Official Title: A Phase Ib/II, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Venetoclax in Combination With Trastuzumab Emtansine in Patients With Previously Treated Her2-Positive Locally Advanced or Metastatic Breast Cancer

NCT Number: NCT04298918

Document Dates: Protocol Version 1: 19-December-2019

Protocol Version 2: 06-April-2020

PROTOCOL

TITLE: **A PHASE Ib/II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH TRASTUZUMAB EMTANSINE IN PATIENTS WITH PREVIOUSLY TREATED HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**

PROTOCOL NUMBER:	CO41863
VERSION NUMBER:	1
EUDRACT NUMBER:	2019-004200-35
IND NUMBER:	137088
NCT NUMBER:	To be determined
TEST PRODUCT:	Venetoclax (RO5537382) Trastuzumab emtansine (RO5304020)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
19-Dec-2019 22:32:51	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH TRASTUZUMAB EMTANSINE IN PATIENTS WITH PREVIOUSLY TREATED HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH TRASTUZUMAB EMTANSINE IN PATIENTS WITH PREVIOUSLY TREATED HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
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PHASE:	Ib/II
INDICATION:	Locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the "randomized Phase II stage").

The dose-escalation phase will assess safety and tolerability, determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D), and evaluate preliminary efficacy of trastuzumab emtansine in combination with venetoclax in patients with previously treated HER2-positive unresectable locally advanced breast cancer (LABC) or metastatic breast cancer (MBC), irrespective of patients' prior trastuzumab emtansine exposure in the metastatic setting.

After the RP2D is established, additional patients may be enrolled in the expansion phase to evaluate the safety, tolerability, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D in patients with previously treated HER2-positive LABC or MBC who have previously received either trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a). The decision to open these cohorts will be data-driven and dependent on the observations made in the dose-escalation phase, as well as emerging data about trastuzumab deruxtecan and other HER 2-targeted therapies. Importantly, the expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

The randomized Phase II stage will aim to evaluate the safety, tolerability, pharmacokinetics, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D compared with trastuzumab emtansine plus placebo in patients with previously treated HER2-positive LABC or MBC who have not received prior trastuzumab emtansine therapy, either alone or in combination with other anticancer therapies. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Endpoints for Dose-Escalation Phase

Primary Safety Objective

The safety objective for the dose-escalation phase is to evaluate the safety and tolerability of trastuzumab emtansine in combination with venetoclax—including estimation of the MTD, determination of the RP2D, and characterization of dose-limiting toxicities (DLTs)—on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Exploratory Efficacy Objective

The exploratory efficacy objective for the dose-escalation phase is to make a preliminary assessment of the anti-tumor activity of trastuzumab emtansine and venetoclax on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR) on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for the dose-escalation phase of this study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Objectives and Endpoints for Expansion Phase

Primary Efficacy Objective

The primary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- ORR

Secondary Efficacy Objective

The secondary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- DOR

Safety Objective

The safety objective for the expansion phase is to evaluate the safety and tolerability of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The PK objective for the expansion phase of the study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Objectives and Endpoints for Randomized Phase II Stage

Primary Efficacy Objective

The primary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following co-primary endpoints:

- ORR
- Progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

Secondary Efficacy Objective

The secondary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- DOR
- Overall survival (OS) after randomization, defined as the time from randomization to death from any cause

Exploratory Efficacy Objective

The exploratory efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Clinical benefit rate (CBR), defined as the proportion of patients with CR, PR, or stable disease (SD) at 6 months after randomization, as determined by the investigator according to RECIST v1.1

Safety Objective

The safety objective for the randomized Phase II stage is to evaluate safety of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Incidence and severity of adverse events with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The PK objective for the randomized Phase II stage of this study is to characterize the pharmacokinetics of trastuzumab emtansine and venetoclax when given in combination on the basis of the following endpoints:

- Serum concentrations of trastuzumab emtansine at specified timepoints
- Plasma concentrations of venetoclax at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to trastuzumab emtansine when given with placebo or in combination with venetoclax on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for the randomized Phase II stage is to evaluate health status utility scores of patients treated with trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoint:

- Change from baseline in patient-reported symptoms and their impact on functioning and health-related quality of life as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and EORTC Item List 46 (EORTC IL46)

Study Design

Description of Study

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the "randomized Phase II stage"). The expansion phase may run concurrent to and parallel with the randomized Phase II stage.

Dose-Escalation Phase

The dose-escalation phase will determine the RP2D and MTD for venetoclax when given in combination with a fixed dose of trastuzumab emtansine (3.6 mg/kg) in patients with previously treated, HER2-positive LABC or MBC, irrespective of prior trastuzumab emtansine exposure in the metastatic setting.

The dose-escalation phase will enroll 6–24 patients and will include 2–4 cohorts:

- Cohort 1A, 400 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (every 3 weeks [Q3W]) and venetoclax 400 mg orally (PO) once a day (QD) continuous on Days 1–21 of each cycle.
- Cohort 1B, 400 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 400 mg PO QD non-continuous (NC) on either Days 1–7 or 1–14 of each cycle.
- Cohort 2A, 800 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD continuous on Days 1–21 of each cycle.
- Cohort 2B, 800 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD non-continuous on either Days 1–7 or 1–14 of each cycle.

The 400-mg and 800-mg cohorts for dose escalation will be run sequentially (i.e., the 400-mg cohort followed by the 800-mg cohort). Dose escalation will be performed based on a standard 3 + 3 design. Each cohort will consist of at least 3 patients, unless 1 of the 3 patients experiences DLTs (refer to the protocol for DLT criteria), in which case 3 additional patients will be treated at the same dose level. The dose escalation will continue until 2 patients among a cohort of 6 patients experience a DLT (i.e., ≥33% of patients with a DLT at that dose level; refer to dose-escalation rules in the protocol). Patients who experience a DLT will continue at the same dose level.

Dose de-escalation may be explored by incorporating non-continuous (NC) dosing of venetoclax (e.g., less than 21 days of dosing, such as 7 days out of 21 days or 14 days out of 21 days) dependent on the severity and timing of DLTs as well as the specific adverse events encountered. For example, if DLTs such as a Grade 3 rash occurred between Day 8 and Day 14, an NC schedule of Days 1–7 would be tested. Alternatively, if DLTs are thought to be possibly mitigated by a 7-day break such as Grade 3 fatigue occurring near the end of the DLT window (e.g., Day 20), then an NC schedule of Days 1–14 could be chosen to be tested. Patients may be treated in up to two NC sub-cohorts (i.e., either 400 mg NC and/or 800 mg NC). At each dose de-escalation level, either a Days 1–7 or Days 1–14 NC treatment schedule will be assessed.

Refer to the protocol for definition of DLT, dose-escalation rules, and determination of DLTs and RP2D.

Expansion Phase

An expansion phase may be initiated to evaluate the safety, tolerability, and efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine in previously treated HER2-positive locally advanced or MBC patients who have received prior trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a).

The decision to open cohorts as part of an expansion phase will be data-driven and dependent on the observations made in the dose-escalation phase, emerging data with trastuzumab deruxtecan, as well as other HER2-targeted therapies. The expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

Randomized Phase II Stage

The randomized Phase II stage will be initiated once the RP2D has been identified based on the cumulative data collected from the dose-escalation phase. It will consist of two interventional arms of trastuzumab emtansine plus placebo or trastuzumab emtansine plus venetoclax in patients with previously treated HER2-positive LABC or MBC, who have not received prior trastuzumab emtansine therapy.

