discontinuation must be recorded on the appropriate eCRF page.

4.6.2 STUDY DISCONTINUATION

Sections 3.1.1 and 3.2 describe the EOS definition and discontinuation of study treatment. Prior to that, 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
- Data recording is inaccurate or incomplete.

5. ASSESSMENT OF SAFETY

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

5.1 SAFETY PLAN

The safety plan for patients receiving trastuzumab emtansine is based on the toxicities of trastuzumab emtansine observed in nonclinical studies; the toxicities related to its components (trastuzumab and maytansine, the parent drug of DM1) observed in clinical studies; and the clinical experience with this molecule in completed and ongoing studies. Please refer to the trastuzumab emtansine and capecitabine (Xeloda®) Investigator’s Brochures for the most recent information.

All patients will be monitored closely for toxicity. The important safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.1 RISKS ASSOCIATED WITH TRASTUZUMAB EMTANSINE

Full details regarding the clinical safety of trastuzumab emtansine are presented in Sections 5 and 6 of the Investigator’s Brochure.

5.1.1.1 Cardiotoxicity

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. 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 according to the algorithm shown in Figure 6. Treatment with trastuzumab emtansine has not been studied in patients with LVEF < 50%.

5.1.1.2 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 central nervous system 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. 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.

5.1.1.3 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. A cumulative effect of trastuzumab emtansine on transaminases has been observed; elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine in the majority of the patients.
Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and some resulting in fatal liver failure, have been observed in patients treated with trastuzumab emtansine in clinical trials. Some of the observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential. Liver function should be monitored before initiation of treatment and each trastuzumab emtansine dose.

Trastuzumab emtansine has not been studied in patients with serum transaminases $> 2.5 \times$ ULN or total bilirubin $> 1.5 \times$ ULN before initiation of treatment. Trastuzumab emtansine treatment in patients with serum transaminases $> 3 \times$ ULN and concomitant total bilirubin $> 2 \times$ ULN should be permanently discontinued.

Cases of NRH of the liver have been identified from liver biopsies in patients 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.

5.1.1.4 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.

5.1.1.5 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. Pre-medication 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 ≥ 3 allergic reaction or acute respiratory distress syndrome will be discontinued from study treatment.

5.1.1.6 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.

5.1.1.7 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.

5.1.1.8 Trastuzumab Emtansine Dose Modification

Trastuzumab emtansine dose modifications are described in Section 5.1.5.1.

5.1.2 RISKS ASSOCIATED WITH CAPECITABINE

Patients treated with capecitabine should be carefully monitored for toxicity. Most AEs are reversible and do not require permanent discontinuation of therapy (please refer to the Xeloda® SmPC for more information).

The spectrum of cardiotoxicity observed with capecitabine is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina,

dysrhythmias, cardiac arrest, cardiac failure and electrocardiographic changes. These AEs may be more common in patients with a prior history of coronary artery disease.

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, mucosal inflammation, neutropenia, and neurotoxicity) associated with 5-FU has been attributed to deficiency of dihydropyrimidine dehydrogenase (DPD) activity. Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil.

Although DPD deficiency cannot be precisely defined, it is known that patients with certain homozygous or certain compound heterozygous mutations in the *DPYD* gene locus, which can cause complete or near complete absence of DPD enzymatic activity (as determined by laboratory assays), have the highest risk of life-threatening or fatal toxicity[47] and should not be treated with capecitabine. No dose has been proven safe for patients with complete absence of DPD activity.

For patients with partial DPD deficiency (such as those with heterozygous mutations in the *DPYD* gene) and where the benefits of capecitabine are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution and frequent subsequent monitoring and dose adjustment according to toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by specific test.

In patients with unrecognized DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as acute overdose may occur. In the event of Grade 2–4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration, and severity of the observed toxicities.

Capecitabine can induce hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema), which is a cutaneous toxicity. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints, which could impact patient identification.[48] For patients receiving capecitabine monotherapy in the metastatic setting, the median time to onset was 79 days (range 11–360 days), with a severity range of Grades 1 to 3. Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living (ADL). Grade 3 is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform ADL. If Grade 2 or 3 hand-foot syndrome occurs, administration of capecitabine should be interrupted until the event resolves or decreases in intensity to Grade 1.

Following Grade 3 hand-foot syndrome, subsequent doses of capecitabine should be decreased.

Patients should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

Capecitabine can induce hyperbilirubinemia. Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of > 3.0 × ULN or treatment-related elevations in hepatic aminotransferases (ALT/AST) of Grade ≥ 2 occur.

Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Acute renal failure secondary to dehydration might be potentially fatal.

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Capecitabine should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to capecitabine treatment.

Leucovorin affects the pharmacodynamics of capecitabine and may increase the toxicity of capecitabine. This may be relevant in patients receiving folic acid supplementation for folate deficiency due to the similarity between folinic acid and folic acid.

5.1.3 Risks Associated with Trastuzumab Emtansine and Capecitabine Combination

The two DLTs observed in Phase I, Cohort 1 (in mBC) were grade 3 vomiting in one patient and grade 3 elevated AST and ALT in one patient (see Section 3.1.1.2). Both patients were treated at dose level 1 (capecitabine 750 mg/m^2 bid, days 1–14) in combination with trastuzumab emtansine 3.6 mg/kg q3w). During Phase I in LA/mGC, DLTs for the combination of trastuzumab emtansine and capecitabine will be observed during Cycle 1 (Days 1–21) of this study. The combination treatment must be considered as a new treatment during Cycle 1, and no individual dose reduction will be allowed during Cycle 1; the general DLT rules will be used instead. Interruptions can be made due to toxicities considered by the investigator to be related to capecitabine. Grade 2–4 toxicities should be interrupted until resolved to Grade 0–1. For Grade 4 toxicities, consideration to discontinue treatment with capecitabine will be made with the adjudication of the SC.

5.1.4 Definition of Dose-Limiting Toxicity

DLTs will be observed during Cycle 1 (Day 1–21). Please refer to the Xeloda® SmPC for recommendations on dose reduction in subsequent cycles.