Approximately 220 patients will be randomized 1:1 to one of the following treatment arms:

- Control Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus placebo at the RP2D and schedule of venetoclax.
- Experimental Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus venetoclax at the RP2D and schedule.

Each arm will include at least 50% Bcl-2 high patients. Randomization will be stratified according to the following criteria:

- Bcl-2 status (Bcl-2 high vs. Bcl-2 low)
- Visceral disease (Yes vs. No)
- HER2 status IHC 3+ (Yes vs. No)

Number of Patients

Approximately 226–284 patients will be enrolled in this study across approximately 145 sites globally. The study will enroll 6–24 patients in Part 1 of the study and approximately 220 patients in Part 2. An additional approximately 20–40 patients may be enrolled in the expansion cohorts.

Target Population

Inclusion Criteria (All Study Phases)

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed invasive MBC or LABC that is incurable, unresectable, and previously treated with multimodality therapy:
  - Prior treatment for BC in the adjuvant, unresectable locally advanced, or metastatic settings, which must include both a taxane and trastuzumab (alone or in combination with another agent)
  - Progression must have occurred during or after most recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy
- Measurable disease that is evaluable per RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Willing to provide tumor biopsy sample at the time of screening

  A tumor biopsy sample (either archival or fresh) must be collected from all patients from either the primary tumor or a metastatic site (preferred and within 6 months of enrollment, if clinically feasible) for determination of HER2 status by central laboratory testing for patient eligibility purposes, for Bcl-2 expression, and for research on biomarkers.

  The tumor specimen must contain adequate evaluable tumor cells (≥ 20% tumor cells) to enable Bcl-2, HER2, and other relevant biomarker analysis. Samples can be a tissue block (preferred) or at least 20 unstained freshly cut serial slides, and should be accompanied by an associated pathology report. If fewer than 20 slides are available, the Sponsor should be consulted. If a tumor sample is not available, a fresh biopsy must be collected.

  The specimen must be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration samples are not acceptable.

- Local histological or cytological confirmation of estrogen receptor (ER) and/or progesterone receptor status as defined by using IHC per American Society of Clinical Oncology/College of American Pathologists criteria
- Percentage of ER and/or progesterone receptor positivity, if available
- Willing to provide blood samples at the time of screening, on-study, and at progression for exploratory research on biomarkers
- HER2-positive breast cancer (BC) as defined by an IHC score of 3+ or gene amplified by in situ hybridization (ISH) as defined by a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of chromosome 17 copies

  For the expansion phase and randomized Phase II stage: Centrally confirmed HER2-positive status prospectively tested by a Sponsor-designated central laboratory prior to enrollment.

  For the dose-escalation phase: Enrollment can be based upon prospective central testing or local IHC or ISH results; however, for local IHC or ISH results, the same tissue sample must be sent for central HER2 confirmation and the testing platform documented in the eCRF.

  Both IHC and ISH assays can be performed; however, unless reflex testing is necessary, only one positive result is required for eligibility.

  If multiple tumor specimens are submitted, the HER2 IHC score and or ISH amplification ratio will first be assessed on the most recently obtained specimen for the purpose of determining eligibility. For patients with bilateral BC, HER2 positivity must be demonstrated in both locations for archival tissue or in a metastatic biopsy.

  Centrally confirmed HER2 results (either IHC or ISH) from a current or previous Sponsor study can be used to determine eligibility for this study. Approval must be obtained from the Medical Monitor prior to randomization.
- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):
  - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte-colony stimulating factor support within 7 days prior to Cycle 1, Day 1)
  - Platelet count $\geq 100{,}000/\mu$L (without transfusion within 7 days prior to Cycle 1, Day 1)
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - Albumin > 2.5 g/dL
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exceptions:

    Patients with previously documented Gilbert syndrome who may have bilirubin $< 5 \times$ ULN

    Patients with documented liver metastases may have bilirubin $\leq 2.5 \times$ ULN
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases may have ALP $\leq 5 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of either 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

- INR or aPTT $\leq 1.5 \times$ ULN

    For patients requiring anticoagulation therapy with warfarin or other coumarins, a stable INR between 2 and 3 is required. If anti-coagulation is required for a prosthetic heart valve, then INR should be between 2.5 and 3.5.

- Screening left ventricular ejection fraction (LVEF) $\geq 50\%$ on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan

    LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.

- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

    The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

    The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later. Women must refrain from donating eggs during this same period.

    A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

    Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

    Hormonal contraceptive methods must be supplemented by a barrier method.

    The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

    With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later.

    With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Inclusion Criteria for Expansion Phase Only

In addition to the general inclusion criteria, patients in the expansion phase of the study must also meet the following criteria for study entry:

- Trastuzumab emtansine experienced cohort:
  - Disease progression during or after trastuzumab emtansine in the advanced/metastatic setting or disease recurrence in the neoadjuvant/adjuvant setting
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high.

    Bcl-2 high is defined as $\geq$ 50% of tumor cells stained with an intensity of IHC 2+ or 3+, and Bcl-2 low is defined as IHC 0 or 1+ or < 50% of tumor cells stained with an intensity of IHC 2+ or 3+.

- Trastuzumab deruxtecan (DS-8201a) experienced cohort:
  - Disease progression during or after trastuzumab deruxtecan in the advanced/metastatic setting
  - Prior trastuzumab emtansine in any setting is allowed
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high.

Inclusion Criteria for Randomized Phase II Stage

In addition to the general inclusion criteria, patients in the randomized Phase II stage of the study must also meet the following criteria for study entry:

- Bcl-2 expression status by IHC either from fresh tissue or the most recent archival tissue (see criteria for all study phases) by a central laboratory using the Ventana Bcl-2 IHC assay prior to randomization.

  At least 50% of patients in the randomized Phase II (e.g., 110 out of 220 patients) must be Bcl-2 high.

Exclusion Criteria

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

- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1
- Radiation therapy within 2 weeks prior to Cycle 1, Day 1
- The patient must have recovered from any resulting acute toxicity (to Grade $<$ 1) prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin $>$ 500 mg/m^2
  - Liposomal doxorubicin $>$ 500 mg/m^2
  - Epirubucin $>$ 720 mg/m^2
  - Mitoxantrone $>$ 120 mg/m^2
  - Idarubicin $>$ 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.

- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence
- Cardiopulmonary dysfunction as defined by:
    - Uncontrolled hypertension (systolic $>$ 150 mm Hg and/or diastolic $>$ 100 mm Hg with or without medication)
    - Inadequate LVEF at baseline, $<$ 50% by either ECHO or MUGA
    - History of symptomatic congestive heart failure (CHF)-Grade $\geq$ 3 per NCI CTCAE version 5.0 or Class $\geq$ II New York Heart Association
    - History of a decrease in LVEF to $<$ 40% or symptomatic CHF with prior trastuzumab treatment
    - Myocardial infarction or unstable angina within 6 months of randomization
    - Concurrent dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
    - Evidence of transmural infarction on ECG
    - Significant symptoms (Grade $\geq$ 2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia
    - High-risk uncontrolled arrhythmias (i.e., supraventricular tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 (Mobitz 2) or third-degree AV-block])
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis, or active infection with HBV or HCV)
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Known HIV infection or human T-cell leukemia virus 1 infection
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $>$ 2 weeks prior to randomization
- Known central nervous system (CNS) disease, except for patients treated and currently with asymptomatic CNS metastases, provided that all of the following criteria are met:
    - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
    - No ongoing requirement for corticosteroids as therapy for CNS disease
    - No stereotactic radiation within 14 days prior to randomization
    - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

        Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium or calcium $>$ 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade $\geq$ 3 peripheral neuropathy (according to the NCI CTCAE v 5.0)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Prior allogeneic stem cell or solid organ transplantation
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine after the final dose of study treatment, whichever is later

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Strong or moderate CYP3A inhibitors
  - Strong or moderate CYP3A inducers

  Additional restrictions for on-study use of CYP3A inhibitors/inducers are outlined in the protocol.
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade-containing Seville oranges), or starfruit (carambola) within 3 days before anticipated first dose of study drug until the last dose of study drug
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History of active inflammatory bowel disease (e.g., Crohn’s disease or ulcerative colitis) requiring specific medication in the 12 months prior to randomization, or active and uncontrolled bowel inflammation (e.g., diverticulitis) at time of randomization
- Inability or unwillingness to swallow a large number of tablets
- Known hypersensitivity to venetoclax or trastuzumab emtansine or to any of their excipients
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Other medical or psychiatric conditions that, in the opinion of the investigator, may interfere with the patient’s participation in the study
- Blood transfusions if performed within 2 weeks prior to screening

Exclusion Criteria for Randomized Phase II Stage

In addition to the general exclusion criteria, patients in the randomized Phase II stage of this study who meet the following criteria will be excluded:

- Prior treatment with trastuzumab emtansine in any setting (neoadjuvant/adjuvant or advanced/metastatic setting)
- Prior treatment with venetoclax in any setting
- Prior treatment with anti-HER2 antibody drug conjugates (e.g. trastuzumab deruxtecan [DS-8201a]), margetuximab, pyrotinib, or tucatinib.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of study is planned to occur approximately 24 months after last patient in (LPI). In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength. Each dose of venetoclax will be taken orally once daily. The venetoclax treatment regimens for the dose-escalation phase, dose-expansion phase, and randomized Phase II stage are summarized in the Description of Study above.

Comparator

The formulation of placebo is equivalent to venetoclax but without the active agent. Each dose of placebo will be taken orally once daily. The placebo treatment regimen for the randomized Phase II stage is summarized in the Description of Study above.

Trastuzumab emtansine will serve as the comparator/active control and will not be blinded. Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W.

The oral dose of venetoclax should be administered first, followed by infusion of trastuzumab emtansine.

Statistical Methods

Primary Analysis for Dose-Escalation Phase

The primary objective for the dose-escalation phase is to evaluate the safety and tolerability of trastuzumab emtansine in combination with venetoclax, including estimation of the MTD, determination of the RP2D, and characterization of DLTs. The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Safety will be assessed separately for each study phase through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

Primary Analysis for Randomized Phase II Stage

The co-primary endpoints for the randomized Phase II stage are ORR and PFS. The primary efficacy analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment (the intent-to-treat [ITT] population). The primary efficacy analysis will occur when 161 patients have experienced a PFS event. It is anticipated that this will occur six months after the last patient enters treatment. Patients with no disease assessments for any reason will be classified as non-responders. An estimate of ORR with 95% CI will be calculated for each treatment arm using the normal approximation to the binomial distribution. An estimate and 95% CI for the difference in ORR between the two treatment groups will be presented based on the normal approximation to the binomial distribution.

PFS is defined as the time from randomization to the first occurrence of disease progression (as defined by the investigator according to RECIST v1.1) or death from any cause, whichever comes first. Data for patients without the occurrence of disease progression or death as of the clinical data cut-off date will be censored at the time of last tumor assessment (or the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Kaplan-Meier curves of time to PFS for each treatment group will be provided. The Cox proportional hazards model stratified by the randomization stratification factors (Bcl-2 status [high, low], visceral disease [yes, no], and HER2 status IHC 3+ [yes, no] will be used to provide an estimate of the hazard ratio of venetoclax plus trastuzumab emtansine to placebo plus trastuzumab emtansine with associated 95% CI and p-value. The unstratified hazard ratio estimate and 95% CI will also be presented.

Determination of Sample Size

The sample size for the dose-escalation phase is based on the dose-escalation rules described in the protocol. The planned enrollment for the dose-escalation phase is approximately 6–24 patients enrolled across 2–4 dose-escalation treatment groups.

Approximately 20 patients each may be enrolled in the expansion phase (trastuzumab emtansine-experienced cohort and trastuzumab deruxtecan-experienced cohort).

With 20 patients per cohort and an observed ORR of 60%, the exact 90% Clopper-Pearson confidence interval for the ORR would be 39%–78%, which would rule out an ORR of 35% or less. The protocol provides exact 90% confidence intervals for a range of observed proportions of ORR based on a sample size of 20 patients. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such event in a cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively. The protocol describes exact 90% confidence intervals for a range of observed proportions of adverse events based on a sample size of 20 patients.

After the RP2D has been determined for venetoclax when given in combination with a fixed dose of trastuzumab emtansine, a total of 220 patients will be enrolled in the randomized Phase II stage of the study. The purpose of the randomized Phase II stage is estimation and hypothesis generation regarding the effect of venetoclax in combination with trastuzumab emtansine on ORR and duration of PFS relative to trastuzumab emtansine plus placebo. The point and interval estimates of the true underlying HR will be obtained.

For the co-primary endpoints of ORR and PFS in the primary efficacy analysis population, the trial will have:

- 85% power ($\alpha = 0.05$) to detect a 20% improvement in ORR (i.e., ORR Δ) (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm). In the meantime, a 20% improvement in ORR will have a 95% CI of (7%, 33%).

- 90% power ($\alpha = 0.05$) to detect a PFS HR of 0.6 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 161 total PFS events have occurred. In the meantime, a PFS HR of 0.6 will have a 95% CI of (0.44, 0.82). The assumptions of the sample size calculation are that the median PFS in the control arm is 6.8 months and that enrollment would occur non-uniformly over 24 months. Enrollment is anticipated to be lower during the second half of the enrolment period because it will be restricted to the Bcl-2 high population.

Within the Bcl-2 high population the study will have:

- 85% power ($\alpha = 0.05$) to detect a PFS HR of 0.5 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 75 total PFS events have occurred. In the meantime, a PFS HR of 0.5 will have a 95% CI of (0.32, 0.79).

The study will not, however, have adequate power to detect all potentially clinically meaningful differences in ORR and PFS. For example, within the entire ITT population:

- With 110 patients in each arm, there is only 60% power ($\alpha = 0.05$) to detect a 15% improvement in ORR (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm), and
- With approximately 161 total PFS events, only 62% power ($\alpha = 0.05$) to detect an HR of 0.70, in venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm.