Definition of DLT:

Hematologic

1. Uncomplicated Grade 4 thrombocytopenia that does not recover to ≥ 75,000/Ml before Day 21
2. Thrombocytopenia (any grade) complicated with clinically significant bleeding requiring medical intervention, such as platelet transfusion or cauterization. However, patients with Grade 1 or 2 epistaxis may have cauterization and this should not be considered as a DLT.
3. Grade 4 neutropenia lasting > 7 consecutive days
4. Febrile neutropenia with an ANC of < 1,000 cells/mm^3

Non-hematologic

5. Grade ≥ 3 diarrhea that does not decrease to Grade ≤ 2 after 24 hours of starting recommended anti-diarrheal treatment
6. Grade 3 hand-foot syndrome (Grade 4 not applicable)
7. Any other treatment-related toxicity Grade ≥ 3 prohibiting the start of the second cycle on Day 22 (3 weeks cycle length plus 1 day)

NOTE: If a Grade 2 event requires a dose delay, it will not be considered as a DLT. However, if the toxicity does not resolve to Grade 1 or baseline by Day 42, this requires discontinuation and will be considered as a DLT.

8. Grade 2 toxicity requiring interruption of treatment for > 14 days

NOTE: Patients experiencing acute early-onset (within 1 week) or unusually severe toxicity of diarrhea, stomatitis, mucosal inflammation, neurotoxicity, neutropenia, or febrile neutropenia with ANC < 500 cells/mm^3 during Cycle 1 must be tested for DPD deficiency (a central laboratory will be appointed). The SC will adjudicate in cases of DLTs that are not covered by the existing DLT criteria.

9. Having taken < 14 full doses of capecitabine due to toxicity
10. Patient not able to receive 100% of the dose level going into Cycle 2, Day 1

5.1.5 MANAGEMENT OF SPECIFIC ADVERSE EVENTS

5.1.5.1 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 those specified below (i.e., infusion reactions, thrombocytopenia, hepatotoxicity, neurotoxicity, cardiotoxicity, and ILD or pneumonitis) are as follows:

- If significant trastuzumab emtansine-related toxicities (other than infusion reactions, thrombocytopenia, hepatotoxicity, neurotoxicity, and cardiotoxicity) 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 qw 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 and Table 3), at the discretion of the investigator. Subsequent cycles should remain the same (q3w or qw), and patients should be assessed for toxicity.
- If a patient requires a dose reduction, dosing will be reduced by one dose level, per Table 2or Table 3. No dose re-escalation will be allowed.
- If 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 PD 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 (Patients with mBC)

Dose Level	q3w Schedule
0	3.6 mg/kg
- 1	3.0 mg/kg
- 2	2.4 mg/kg
Indication for further dose reduction	Off study treatment

q3w = every 3 weeks

Table 3 Dose Reductions for Trastuzumab Emtansine (Patients with mGC)

Dose Level	qw Schedule
0	2.4 mg/kg
- 1	2.0 mg/kg
- 2	Off study
Indication for further dose reduction	Off study

qw = weekly

In case of toxicities requiring the discontinuation of trastuzumab emtansine, the patient will be followed-up until the EOS.

Protocol requirements for specific toxicities are outlined below.

5.1.5.1.1 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.

5.1.5.1.2 Trastuzumab Emtansine Dose Modification for Hepatotoxicity

5.1.5.1.2.1 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, activated partial thromboplastin time [aPTT], INR, and albumin) will be entered into the clinical database.

5.1.5.1.2.2 Nodular regenerative hyperplasia

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

5.1.5.1.2.3 Transaminase elevations or bilirubin elevation requiring dose adjustment

Patients who experience a Grade 3 elevation of liver function should be checked twice weekly for the recovery of transaminases and/or total bilirubin. If a patient's transaminases and/or total bilirubin do not recover according to Table 4 and Table 5, 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 4 and Table 5 describe the dose modification guidelines for increases in serum bilirubin and transaminases, respectively.

Table 4 Trastuzumab Emtansine Dose Modification: Total Serum Bilirubin

Grade 2 (> .5 to ≤ 3 × ULN)	Grade 3 (> 3 to ≤ 10 × ULN)	Grade 4 (> 10 × ULN)
Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1, and then treat at the same dose level	Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ and then reduce one dose level	Discontinue 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 5 Trastuzumab Emtansine Dose Modification: Serum ALT or AST

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

ALT = alanine transaminase; AST = aspartate transaminase; 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.

5.1.5.1.3 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.

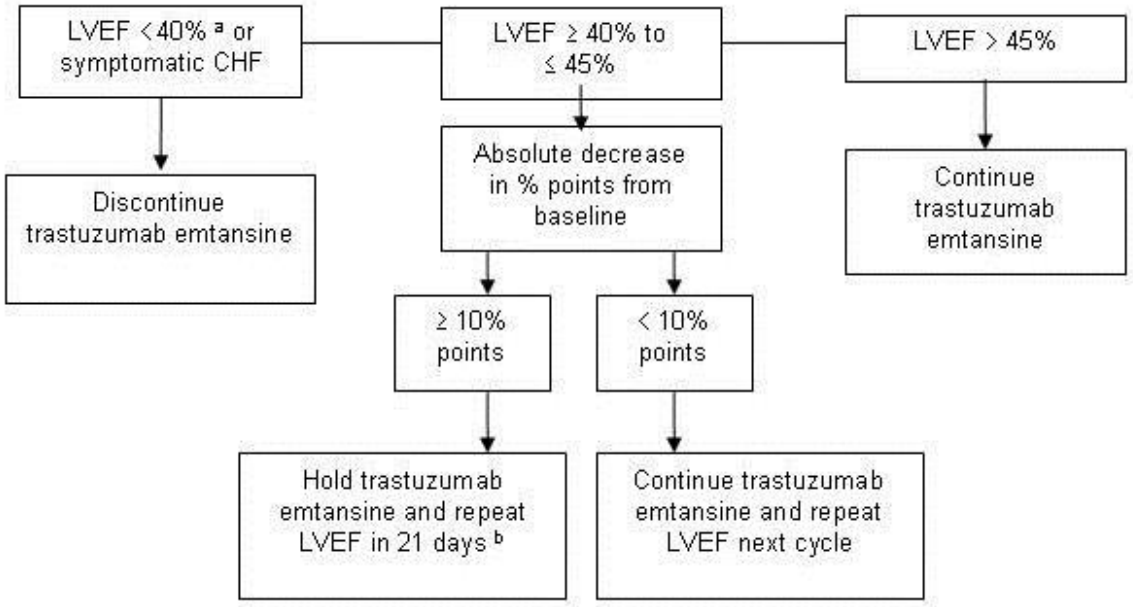
5.1.5.1.4 Trastuzumab Emtansine Dose Modification for Cardiotoxicity

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

Figure 6 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.