Thus, a statistically negative outcome in any of the co-primary endpoints does not necessarily rule out a clinically meaningful outcome. The protocol describes the power and CIs for several possible true underlying improvements in ORR and PFS in favor of the venetoclax plus trastuzumab emtansine arm.

Due to the smaller sample size of the Bcl-2 high population the power to detect a HR of 0.60 in the Bcl-2 population is 60% compared to 90% for the entire ITT population. The study has adequate power (85%) to detect a HR of 0.5 in the Bcl-2 high population.

Interim Analyses (Randomized Phase II Stage Only)

Periodic analyses of cumulative safety data and one interim analysis is planned for this study. Given the hypothesis-generating nature of this study, the Sponsor considers the interim efficacy analysis as exploratory.

The planned interim efficacy analysis of cumulative safety, ORR, and PFS will occur when approximately 56 PFS events have occurred. This is expected to occur after the enrollment of the first 110 patients who have been followed up for at least 6 months.

If the interim analysis coincides within approximately 1 month of a planned safety review, the safety review may be combined with the efficacy interim analyses. Outcomes from these reviews that may affect study conduct will be communicated in a timely manner to the investigators, and IRBs/ECs will be notified.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AML	acute myeloid leukemia
AV	atrioventricular
BC	breast cancer
Bcl-2	B-cell lymphoma 2
CBR	clinical benefit rate
CHF	congestive heart failure
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DDI	drug–drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
EBC	early breast cancer
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EORTC IL46	EORTC Item List 46
EORTC QLQ-C30	EORTC Quality of Life–Core 30 Questionnaire
ER	estrogen receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio

ICH	International Council for Harmonisation
IHC	immunohistochemistry
IL46	Item List 46
ILD	interstitial lung disease
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LABC	locally advanced breast cancer
LDAC	low-dose cytarabine
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition (scan)
NC	non-continuous (dose)
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal product
NRH	nodular regenerative hyperplasia
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PO	by mouth; orally
PR	partial response

PRO	patient-reported outcome
Q3W	every 3 weeks
QD	once a day
QLQ-C30	Quality of Life–Core 30 Questionnaire
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SD	stable disease
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
TGI	tumor growth inhibition
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
TPC	treatment of physician’s choice
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE BREAST CANCER

Breast cancer (BC) is the most common cancer among women in the world, with an estimated 2.09 million cases diagnosed globally per year and a mortality rate of approximately 627,000 deaths (Bray et al. 2018). While advances in early diagnosis and adjuvant therapy have led to a decrease in mortality rates from BC in developed countries, the prevalence of metastatic breast cancer (MBC) is still high and it is not curable, with the main goals of treatment being to prolong survival while maintaining or improving patients' quality of life (Cardoso et al. 2018).

BC risk assessment, prognosis, and treatment strategy rely on the status of key biomarkers: hormonal receptors (estrogen receptor [ER] and progesterone receptor) and HER2, also known as erbB2, neu, and p185HER2. Approximately 15%–20% of patients with primary invasive BC overexpress the HER2 receptor (Reese and Slamon 1997; Owens et al. 2004; Wolff et al. 2013; Zhang et al. 2015). Before HER2-targeted therapy became available, primary BCs that overexpressed HER2 were associated with a poorer prognosis, including a greater risk of relapse and shortened survival compared with that of HER2-negative tumors (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001). That changed with the introduction of trastuzumab, the first anti-HER2 therapy approved for HER2-positive BC, with HER2 positivity being designated as an immunohistochemistry (IHC) score of 3+ or HER2 gene amplification ratio of $\geq$ 2.0 by in situ hybridization (ISH).

Until recently, for patients with HER2-positive MBC, the combination of trastuzumab and a taxane was widely accepted as the first-line treatment option of choice on the basis of the survival advantage demonstrated in two large pivotal trials (Studies H0648g [Slamon et al. 2001] and M77001 [Marty et al. 2005]). More recently, the regimen of pertuzumab in combination with trastuzumab and docetaxel has shown clear superiority in terms of both progression-free survival (PFS) and overall survival (OS) with a generally similar safety profile (Study WO20698/TOC4129g [Baselga et al. 2012]), and became the new standard of care for first-line HER2-positive MBC.

In patients with HER2-positive advanced BC previously treated with trastuzumab and a taxane, trastuzumab emtansine has significantly prolonged PFS (up to 3 months improvement) and OS (up to 7 months increase) with a more favorable safety profile than lapatinib plus capecitabine (Study BO21977/TDM4370g, EMILIA [Verma et al. 2012]) or compared with a treatment of physicians' choice (TPC) in patients who previously received trastuzumab, taxane, and lapatinib (Wildiers et al. 2015). Trastuzumab emtansine is considered the standard of care in the aforementioned patient population (Cardoso et al. 2018; National Comprehensive Cancer Network [NCCN] 2019).

Based on the clinical data mentioned above, for patients with HER2-positive BC, the continuous blockage of HER2 through the initial lines of therapy in the metastatic setting is recommended (NCCN 2019). Even though the survival time of patients with HER2-positive BC has been prolonged in recent years, there remains a significant need for further outcome improvement. This could be achieved with the addition of new agents with novel mechanisms of action and acceptable toxicity, such as the pro-apoptotic molecule venetoclax, that can be combined with established HER2-targeted therapies.

1.2 BCL-2 SIGNALING PATHWAY AND HER2-POSITIVE BREAST CANCER

Cancer cells are characterized by their capacity for relentless growth, survival, and evasion of cell death (Adams and Cory 2007; Strasser et al. 2011). Apoptosis is the dominant mode of programmed cell death with two distinct pathways: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway (Strasser et al. 2011). Intrinsic apoptosis is regulated by the B-cell lymphoma 2 (Bcl-2) family of anti-apoptotic proteins of which key members are Bcl-2, Bcl-X_L, Bcl-w, A1, and MCL-1 (Cory et al. 2003). Bcl-2 family proteins have been described to be overexpressed in numerous cancer types. BCL-2 overexpression has been described in approximately 54%–75% of BC cases.

Bcl-2 is a relevant therapeutic target in hematologic malignancies, including chronic lymphocytic leukemia (CLL])/small lymphocytic lymphoma (SLL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), myelodysplastic syndrome, and acute myeloid leukemia (AML) (Perini et al. 2018), and may have an important role in the survival of solid tumors such as BC and lung cancer. For example, patient-derived xenograft (PDX) tumor models of luminal B BC have demonstrated significant improvement in tumor responses and OS when treated with the dual BCL-2/BCL-X_L inhibitor ABT-737 in combination with tamoxifen, compared with tamoxifen alone (Oakes et al. 2012; Vaillant et al. 2013). Similar efficacy was observed using the Bcl-2–specific inhibitor venetoclax (GDC-0199/ABT-199), suggesting that Bcl-2 may be a critical target (Vaillant et al. 2013; Lok et al. 2019) in patients with ER-positive, Bcl-2–positive MBC. The combination appears to show preliminary efficacy as well as a favorable toxicity profile when compared with other adjunctive therapies used with endocrine therapy, such as the mTOR, PIK3CA, and CDK4/6 inhibitors (Lok et al. 2019).

Bcl-2 is believed to be an important target in HER2-positive BC. Internal Genentech and Roche biomarker data in HER2-positive BC suggest that higher levels of Bcl-2 expression may be a poor prognostic factor in early breast cancer (EBC). Analysis of EBC tumor samples demonstrated that 24% of HER2-positive tumors were Bcl-2 high by IHC analysis (Genentech internal, unpublished). These data are consistent with previously reported data indicating that 21%–26% of HER2-positive samples are Bcl-2–positive (Honma et al. 2015; Eom et al. 2016).

1.3 BACKGROUND ON TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (Kadcyla®) is a regulatory authority–approved antibody-drug conjugate. Linkage of a cytotoxic agent to highly specific monoclonal antibodies targeting unique and/or overexpressed cell-surface tumor antigens focuses the delivery of such agents to tumor cells, creating a more favorable therapeutic window than can be achieved by their administration as free drugs. Trastuzumab emtansine is specifically designed for the treatment of HER2-positive cancer. It is composed of the cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent; N2'deacetyl-N2'-[3-mercapto-1-oxopropyl]-maytansine) conjugated to trastuzumab via lysine side chains, with an average drug-to-antibody ratio of approximately 3.5:1.

Trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. After binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity.

Based on Phase I, II, and III studies in which trastuzumab emtansine demonstrated clinical activity, it is currently approved as a single agent for the treatment of patients with HER2-positive MBC who previously received trastuzumab and a taxane, separately or in combination (Kadcyla U.S. Package Insert; E.U. Summary of Product Characteristics [SmPC]). Trastuzumab emtansine is also approved for the adjuvant treatment of patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Data from clinical trials of trastuzumab emtansine that are relevant to the design of the current trial are summarized in the following sections. Refer to the most recent version of the Trastuzumab Emtansine Investigator's Brochure for further information on all of the completed and ongoing trastuzumab emtansine studies.

1.3.1 Study TDM4370g/BO21977 (EMILIA)

Study TDM4370g/BO21977 was a randomized Phase III study of trastuzumab emtansine versus lapatinib plus capecitabine in patients with HER2-positive, unresectable locally advanced BC (LABC) or MBC previously treated with trastuzumab and a taxane (n = 991). Patients received trastuzumab emtansine (3.6 mg/kg IV every 3 weeks [Q3W]) or capecitabine (1000 mg/m^2 orally [PO] twice a day, Days 1–14 Q3W) plus lapatinib (1250 mg PO once a day [QD]) until progressive disease or unmanageable toxicity.

Primary endpoints were PFS by independent review, OS, and safety. A total of 991 patients were enrolled, and 978 patients received treatment. Baseline patient demographics, prior therapy, and disease characteristics were balanced. There was a significant improvement in PFS favoring trastuzumab emtansine (hazard ratio [HR] = 0.650; 95% CI: 0.549 to 0.771; p = 0.0001; median PFS: 9.6 vs. 6.4 months). Objective response rate (ORR) was 43.6% for the trastuzumab emtansine arm versus

30.8% for the lapatinib plus capecitabine arm, with a median duration of response (DOR) of 12.6 months versus 6.5 months, respectively. Final OS analysis showed a consistent survival benefit for trastuzumab emtansine compared with lapatinib plus capecitabine (median OS = 29.9 vs. 25.9 months; stratified HR = 0.75), despite 27% of patients crossing over from the control arm to trastuzumab emtansine (Diéras et al. 2017).

Trastuzumab emtansine was well tolerated, with no unexpected safety signals. The most common Grade ≥ 3 adverse events in the trastuzumab emtansine arm were thrombocytopenia (12.9% vs. 0.2%, respectively), increased AST (4.3% vs. 0.8%), and increased ALT (2.9% vs. 1.4%); the most common Grade ≥ 3 adverse events in the lapatinib plus capecitabine arm were diarrhea (20.7% vs. 1.6%), palmar plantar erythrodysesthesia (16.4% vs. 0%), and vomiting (4.5% vs. 0.8%). The incidence of Grade 3 adverse events in the trastuzumab emtansine arm was 40.8% versus 57.0% in the lapatinib plus capecitabine arm (Verma et al. 2012). Based on the results of the EMILIA study, trastuzumab emtansine was granted regulatory approval in the U.S. and E.U. for treatment-refractory HER2-positive LABC or MBC.

1.3.2 Study WO30085 (KATE2)

Study WO30085 (KATE2) is an ongoing, randomized, multicenter, double-blind, placebo-controlled Phase II study of the efficacy and safety of trastuzumab emtansine (3.6 mg/kg IV Q3W) in combination with atezolizumab (1200 mg IV Q3W) or trastuzumab emtansine plus placebo in patients with HER2-positive LABC or MBC who have received prior trastuzumab and taxane-based therapy. A total of 202 patients have been randomized to study treatment in a 2:1 ratio. Based on the primary efficacy endpoint of PFS, as determined by investigator-assessed Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), the study did not demonstrate a statistically significant benefit from the addition of atezolizumab to trastuzumab emtansine in the intent-to-treat (ITT) population. The stratified PFS HR was 0.82 (95% CI: 0.55 to 1.23), and p-value was 0.3332, with a median PFS of 8.2 months (95% CI: 5.8 to 10.7 months) for the treatment arm versus 6.8 months (95% CI: 4.0–11.1 months) for the control arm. However, in the exploratory analysis of the PD-L1 immune cell-positive subgroup, the stratified HR was 0.60 (95% CI: 0.32–1.11) with a median PFS of 8.5 months (95% CI: 5.7 months to non-evaluable) for the treatment arm versus 4.1 months (95% CI: 2.7 to 11.1 months) for the control arm, suggesting a potential benefit for this patient subgroup (Emens et al. 2019b).

The ORR as assessed by investigator using RECIST v1.1 was similar between the treatment arms (43.5% vs. 45.5%). Of the 69 patients with measurable disease at baseline in the trastuzumab emtansine plus placebo arm, 36.2% had a partial response (PR) and 7.2% had a complete response (CR). Of the 132 patients with measurable disease at baseline in the trastuzumab emtansine plus atezolizumab arm, 39.4% had a PR and 6.1% had a CR. The DOR data based on investigator assessment in both arms were immature at the primary cancer-related causes of death with low event rates in

each arm (26.7% in the trastuzumab emtansine plus placebo arm vs. 28.3% in the trastuzumab emtansine plus atezolizumab arm). The median DOR was not reached.

At a second planned analysis (Emens et al. 2019a) with at least 18 months of follow-up in the ITT population, the median OS was not reached in either arm, but numerically favored the trastuzumab emtansine plus atezolizumab arm. One-year survival was 89.1% versus 89.0% (stratified HR = 0.74; 95% CI: 0.42 to 1.30) in the trastuzumab emtansine plus atezolizumab and trastuzumab emtansine plus placebo arms, respectively. In PD-L1–selected patients, 1-year survival rates were higher with trastuzumab emtansine plus atezolizumab as compared with trastuzumab emtansine plus placebo (94.3% vs. 87.9%; stratified HR = 0.55; 95% CI: 0.22 to 1.38). All biomarkers of T-cell activation and quantity were enriched in the PD-L1–selected subgroup. This included higher expression of PD-L1, Teff signature, and CD8 RNA, as well as greater numbers of tumor-infiltrating lymphocytes (TILs) observed in PD-L1–positive tumors. Overall, the safety profile of the combination was consistent with the known safety profile of each drug. Rate of high-grade adverse events (≥ Grade 3) was 53% versus 45% in the trastuzumab emtansine plus atezolizumab as compared with trastuzumab emtansine plus placebo. Fatal Grade 5 events were similar in the two arms at 1.5% versus 1.5%. Adverse events leading to discontinuation of any study treatment was higher in the in the trastuzumab emtansine plus atezolizumab arm as compared with trastuzumab emtansine plus placebo arm (29% vs. 15%, respectively).