The decision to stop or continue trastuzumab emtansine should be based on the algorithm shown in Figure 6. 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.

Figure 6 Algorithm for Continuation and Discontinuation of Trastuzumab Emtansine Based on Left Ventricular Ejection Fraction Assessments in Patients



CHF = congestive heart failure; 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.

5.1.5.1.5 Trastuzumab Emtansine Dose Modification/Management 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. Pre-medication 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. In the event of a true hypersensitivity reaction (i.e., if the severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued. Patients who experience a Grade ≥ 3 hypersensitivity reaction or acute respiratory distress syndrome (ARDS) will be discontinued from the study.

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

5.1.5.1.6 Trastuzumab Emtansine Dose Modification for Pulmonary Toxicity

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

5.1.5.1.7 Trastuzumab Emtansine Dose Modification for Extravasation

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

5.1.5.2 Capecitabine Dosage Modification

Phase I: Patients with mBC

The dose of capecitabine can be modified from Cycle 2 onwards if considered appropriate by the investigator (please refer to the Xeloda® SmPC for recommendations).

In case of toxicities requiring the discontinuation of capecitabine, single-agent trastuzumab emtansine may be continued in patients with mBC.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

During the Randomized Phase II part of the study, the dose of capecitabine will be modified according to the Xeloda® SmPC.

In case of toxicities requiring the discontinuation of capecitabine, single-agent trastuzumab emtansine may be continued in patients with mBC.

Phase I: Patients with mGC

The dose of capecitabine can be modified from cycle 2 onwards if considered appropriate by the investigator (please refer to Xeloda® SmPC for recommendations).

In case of toxicities requiring the discontinuation of capecitabine, single-agent trastuzumab emtansine may be continued (see Section 3.1.1).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central Institutional Review Boards/Ethics Committees (IRBs/ECs) by a written safety report within 15 calendar days of notification.

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 it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.8)
- 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) regardless of the attribution of causality. AESIs for this study include the following:

- Potential drug-induced liver injury

  Any case of potential 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 with 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:

- Defined as any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), both pathogenic and non-pathogenic. 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 7 months following last dose of study drug (follow-up period based on PK considerations).

Trastuzumab, a component of trastuzumab emtansine, can cause fetal harm when administered to a pregnant woman; postmarketing 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 or partner of a male 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, including the partners of male patients, to the Sponsor within 24 hours. 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.[49] 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 AE 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 AE 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 AE 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 treatment**, all AEs, regardless of relationship to study drug, will be reported until 28 days after the last administration of study drug. After this period, the investigator is not required to actively monitor for AEs; however, the Sponsor should be notified if the investigator becomes aware of any poststudy SAEs (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 grading (severity) scale found in the NCI CTCAE (v. 4.0) will be used for assessing AE severity (see Table 6).

Table 6 Adverse Event Severity Grading Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[b]
3	Severe (apply event-specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[c]
4	Very severe, life-threatening, or disabling (apply event-specific NCI CTCAE grading criteria)	Life-threatening consequences; urgent intervention indicated
5	Death related to AE	

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

The NCI CTCAE v4.0 can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Note: Regardless of severity, some events may also meet regulatory seriousness criteria. Refer to definition of a serious AE (see Section 5.2.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

[b] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, temporal relationship of event onset to the initiation of study drug, course of the event considering especially the effects of dose reduction or discontinuation of study drug or reintroduction of study drug (as applicable), known association of the event with the study drug or with similar treatments, known association of the event with the disease under study, presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event, presence of non-treatment-related factors that are known to be associated with the occurrence of the event, 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 7.

Table 7 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 serious AEs 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 AE eCRF. Avoid colloquialisms and abbreviations.

There is one eCRF page for recording AEs or SAEs.

Only one AE term should be recorded in the event field on the AE 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-related reaction. However, a diagnosis has to be captured as an AE if signs and symptoms constitute a diagnosis of allergic reaction/hypersensitivity or infusion-related reaction and are classified as SAEs; all such symptoms have to be described in the narrative (e.g., in the Additional Case Details field of the eCRF).

Other Adverse Events

For AEs other than infusion-related reactions, a diagnosis (if known) should be recorded on the AE 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 AE 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. All AEs should be recorded separately on the Adverse Event eCRF if it is unclear whether the events are associated.

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 AE 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 AE 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 AE 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.

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 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious AE of special interest (see Section 5.4.2).

5.3.5.7 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 mBC or mGC 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 AE eCRF and immediately reported to the Sponsor (see Section 5.4.2). The IDMC will monitor the frequency of death 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 AE eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **“unexplained death”** should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.

During post-study survival follow-up, deaths attributed to progression of mBC or LA/mGC should be recorded only on the Survival eCRF.

5.3.5.8 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of this study. Such conditions should be recorded on the Medical and Surgical History 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 AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches” or "worsening gastrointestinal reflux disease").

5.3.5.9 Lack of Efficacy or Clinical Worsening

Events that are clearly consistent with the expected pattern of progression of mBC or LA/mGC 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 the RECIST criteria. 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 PD, it should be reported as an AE.

5.3.5.10 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

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

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All overdose or incorrect administrations of study drug with/without AEs associated should be recorded on the AE eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO THE 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 (SPONSOR'S 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 immediately (i.e., no more than 24 hours) on the AE eCRF and submit the report via the electronic data capture (EDC) system.

A 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 immediately (i.e., no more than 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 immediately (i.e., no more than 24 hours) after learning of the pregnancy and submitted via the EDC system. A Pregnancy Report will automatically be generated and sent to the Sponsor Safety Risk Management. Pregnancy should not be recorded on the AE eCRF. The investigator should have the patient discontinue the study drug and discuss with the patient the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to the Sponsor Safety Risk Management or its designee immediately (i.e., no more than 24 hours) after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

Additional information on any trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 2 months of the infant’s life).

Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the

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

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 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 an SAE, recorded on the AE eCRF, and reported to the Sponsor immediately (i.e., no more than 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 all unresolved AEs and until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification (SDV).

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

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent AEs that the patient's physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for AEs after the end of the AE reporting period (defined as 28 days after the last dose of study drug). However, the Sponsor should be notified if the investigator becomes aware of any death or other SAE occurring after the end of the AE reporting period, regardless of causality.

The investigator should report these events directly to Roche Safety Risk Management via telephone or via facsimile using the Roche Clinical Trial (SAE) Reporting Form.

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 following reference documents:

- Trastuzumab emtansine and capecitabine Investigator's Brochures

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 IDMC will closely monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The design of this study includes: Phase I, Randomized Phase II and different cohorts. Corresponding analyses as described in the protocol will be performed when all data for a particular cohort and study phase are collected and cleaned.

Phase I: Patients with mBC:

Enrollment into Cohort 1, patients with HER2-positive mBC, will open first.

Enrolled patients will receive study drug until Investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

Patients randomized in Phase II will receive study drug until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor.

The primary analysis of BOR will be performed when 70% of the patients have experienced a PFS event or at the end of the trial, whichever comes first. It is estimated that 70% of patients will have experienced a PFS event approximately 26 months after the randomization of the first patient.

The EOS analysis will include an updated analysis of BOR, which will be done in a purely exploratory manner.

Phase I: Patients with mGC:

Once the MTD is established for Cohort 1, enrollment of patients with HER2-positive and LA/mGC into Cohort 2 will be opened.

Enrolled patients will receive study drug until investigator-assessed PD, unacceptable toxicity, withdrawal of consent, death, reasons deemed by the treating physician, or study termination by the Sponsor.

6.1 DETERMINATION OF SAMPLE SIZE

Sample Size for Phase I: mBC

This part will be based on a classical 3 plus 3 Phase I design. A minimum of 6 and up to 18 patients will be enrolled into Cohort 1. There is no formal sample size estimation for this part.

Sample Size for Randomized Phase II: Exploration of Efficacy and Safety in mBC

The sample size for the primary endpoint BOR is based on a Fisher's exact test with an alpha level of 5% (one-sided),[50,51] power of 70% and the clinical assumption of a BOR rate of 43% with trastuzumab emtansine alone and 62.5% with the combination of trastuzumab emtansine and capecitabine. Approximately 160 patients (approximately 80 patients in each treatment group), including a 15% withdrawal rate, will be randomized with a 1:1 ratio to trastuzumab emtansine alone or the combination of trastuzumab emtansine and capecitabine.

An expected BOR rate of 43.6% (95% CI: 38.6%–48.6%) for patients receiving trastuzumab emtansine alone was chosen based on previously published data for T-DM1 in patients with unresectable, locally advanced or mBC previously treated with a taxane and trastuzumab (EMILIA study).[27]

The BOR rates for patients treated with the combination of T-DM1 and capecitabine were chosen based on recent results from other combination studies of T-DM1 plus chemotherapy or trastuzumab plus capecitabine. Response rates were based on those observed in patients with HER2-positive mBC in a Phase Ib/IIa study (BP22752) that compared the combination of trastuzumab emtansine with docetaxel, with or without pertuzumab (ORR: 76% [95% CI: 53%–92%]), and also in a Phase II study that compared the combination of trastuzumab with docetaxel, with or without capecitabine (ORRs: 72.7% [95% CI: 63.4%–80.8%] and 70.5% [95% CI: 61.2%–78.8%]).[41]

Increased BOR rates for the combination treatment compared with single-agent trastuzumab emtansine are in line with previously published results of a randomized Phase III study in patients with locally advanced or mBC treated with the combination of trastuzumab with capecitabine *versus* capecitabine alone (ORR: 48.1% *versus* 27.0%, odds ratio = 2.50, p = 0.0115).[9]

The estimation of sample size was performed by Nquery® and EAST® programs.

Stratification Factors

The following stratification factor will be implemented in the Randomized Phase II of the study:

- Number of prior lines of treatment for metastatic disease (≤1 or >1; excluding single-agent hormones)

A treatment line is any regimen given to a patient from treatment initiation until confirmed PD.

Sample Size for Phase I: mGC

This part will be based on a classical 3 plus 3 Phase I design. From 3 to 12 patients might be enrolled into Cohort 2. There is no formal sample size estimation for this part.

6.2 SUMMARIES OF CONDUCT OF STUDY

Phase I: Patients with mBC

Due to the small sample size, per-protocol (PP) population will not be defined for the Phase I, Cohort 1.

Major protocol violations will be summarized by treatment dosage. Median follow-up will be estimated for Phase I, Cohort 1.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

For the Randomized Phase II part of the study, a PP population will be defined (Section 6.4).

Patient enrollment, duration of follow-up, discontinuation from study treatment and study, and reasons for study discontinuation will be summarized by treatment group for all randomized patients. In addition, major protocol violations will be summarized by treatment arm.

Phase I: Patients with LA/mGC

Due to the small sample size, a PP population will not be defined for the Phase I, Cohort 2.

Major protocol violations will be summarized by treatment dosage. Median follow-up will be estimated for Phase I, Cohort 2.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Phase I: mBC

As Phase I is the MTD-Finding part of the study, there are no treatment group comparisons for this part of the study.

Demographics, medical history, and baseline characteristics will be summarized. Continuous variables will be summarized using median, mean, standard deviation, 25th and 75th percentiles and range. Categorical variables will be summarized by the number and percentage of patients for each treatment dosage.

Randomized Phase II: Exploration of Efficacy and Safety in mBC

The Randomized Phase II part of the study is designed to explore the efficacy and safety of the combination of trastuzumab emtansine and capecitabine compared with trastuzumab emtansine alone.

Demographics, medical history, and baseline characteristics will be summarized. Continuous variables will be summarized using median, mean, standard

deviation, 25th and 75th percentiles and range. Categorical variables will be summarized by the number and percentage of patients for each treatment group.

Phase I: mGC

As Phase I is the MTD-Finding part of the study, there are no treatment group comparisons for this part of the study.

Demographics, medical history and baseline characteristics will be summarized. Continuous variables will be summarized using median, mean, standard deviation, 25th and 75th percentiles and range. Categorical variables will be summarized by the number and percentage for each treatment dosage.

6.4 EFFICACY ANALYSES

Phase I, Cohort 1: mBC

The main analysis population will be the DLT-evaluable population as defined in Section 6.5.

Randomized Phase II: Exploration of Efficacy in mBC

The main analysis population for the efficacy analysis will be the intent-to-treat population (ITT), which will include all patients in the Randomized Phase II part of the study. The PP population will include all ITT patients who have at least one post-baseline tumor assessment during the Phase II part and no major protocol violations, which will be defined in the statistical analysis plan (SAP).

Phase I, Cohort 2: mGC

The main analysis population will be the DLT-evaluable population as defined in Section 6.5.

6.4.1 PRIMARY EFFICACY ENDPOINT

Phase I, Cohort 1: Patients with mBC

The primary objectives are defining the MTD and establishing the safety profile. The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination.

ORR, as a main efficacy endpoint, will be assessed via BOR rate. The BOR is defined as the best response recorded from the date of enrollment until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first. The number of patients is very small in this part of the study. Therefore, all analyses will be descriptive.

Randomized Phase II: Exploration of Efficacy in mBC

The primary efficacy endpoint for the Randomized Phase II part of the study is the ORR as assessed via BOR. The BOR is defined as the best response recorded from the start or randomization into the Phase II part of the study and until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first. 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 28 days after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR.

The primary hypothesis of interest when comparing ORR – as assessed via BOR – between the two treatment groups (combination of trastuzumab emtansine and capecitabine *versus* trastuzumab emtansine alone) is:

- H0: $\pi_{TDM1} = \pi_{trastuzumab\ emtansine + capecitabine}$ where $\pi_{trastuzumab\ emtansine}$ is BOR in TDM and $_{trastuzumab\ emtansine + capecitabine}$ is BOR in trastuzumab emtansine + capecitabine
- H : $_{trastuzumab\ emtansine}$ $_{trastuzumab\ emtansine + capecitabine}$

The number and proportions of responders and non-responders (based on BOR) together with 90% Clopper-Pearson CIs will be presented for each treatment group.

The difference in BOR between treatment groups will be displayed with associated 90% CIs using the Hauck-Anderson approach and p-values for the Fisher's exact test.

Logistic analysis will be used to assess the influence of the stratification factor and baseline covariates in an exploratory manner.

The primary analysis of BOR will be performed when 70% of the patients have experienced a PFS event or at the end of the trial, whichever comes first. It is estimated that 70% of patients will have experienced a PFS event approximately 26 months after the randomization of the first patient.

Phase I, Cohort 2: Patients with LA/mGC

The primary objectives are defining the MTD and establishing the safety profile. The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination.

ORR, as a main efficacy endpoint, will be assessed via BOR rate. The BOR is defined as the best response recorded from the date of enrollment until PD, death, withdrawal of consent, start of new anticancer treatment, or EOS, whichever occurs first. The number of patients is very small in this part of the study. Therefore, all analyses will be descriptive.

6.4.2 SECONDARY EFFICACY ENDPOINTS

Phase I, Cohort 1: mBC

Due to the small number of patients and the design of this part of the study, no secondary efficacy endpoints will be investigated.

Randomized Phase II: Exploration of Efficacy in mBC

The secondary efficacy endpoints for the Randomized Phase II will be:

- TTR
- DoR
- TTP
- TTF
- PFS
- CBR
- OS

TTR is defined as the time from randomization to first documentation of confirmed PR or CR (whichever occurs first). Patients who do not have a confirmed response will be censored at the date of the last tumor assessment.

DoR is defined as the period from the date of first recorded 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. The method for handling censoring is the same as described for PFS below. Only patients with a BOR of CR or PR (i.e., responders) will be included in the analysis of DoR.

For patients with a BOR of CR or PR, TTR is defined as the time from randomization to the date of first CR or PR. The censoring rules will be similar to those of the PFS.

TTP is defined as time from randomization to the first occurrence of PD. Patients who have not progressed at the time of study completion (including patients who have died before PD) or who are lost to follow-up are censored at the date of the last tumor assessment.

TTF is defined as time from randomization until treatment failure, i.e., to PD, death, withdrawal due to AE or laboratory abnormality, or refusal of treatment. Patients who do not experience any of the above events while on study will be censored on the day of their last tumor assessment.

PFS is defined as the time from randomization 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 post-baseline tumor assessment will be censored at the time of randomization plus 1 day.

OS is defined as the time from randomization until the date of death, regardless of the cause of death. Patients who are alive at the time of data cut-off will be censored at the date of the last follow-up assessment.

Estimates for the survivor function of both treatment groups for TTR, DoR, TTP, TTF, and OS will be obtained by using the Kaplan-Meier method. HRs and associated 90% CIs will be estimated from non-stratified and stratified (based on the stratification factor) Cox regression models.

CBR includes patients whose best (confirmed) response was PR, CR or SD that lasted at least 6 months. CBR will be summarized in a similar way to the primary efficacy endpoint, ORR as assessed by BOR.

Phase I, Cohort 2: mGC

Due to the small number of patients and the design of this part of the study, no secondary efficacy endpoints will be investigated.

6.5 SAFETY ANALYSES

Safety Population Phase I, Cohort 1: mBC

The DLT-evaluable population is defined as all enrolled and treated patients who have not experienced any major protocol violation (including violation of the inclusion and exclusion criteria) and completed Cycle 1.

The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination. The definition of DLTs is presented in Section 5.1.4. DLTs for this part of the study will be summarized by treatment dose.

The safety population (SP) will include all patients who received at least one dose of study medication during Phase I. Safety endpoints will be summarized by treatment dosage.

Safety parameters for this part of the study will be summarized by treatment dose. The summaries of AEs, SAEs, AEs that caused discontinuation from the study treatment and/or study, and AESIs will be analyzed in a similar way to AEs in Phase II.

The incidence of AEs and SAEs will be summarized according to the primary SOC and, within each SOC, by MedDRA preferred term. Based on the safety profile of trastuzumab emtansine, time to onset of the first episode of any AESI described in Section 5 will also be summarized via Kaplan-Meier estimates. Additional summaries by frequency tables will also be provided for the AESIs. Patients who died will be listed together with the cause of death.