1.3.3 Study TDM4997g/BO25734 (TH3RESA)

Study TDM4997g/BO25734 was a Phase III, randomized, open-label trial to evaluate trastuzumab emtansine compared with TPC (these were approved or standard-of-care therapies based on frequently used regimens) in patients with HER2-positive MBC. Patients had received prior treatments with trastuzumab, lapatinib, and a taxane in any setting, and disease progression occurred after at least two regimens of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting.

The study demonstrated a statistically significant and clinically meaningful improvement in PFS for trastuzumab emtansine compared with TPC. The median PFS was 6.2 months for the trastuzumab emtansine arm and 3.3 months for the TPC arm, with a stratified HR of 0.528 (95% CI: 0.422, 0.661); p = 0.0001. The ORR was 31% for the trastuzumab emtansine arm versus 9% for the TPC arm, resulting in an ORR difference of 22.7% (95% CI: 16.2 to 29.2; p = 0·0001).

At the final OS analysis with a median 30.5 months of follow-up, trastuzumab emtansine demonstrated a clinically meaningful and statistically significant improvement in OS compared with TPC. The median OS improved from 15.8 months (95% CI: 13.5 to 18.7 months) with TPC to 22.7 months (95% CI: 19.4 to 27.5 months) with trastuzumab emtansine. The stratified HR was 0.68 (95% CI: 0.54 to 0.85; p = 0.0007). Despite the longer treatment duration relative to control (4.1 months; [0.03–31.2]), trastuzumab

emtansine (7.9 months [0.03–38]) had a favorable safety profile, which was consistent with prior studies (Krop et al. 2017).

In the updated safety analysis, fewer patients receiving trastuzumab emtansine than those receiving TPC had Grade ≥3 adverse events (40% vs. 47%). The most common Grade ≥3 adverse events (affecting ≥2% of patients in either group) that were more frequent with trastuzumab emtansine included thrombocytopenia (6% vs. 3%) and hemorrhage of any type (4% vs. <1%). Serious adverse events were reported in 25% of patients in the trastuzumab emtansine group and 22% in the TPC group. Deaths from adverse events were reported in 3 patients (2%) in the TPC group (of which 1 death was judged to be treatment related) and 9 patients (2%) in the trastuzumab emtansine group (of which 3 deaths were judged to be treatment related) (Krop et al. 2017).

1.3.4 Study BO27938 (KATHERINE)

Study BO27938 is a multicenter, Phase III, randomized, open-label trial to evaluate patients with HER2-positive EBC who had residual invasive disease after completion of neoadjuvant therapy. At the interim analysis, among 1486 randomly assigned patients (743 in the trastuzumab emtansine group and 743 in the trastuzumab group), invasive disease or death had occurred in 91 patients in the trastuzumab emtansine group (12.2%) and 165 patients in the trastuzumab group (22.2%). The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the trastuzumab emtansine group and 77.0% in the trastuzumab group. Invasive disease-free survival was significantly higher in the trastuzumab emtansine group than in the trastuzumab group (HR for invasive disease or death was 0.50; 95% CI: 0.39–0.64; p<0.001). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the trastuzumab emtansine group and 15.9% of those in the trastuzumab group. The safety data were consistent with the known safety profile of trastuzumab emtansine, with more adverse events associated with trastuzumab emtansine than with trastuzumab alone. As of December 2019, based on the results of the KATHERINE study, trastuzumab emtansine (Kadcyla) was approved in the U.S. and has received recommendation for approval in the E.U. from the Committee for Medicinal Products for Human Use for the adjuvant treatment of patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

1.4 BACKGROUND ON VENETOCLAX

Venetoclax (also referred to as GDC-0199, RO5537382, ABT-199, A-1195425.0, Venclexta®, and Venclyxto®) is an orally bioavailable, selective small-molecule inhibitor of Bcl-2 in the biaryl acylsulfonamide chemical class. Venetoclax binds with high affinity (Ki<0.01 nM) to the anti-apoptotic protein Bcl-2 and with lower affinity to other anti-apoptotic Bcl-2 family proteins such as Bcl-X_L and Bcl-w (>4,000-fold and >2,000- to >20,000-fold lower affinity than to Bcl-2, respectively; Souers et al. 2013). Survival of platelets depends on Bcl-X_L, and thrombocytopenia is therefore a major dose-limiting toxicity (DLT) caused by inhibition of BCL-X_L in the clinic. Venetoclax has an improved

therapeutic index by maintaining efficacy against tumor cells while avoiding dose-limiting thrombocytopenia.

Venetoclax has been extensively studied in oncology, particularly in hematologic malignancies but also in some solid tumors. Efficacy data indicate that venetoclax, both as a monotherapy and in combination with other therapeutic agents, shows promising safety, tolerability, pharmacokinetics, and efficacy. This includes combinations with rituximab; obinutuzumab; bendamustine plus rituximab; O6-benzylguanine; rituxan plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); obinutuzumab plus CHOP (G-CHOP); bortezomib plus dexamethasone, azacitidine, or decitabine; and cytarabine in patients with hematologic malignancies, including CLL/SLL, NHL, MM, myelodysplastic syndrome, and AML.

In the United States, venetoclax (Venclexta®) is indicated for the treatment of adult patients with CLL or SLL. In addition, it is approved in combination with azacitidine or decitabine or low-dose cytarabine (LDAC) for the treatment of adults with newly diagnosed AML who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy. The AML indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

In the European Union, venetoclax (Venclyxto®) in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. Monotherapy is indicated for the treatment of CLL in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

In solid tumors, such as ER-positive, Bcl-2 positive MBC, venetoclax has shown promising activity (Lok et al. 2019). In a Phase Ib dose-escalation study, venetoclax administered at 200, 400, 600, or 800 mg QD in combination with tamoxifen at 20 mg QD was shown to be well tolerated. No DLTs, including Grade ≥3 toxicity, were observed in any of the cohorts and the maximum tolerated dose (MTD) was not reached. The 800 mg QD dose was selected as the recommended Phase II dose (RP2D). Efficacy was promising with 54% ORR and a clinical benefit rate (CBR) of 75% for the 800 mg QD cohort, comparing favorably with historical studies of patients treated with tamoxifen in the first-line relapse setting (e.g., ORR 17%–33% and CBR 38%–56%).

The combination of venetoclax plus hormonal therapy (fulvestrant) in ER-positive MBC is being further evaluated in the ongoing randomized Phase II Study WO40181 (VERONICA). Study results will be reported in the Venetoclax Investigator's Brochure(s) when available.

Refer to the Venetoclax Investigator's Brochure(s) for details on nonclinical and clinical studies.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Trastuzumab emtansine is an active regimen and the standard of care in second-line HER2-positive MBC (Verma et al. 2012). The safety of trastuzumab emtansine is well established, having been evaluated in over 2000 patients with BC in clinical studies. Trastuzumab emtansine is generally well tolerated, with the most common adverse events being nausea, fatigue, and headache. Adverse events of particular relevance include thrombocytopenia, hemorrhage, hepatotoxicity (increases in serum transaminases and nodular regenerative hyperplasia [NRH] of the liver), infusion related-reactions/hypersensitivity, cardiac dysfunction (left ventricular dysfunction), peripheral neuropathy, and pulmonary toxicity (interstitial lung disease [ILD].

Venetoclax has been evaluated in a variety of oncological indications, particularly in hematological malignancies, and has been generally well tolerated as a single agent as well as in combination with targeted therapies and chemotherapy (refer to the Venetoclax Investigator's Brochure for more details). Adverse events commonly observed with venetoclax include nausea, vomiting, diarrhea, and myelotoxicity (including anemia, thrombocytopenia, and leukopenia). To date, the majority of these adverse events have been manageable without requiring treatment discontinuation. Important identified risks for venetoclax include tumor lysis syndrome (TLS), particularly in CLL and mantle cell lymphoma, and neutropenia. Serious infection is also an identified risk. Of note, cytopenias and TLS are commonly observed in hematologic malignances and in some cases independently of treatment, and their prevalence in solid tumors remains to be elucidated.

Nonclinical data indicate a potential synergistic mechanism of action between venetoclax and trastuzumab emtansine. Microtubule inhibitors, such as taxanes and vinca alkaloids, have been described to promote degradation of the anti-apoptotic protein MCL-1 (Wertz et al. 2011), which can be a resistance factor for venetoclax monotherapy (Bose et al. 2017). The mechanism of DM1 inhibition of microtubules is similar to that of vinca alkaloids and, as such, DM1 also induces degradation of MCL-1 (Genentech unpublished data). Direct inhibition of MCL-1 in combination with venetoclax has been shown to be synergistic nonclinically across various hematologic and solid tumor malignancies (Phillips et al. 2015; Li et al. 2019; Moujalled et al. 2019). These nonclinical data support the investigation of venetoclax with combination partners that inhibit MCL-1, either directly or indirectly, and provide scientific rationale to test the combination of trastuzumab emtansine (via MCL-1 degradation) and venetoclax. Further, Bcl-2 upregulation has been associated with resistance to trastuzumab emtansine in various BC cell lines (unpublished data; Saatci et al. 2018). Combining venetoclax with trastuzumab emtansine was shown to enhance apoptosis in vitro compared to single agent treatments in these trastuzumab emtansine–resistant cell lines

(Genentech unpublished data). The combination of trastuzumab emtansine and venetoclax has been tested in vivo in trastuzumab emtansine naive and resistant models, and the results of the data are summarized as follows (Genentech unpublished data):

- In the MDA-MB-361 HER2-positive trastuzumab emtansine naive–BC xenografts grown orthotopically in NOD-SCID mice, trastuzumab emtansine administered intravenously once in combination with venetoclax administered PO QD for 21 days demonstrated enhanced tumor growth inhibition (TGI) compared to trastuzumab emtansine or venetoclax monotherapy. TGI on Day 21 of the dosing period was 38% for trastuzumab emtansine, 34% for venetoclax, and 70% for the combination of trastuzumab emtansine and venetoclax.
- KPL-4 trastuzumab emtansine–resistant cell line clones were generated to be trastuzumab emtansine resistant in vitro through long-term drug treatment. KPL-4 clones 8 and 17 demonstrated upregulation of Bcl-2 protein at resistance. The combination of trastuzumab emtansine and venetoclax showed enhanced anti-tumor efficacy for both clones when grown orthotopically as xenografts in NOD-SCID mice. Trastuzumab emtansine was administered once intravenously and venetoclax was administered PO QD for 21 days. For KPL-4 clone 17, TGI on Day 21 of the dosing period was 27% for trastuzumab emtansine, 3% for venetoclax, and 74% for the combination of trastuzumab emtansine and venetoclax. For KPL-4 clone 8, TGI 2 days after end of treatment (Study Day 23) was 93% for trastuzumab emtansine, 8% for venetoclax, and 143% for the combination of trastuzumab emtansine and venetoclax.

Importantly, in vivo assessment of altering venetoclax schedules dosed for either 10 or 21 consecutive days has demonstrated equivalent anti-tumor efficacy when administered in combination with trastuzumab emtansine (Genentech unpublished data). Furthermore, a shorter schedule of venetoclax dosing (5 continuous days) was also shown to improve responses in combination with trastuzumab emtansine in HER2-positive BC PDX models that are sensitive as well as resistant to trastuzumab emtansine (unpublished data). In separate studies using additional HER2-positive PDX models, inhibition of Bcl-2 and Bcl-X_L with navitoclax (ABT-263) significantly enhanced cytotoxicity of trastuzumab emtansine (Zoeller et al. 2019). The nonclinical data cited herein provide rationale for testing continuous and non-continuous schedules of venetoclax in combination with trastuzumab emtansine. Therefore, this study will offer an opportunity to evaluate the safety and activity of a promising novel approach combining venetoclax and trastuzumab emtansine for the treatment of HER2-positive MBC in the clinical setting.

The safety and tolerability of the combination of trastuzumab emtansine and venetoclax is currently unknown and will be evaluated in the Phase Ib portion of this study. Although the combination is expected to have limited overlapping toxicities, there remains the potential for unknown toxicities. Key overlapping toxicities for the combination include hematologic toxicities, such as neutropenia, febrile neutropenia, thrombocytopenia, and gastrointestinal toxicities (e.g., nausea, vomiting, diarrhea).

To minimize this risk, stringent inclusion and exclusion criteria (Sections 4.1.1 and 4.2.2) and close safety monitoring (Section 5.1), together with rules for dose modifications and safety management guidelines for known risks of single-agent trastuzumab emtansine and venetoclax, have been implemented in the current study. Furthermore, guidance on management of potential overlapping toxicities is described in Section 5.1.3.3. Specifically, during the Phase Ib portion of this study, safety review will be led by the Medical Monitor in consultation with the study investigators and a committee composed at a minimum of the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist. During the randomized Phase II stage of the study, an Internal Monitoring Committee (IMC; Section 3.1.4) has also been incorporated into the trial design to periodically review aggregate efficacy and safety data (refer to the IMC charter for a detailed monitoring plan).

HER2-positive MBC remains an incurable disease despite advances in patient care. Nearly all patients with HER2-positive MBC will eventually suffer disease progression and succumb to their disease. There continues to be a need for more efficacious therapies with acceptable safety profiles in patients with HER2-positive disease. Therefore, the addition of venetoclax based on its pro-apoptotic mechanism of action and potential to overcome resistance to trastuzumab emtansine, as well as a manageable safety profile, can represent a potential valuable treatment option and offers a favorable benefit–risk balance for patients in this study.

2. OBJECTIVES AND ENDPOINTS

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the “randomized Phase II stage”).

The dose-escalation phase will assess safety and tolerability, determine the MTD and the RP2D, and evaluate preliminary efficacy of trastuzumab emtansine in combination with venetoclax in patients with previously treated HER2-positive LABC or MBC, irrespective of patients' prior trastuzumab emtansine exposure in the metastatic setting.