Laboratory parameters, hematology and biochemistry will be presented in shift tables of NCI-CTC grade at baseline *versus* worst grade during treatment for Phase I, Cohort 2, and overall.

LVEF will be summarized over time using mean, median and range (minimum and maximum) and will be presented graphically.

Other safety variables, such as exposure to study medication, concomitant medications and physical examinations will be analyzed in a similar way. The exposure of study medication will be summarized by frequency tables.

ECOG performance status will be summarized over time and the percentage of patients in different categories will be presented by bar charts at different time points.

Randomized Phase II: Exploration of Safety in mBC

The SP will include all patients who received at least one dose of study medication during the Randomized Phase II part of the study. Safety endpoints will be summarized by treatment group.

Safety endpoints during Phase II will be assessed via total AEs, Grade ≥3 AEs, SAEs, AESIs (as described in Section 5), fatal AEs and their causes, events to monitor, premature withdrawal from study medication and/or study, laboratory parameters, LVEF, exposure to study medication, concomitant medications, ECOG performance status, and physical examination.

The incidence of AEs and SAEs 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 any AESI described in Section 5 will also be summarized via Kaplan-Meier estimates. Additional summaries by frequency tables will be provided for the AESIs. Patients who died will be listed together with the cause of death.

Laboratory parameters, hematology, and biochemistry will be presented in shift tables of NCI-CTCAE grade at baseline *versus* worst grade during treatment for the Randomized Phase II part of the study.

LVEF will be summarized over time using mean, median and range (minimum and maximum) and will be presented graphically.

Other safety variables, such as exposure to study medication, concomitant medications and physical examinations, will be analyzed in a similar way. The exposure to study medication will be summarized by frequency tables.

ECOG performance status will be summarized over time and the percentage of patients in different categories will be presented by bar charts at different time points.

Safety Population Phase I, Cohort 2: LA/mGC

The DLT-evaluable population is defined as all enrolled and treated patients who have not experienced any major protocol violation (including violation of the inclusion and exclusion criteria) and have completed Cycle 1.

The number and the proportion of patients with DLTs will be used as the primary measure for the MTD determination. The definition of DLTs is presented in Section 5.1.4. DLTs for this part of the study will be summarized by treatment dose.

The SP will include all patients who received at least one dose of study medication during Phase I. Safety endpoints will be summarized by treatment dosage.

Safety parameters will be analyzed in a similar way to safety parameters in Phase I, Cohort 1: mBC.

6.6 PHARMACODYNAMIC ANALYSES

No pharmacodynamic analyses are planned for this study.

6.7 PHARMACOKINETIC ANALYSES

For Phase I only (Patients with mBC and LA/mGC):

The following PK parameters of trastuzumab emtansine, capecitabine and their metabolites (including but not limited to those listed below) will be determined only in the Phase I part of the study for Cohort 1 and Cohort 2 in all patients who receive study treatment using either non-compartmental and/or population methods, if data allow:

- Serum concentrations of trastuzumab emtansine (conjugate) and total trastuzumab
- Plasma concentrations of DM1, capecitabine and its active metabolite 5-FU
- Total exposure (e.g., AUC)
- C_{max}
- CL
- V_d
- $T_{1/2}$

The PK of trastuzumab emtansine, total trastuzumab and DM1 will be compared with historical single-agent PK data to evaluate the potential effect of capecitabine on the PK of trastuzumab emtansine and related analytes. The PK of capecitabine and its active metabolite 5-FU in Cycle 1 (in the absence of trastuzumab emtansine) will be compared with the PK of Cycle 2 (in the

presence of trastuzumab emtansine) to evaluate the potential effect of trastuzumab emtansine on the PK of capecitabine and 5-FU.

All PK parameters will be listed and tabulated by treatment dose and by Cohort. Descriptive summary statistics including arithmetic mean, geometric mean (e.g., AUC and C_{max}), median, range, s.d., and coefficient of variation will be presented for each cohort. Nonlinear mixed effects modeling will also be used; details will be presented in the SAP.

PK samples can be obtained ad hoc in case of a SAE or unexpected toxicities which may suggest a potential drug-drug interaction.

6.8 EXPLORATORY ANALYSES

For all patients with mBC (Phase I, cohort 1; Phase II Exploration of Efficacy and Safety in mBC), a retrospective central confirmation of the HER2 status will be done. Further exploratory analysis for HER2-positive patients (based on central confirmation) will be done for selected endpoints such as BOR and safety endpoints (AEs, SAEs, Grade ≥ 3 AEs, and AESIs).

For the Randomized Phase II only: Exploration of Efficacy and Safety in Patients with mBC:

Subgroup analysis for BOR, safety endpoints (AEs, SAEs, Grade ≥ 3 AEs, and AESIs) in Phase II will be presented for: elderly *versus* younger patients, patients with ECOG 0–1 *versus* ECOG 2, and patients with ≤ versus > prior treatment regimen for metastatic disease.

More details about subgroups will be provided in the SAP.

Pharmacoeconomic Endpoint:

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 (PD *versus* AE) will also be assessed.

6.9 INTERIM ANALYSES

There is no formal efficacy interim analysis.

However, an IDMC will recommend whether the Randomized Phase II part of the study can commence. The IDMC will also monitor safety outcomes after 25, 75, and 150 patients have received at least 3 cycles (Cycle 3 Day 21) of treatment in the Randomized Phase II part of the study. Afterwards, the IDMC will monitor accumulating patient safety data every 6 months during the course of the Randomized Phase II of the study or as requested.

Efficacy data will be provided only if required by the IDMC to estimate the risk-benefit balance for the patients. Further details on the function and logistics of the IDMC will be provided in the IDMC Charter.

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. Central laboratory data and other 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 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. Acknowledgment of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are

certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed.

To facilitate SDV, the investigators and institutions must provide the Sponsor with 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, 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 Good Clinical Practice (GCP) (see Section 4.9 of the 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 (IND) application, 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 GCP 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 European Union (EU)/European economic area (EEA) will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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 Form 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 Form 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/IEC 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.

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, the 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.

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, the 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 a SC, IDMC, central laboratory, IxRS, eCRF, and will be conducted by a contract research organization (CRO) together with the Sponsor.

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 the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate the 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

Table 1 Schedule of assessments for mBC patients (Phase I, Cohort 1 and Randomized Phase II)

	Screening[1]	Cycle 1			Cycle 2–3			Cycle 4 Onwards			Safety Follow-Up Visit	Follow-Up[2]
Day	-28 to -1	1	8	15	1	8	15	1	8	15	28-42 days after last dose	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			X			X	
Height and Weight[d]	X	X			X			X			X	
Vital Signs[e]	X	X			X			X			X	
ECOG Performance Status	X	X			X			X			X	
Concomitant Medication Reporting	X[f]	X	Ongoing									
AE Reporting	X[g]	Ongoing									X	X[h]
12-lead ECG	X											
ECHO/MUGA[i]	X[i]			X[i]			X[i]			X[i]	X[i]	
Tumor Assessments[j]	X	At Cycle 3 (9 weeks after randomization), and then every 4th cycle (12 weeks thereafter, regardless of dose delay or early discontinuation) until PD or study termination, whichever occurs earlier									X	X
Brain CT or MRI[k]	X	At the discretion of the investigator, if clinically indicated, until PD										
Bone Scan/Imaging[l]	X	As clinically indicated										

Appendix 1
Schedule of Assessments (cont.)

Table 1 Schedule of assessments for mBC patients (Phase I, Cohort 1 and Randomized Phase II) (cont.)

	Screening[1]	Cycle 1			Cycle 2–3			Cycle 4 Onwards			Safety Follow-Up Visit	Follow-Up[2]
Day	-28 to -1	1	8	15	1	8	15	1	8	15	28-42 days after last dose	every 3-6 months
Hematology[m]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X	
Biochemistry[o]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X	
Urinalysis[p]	X	As clinically indicated									X	
INR/aPTT	X	As clinically indicated, e.g. for patients receiving anticoagulation therapy									X	
Pregnancy Test[q]	X						X[q]			X[q]	X	X
PK Samples (see Appendix 2)[r]		X[r]			X[r]							
Assessment of Patient Hospitalizations and/or Hospital Visits		X			X			X			X	
Administration of Trastuzumab Emtansine		D 2[s]			D 1[s]			D 1[s]				
Administration of Capecitabine[t]		D 1–14			D 1–14			D 1–14				
Overall Survival		X									X	X
Randomization into the Phase II Part of the Study	X[tu]											

Appendix 1
Schedule of Assessments (cont.)

AE = Adverse Event; aPTT = Activated Partial Thromboplastin Time; CT = Computed Tomography; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; D= Day; 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, INR and aPTT assessments) at Screening: to be performed within **14 days** prior to first treatment. Screening laboratory assessments may be done on the same day of first study treatment (Cycle1 Day1).

2.All patients will be followed-up every 6 months (except for pregnancy, which is at 3 and 6 months after safety follow-up visit until disease progresses for tumor assessment or study closure, whichever occurs first. Patients who discontinue study treatment for reasons other than PD will continue to undergo tumor assessments every 3–6 months.

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 for patients with mBC.

c)Limited symptom-directed physical examination.

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.

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 or until the early termination visit, until treatment-related AEs resolve or stabilize, or until the initiation of another anti-cancer therapy, whichever occurs first. 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, between Days 15 and 21 in cycles 1 and 3, and between Days 15 and 21 of 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.

Appendix 1
Schedule of Assessments (cont.)

j)Tumor assessments (± 5 business days), including a CT or MRI with contrast of the chest, abdomen, and pelvis should be performed according to the indicated schedule. 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, 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 until PD, withdrawal of consent, or study terminaton (whichever occurs earlier).

k)Patients with isolated brain metastases may continue study treatment if they demonstrate clinical benefit (CR or PR of any duration or SD ≥ 3 months) as detailed in Section 4.5.1.4 of the protocol and in Appendix 3. 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 study treatment, non-isotopic radiographic modalities should be utilized to document the extent of bony metastatic disease. Refer to Appendix 4 in the protocol 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)Assessments should be performed at screening, on Day 1, 8 and 15 of Cycles 1–3, on Day 1 of all subsequent cycles, and weekly following any hematologic AE. If capecitabine is discontinued due to toxicity, assessments should be performed weekly (minimum) until resolution of the AE (Grade ≤ 1/ baseline), and on Day 1 of subsequent cycles thereafter. All assessments should 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, blood urea nitrogen (BUN)/urea (mandatory), creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), G-GT, LDH, total bilirubin (and direct bilirubin where total bilirubin > ULN). Fasting is required before biochemistry assessment.

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

Appendix 1
Schedule of Assessments (cont.)

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. 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 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.

r)Pharmacokinetic assessments will be performed during the MTD-Finding part of the study only (see Appendix 2).

s)Trastuzumab emtansine will be administered on Day 1 of each 3-weekly cycle for all patients with mBC in Cohort 1 and Randomized Phase II period of the study except in the first cycle where trastuzumab emtansine will be given on Day 2 (to allow PK sampling).

t) Capecitabine must be given within 30 minutes after a meal.

u)Patients will be randomized only in the Randomized Phase II part of the study. No blinding will be used, as this is an open-label study.

Appendix 1
Schedule of Assessments (cont.)

Table 2 Schedule of assessments for patients with LA/mGC (Phase I, Cohort 2)

	Screening[1]	Cycle 1			Cycle 2–3			Cycle 4 Onwards			Safety Follow-Up Visit	Follow-Up[2]
Day	-28 to -1	1	8	15	1	8	15	1	8	15	28–42 days after last dose	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			X			X	
Height and Weight[d]	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[e]	X	X			X			X			X	
ECOG Performance Status	X	X			X			X			X	
Concomitant Medication Reporting	X[f]	X	Ongoing									
AE Reporting	X[g]	Ongoing									X	X[h]
12-lead ECG	X											
ECHO/MUGA[i]	X[i]			X[i]			X[i]			X[i]	X[i]	
Tumor Assessments[j]	X	At 9 weeks after C1D1, and every 12 weeks thereafter, regardless of dose delay or early discontinuation, until PD or study termination, whichever occurs earliest									X	
Brain CT or MRI[k]	X	At the discretion of the investigator, if clinically indicated, until PD										
Bone Scan/Imaging[l]	X	As clinically indicated										

Hematology[m]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	
Biochemistry[o]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	
Urinalysis[p]	X	As clinically indicated									X	
INR/aPTT	X	As clinically indicated, e.g. for patients receiving anticoagulation therapy									X	
Pregnancy Test[q]	X						X[q]			X[q]	X	X
PK/PD Samples (see Appendix 2)		X			X							
Assessment of Patient Hospitalizations and/or Hospital Visits		X			X			X			X	
Administration of Trastuzumab Emtansine		D 2[r]	X	X	X	X	X	X	X	X		
Administration of Capecitabine[s]		D 1–14			D 1–14			D 1–14				
Overall Survival		X									X	X

AE = Adverse Event; aPTT = Activated Partial Thromboplastin Time; CT = Computed Tomography; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; D= Day; 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

Appendix 1
Schedule of Assessments (cont.)

1.NOTE: Local laboratory (hematology, biochemistry, urinalysis, INR and aPTT assessments) at Screening: to be performed within **14 days** prior to first study treatment. Screening laboratory assessments may be done on the same day of first study treatment (Cycle1 Day1) visit.

2.All patients will be followed-up every 6 months (except for pregnancy, which is at 3 and 6 months after safety follow-up visit) until disease progresses for tumor assessment or study closure, whichever occurs first. Patients who discontinue study treatment for reasons other than PD will continue to undergo tumor assessments every 3–6 months.

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+ alone or IHC 2+ in combination with gene amplification by ISH. For patients with mGC enrolled into Cohort 2, central confirmation of HER2 status is required.

c)Limited symptom-directed physical examination.

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 fist study treatment.

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 or until the early termination visit, until treatment-related AEs resolve or stabilize, or until the initiation of another anti-cancer therapy, whichever occurs first. 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, between Days 15 and 21 in cycles 1 and 3, and between Days 15 and 21 of every 3rd 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.

Appendix 1
Schedule of Assessments (cont.)

j)Tumor assessments (± 5 business days), including a CT or MRI with contrast of the chest, abdomen, and pelvis should be performed according to the indicated schedule. 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, e.g. the same contrast protocol for CT scans. For patients who discontinue study treatment for reasons other than PD, continue tumor assessments according to the protocol every 3–6 months until PD, withdrawal of consent, or study termination (whichever occurs earliest).

k)Patients with isolated brain metastases may continue study treatment if they demonstrate clinical benefit (CR or PR of any duration or SD ≥ 3 months) as detailed in Section 4.5.1.4 of the protocol and in Appendix 3. 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 4 in the protocol for additional details.

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

n)Assessments should be performed at screening, on Day 1, 8 and 15 of all cycles. All assessments should 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/urea (mandatory), creatinine, uric acid, total protein, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), G-GT, LDH, total bilirubin (and direct bilirubin where total bilirubin > ULN). Fasting is required before biochemistry assessment.

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. 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 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.

r)Trastuzumab emtansine will be administered on Day 1 of each weekly cycle for all patients enrolled in Cohort 2 (A&B) except in the first cycle where trastuzumab emtansine will be given on DAY 2 (to allow drug interaction assessment).

s)Capecitabine must be given within 30 minutes after a meal.

Appendix 2
Pharmacokinetic Sampling for Phase I, Metastatic Breast and Gastric Cancer Patients

	Trastuzumab emtansine, total trastuzumab and DM1[a] PK samples (serum)	Capecitabine and 5-FU PK samples (plasma)
Cycle 1 Day 1		
Pre-capecitabine dose		x
30 min post capecitabine dosing		x
60 min post capecitabine dosing		x
1.5 hours post capecitabine dosing		x
2 hours post capecitabine dosing		x
2.5 hours post capecitabine dosing		x
4 hours post capecitabine dosing		x
6 hours post capecitabine dosing		x
Cycle 1 Day 2		
Pre-trastuzumab emtansine dose	x	
15-30 min after end of trastuzumab emtansine infusion	x	
Pre-capecitabine dose		x
30 min post capecitabine dosing		x
2 hours post capecitabine dosing		x
6 hours post capecitabine dosing		x
Cycle 1 Day 3		
24 hours (± 2 hours) after the end of infusion of trastuzumab emtansine	x	
Cycle 1 Day 9		
7 days (± 1 day) after the end of infusion of trastuzumab emtansine[a]	x	
Cycle 2 Day 1		
Pre- capecitabine and trastuzumab emtansine dose[a]	x	
15–30 min after end of trastuzumab emtansine infusion	x	

30 min post capecitabine dosing		x
60 min post capecitabine dosing		x
1.5 hours post capecitabine dosing		x
2 hours post capecitabine dosing		x
2.5 hours post capecitabine dosing		x
4 hours post capecitabine dosing		x
6 hours post capecitabine dosing		x
Cycle 2 Day 2		
24 hours (± 2 hours) after the end of infusion of trastuzumab emtansine	x	
Cycle 2 Day 7		
7 days (± 1 day) after the end of infusion of trastuzumab emtansine [a]	x	
Cycle 3		
Pre trastuzumab emtansine dose	x	

PK = pharmacokinetic; 5-FU = 5-fluoruracil

[a] = Plasma DM1 samples will not be collected at Day 7 post-infusion of trastuzumab emtansine neither at pre-dose of Cycle 2 and Cycle 3.

Data from historic studies have determined that results are the lower limit of quantitation.

Appendix 3
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 CT or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10mm 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.

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

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.

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, 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.

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Target Lesions: Specifications by Methods of Measurements

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 28 days 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 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, if not, the patient should be considered not evaluable from that point forward. Care must

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

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

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

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

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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
- 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

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but 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

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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.

- Complete response (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
- Progressive disease (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

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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 PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial 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 PD.

If a new lesion is equivocal, e.g., because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of 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.

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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

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.

Appendix 3 (cont.)
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of “zero” on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD 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**, **Table 3**.

Appendix 3
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.

Appendix 3
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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 4
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 5
New York Heart Association Classification of Functional Cardiac Capacity

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

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

Appendix 6
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

52. http://www.ecog.org/general/perf_stat.html