After the RP2D is established, additional patients may be enrolled in the expansion phase to evaluate the safety, tolerability, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D in patients with previously treated HER2-positive LABC or MBC who have previously received either trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a). The decision to open these cohorts will be data-driven and dependent on the observations made in the dose-escalation phase, as well as emerging data about trastuzumab deruxtecan and other HER2-targeted therapies. Importantly, the expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

The randomized Phase II stage will aim to evaluate the safety, tolerability, pharmacokinetics, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D compared with trastuzumab emtansine plus placebo in patients with previously treated HER2-positive LABC or MBC who have not received prior trastuzumab emtansine therapy, either alone or in combination with other anticancer therapies.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 OBJECTIVES AND ENDPOINTS FOR DOSE-ESCALATION PHASE

2.1.1 Primary Safety Objective

The safety objective for the dose-escalation phase is to evaluate the safety and tolerability of trastuzumab emtansine in combination with venetoclax—including estimation of the MTD, determination of the RP2D, and characterization of DLTs (see Section 3.1.1.1)—on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.1.2 Exploratory Efficacy Objective

The exploratory efficacy objective for the dose-escalation phase is to make a preliminary assessment of the anti-tumor activity of trastuzumab emtansine and venetoclax on the basis of the following endpoints:

- ORR, defined as the proportion of patients with CR or PR on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using RECIST v1.1 (see Appendix 11)
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first

2.1.3 Pharmacokinetic Objective

The PK objective for the dose-escalation phase of this study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

2.1.4 Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue (see Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.2 OBJECTIVES AND ENDPOINTS FOR EXPANSION PHASE

2.2.1 Primary Efficacy Objective

The primary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- ORR

2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- DOR

2.2.3 Safety Objective

The safety objective for the expansion phase is to evaluate the safety and tolerability of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.2.4 Pharmacokinetic Objective

The PK objective for the expansion phase of the study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

2.2.5 Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue (see Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.3 OBJECTIVES AND ENDPOINTS FOR RANDOMIZED PHASE II STAGE

2.3.1 Primary Efficacy Objective

The primary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following co-primary endpoints:

- ORR
- PFS after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

2.3.2 Secondary Efficacy Objective

The secondary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- DOR

- OS after randomization, defined as the time from randomization to death from any cause

2.3.3 Exploratory Efficacy Objective

The exploratory efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- CBR, defined as the proportion of patients with CR, PR, or stable disease (SD) at 6 months after randomization, as determined by the investigator according to RECIST v1.1

2.3.4 Safety Objective

The safety objective for the randomized Phase II stage is to evaluate safety of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Incidence and severity of adverse events with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3.5 Pharmacokinetic Objective

The PK objective for the randomized Phase II stage of this study is to characterize the pharmacokinetics of trastuzumab emtansine and venetoclax when given in combination on the basis of the following endpoints:

- Serum concentrations of trastuzumab emtansine at specified timepoints
- Plasma concentrations of venetoclax at specified timepoints

2.3.6 Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to trastuzumab emtansine when given with placebo or in combination with venetoclax on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.3.7 Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- The relationship between biomarkers in blood, plasma, and tumor tissue (see Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.3.8 Health Status Utility Objective

The exploratory health status utility objective for the randomized Phase II stage is to evaluate health status utility scores of patients treated with trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoint:

- Change from baseline in patient-reported symptoms and their impact on functioning and health-related quality of life as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and EORTC Item List 46 (EORTC IL46)

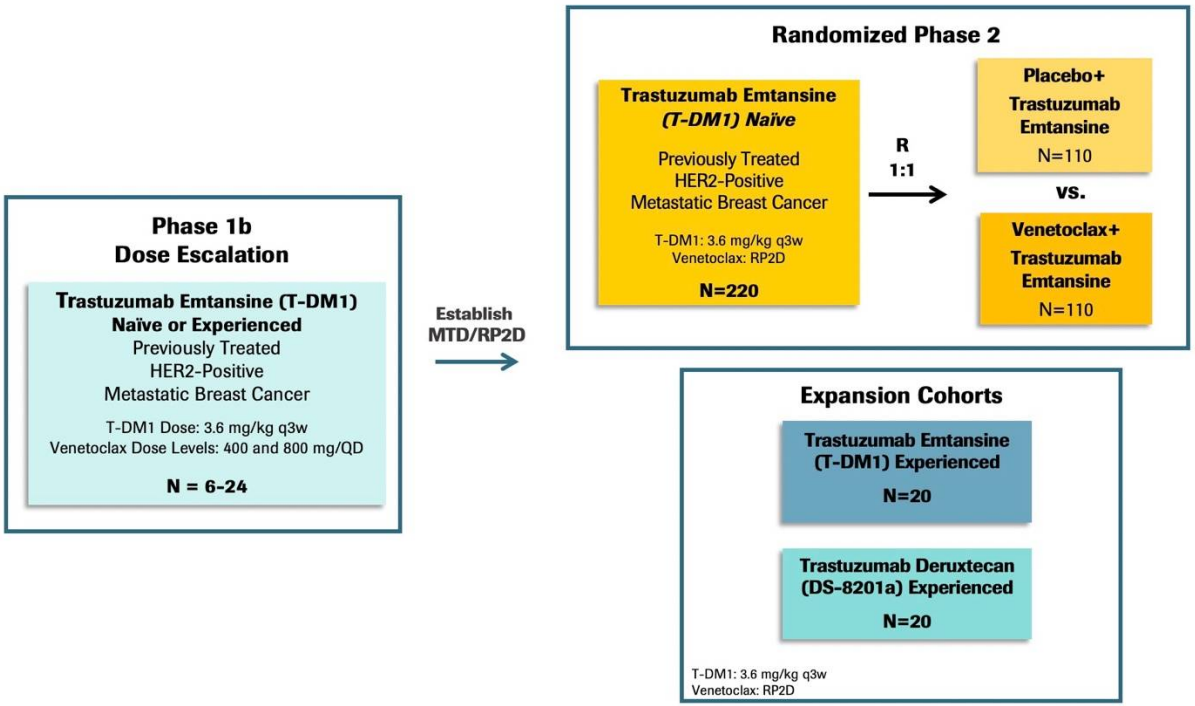
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the “randomized Phase II stage”). The expansion phase may run concurrent to and parallel with the randomized Phase II stage.

Approximately 226–284 patients will be enrolled in this study across approximately 145 sites globally. The study will enroll 6–24 patients in the Phase Ib dose-escalation phase and approximately 220 patients in the Phase II stage. An additional approximately 20–40 patients may be enrolled in the Phase Ib expansion cohorts.

Figure 1 Overall Study Schema



2L = second line; 3L = third line; MBC = metastatic breast cancer; MTD = maximum tolerated dose; Q3W = every 3 weeks; QD = once a day; RP2D = recommended Phase II dose.

3.1.1 Dose-Escalation Phase

The dose-escalation phase will determine the RP2D and MTD for venetoclax when given in combination with a fixed dose of trastuzumab emtansine (3.6 mg/kg) in patients with previously treated, HER2-positive LABC or MBC, irrespective of prior trastuzumab emtansine exposure in the metastatic setting.

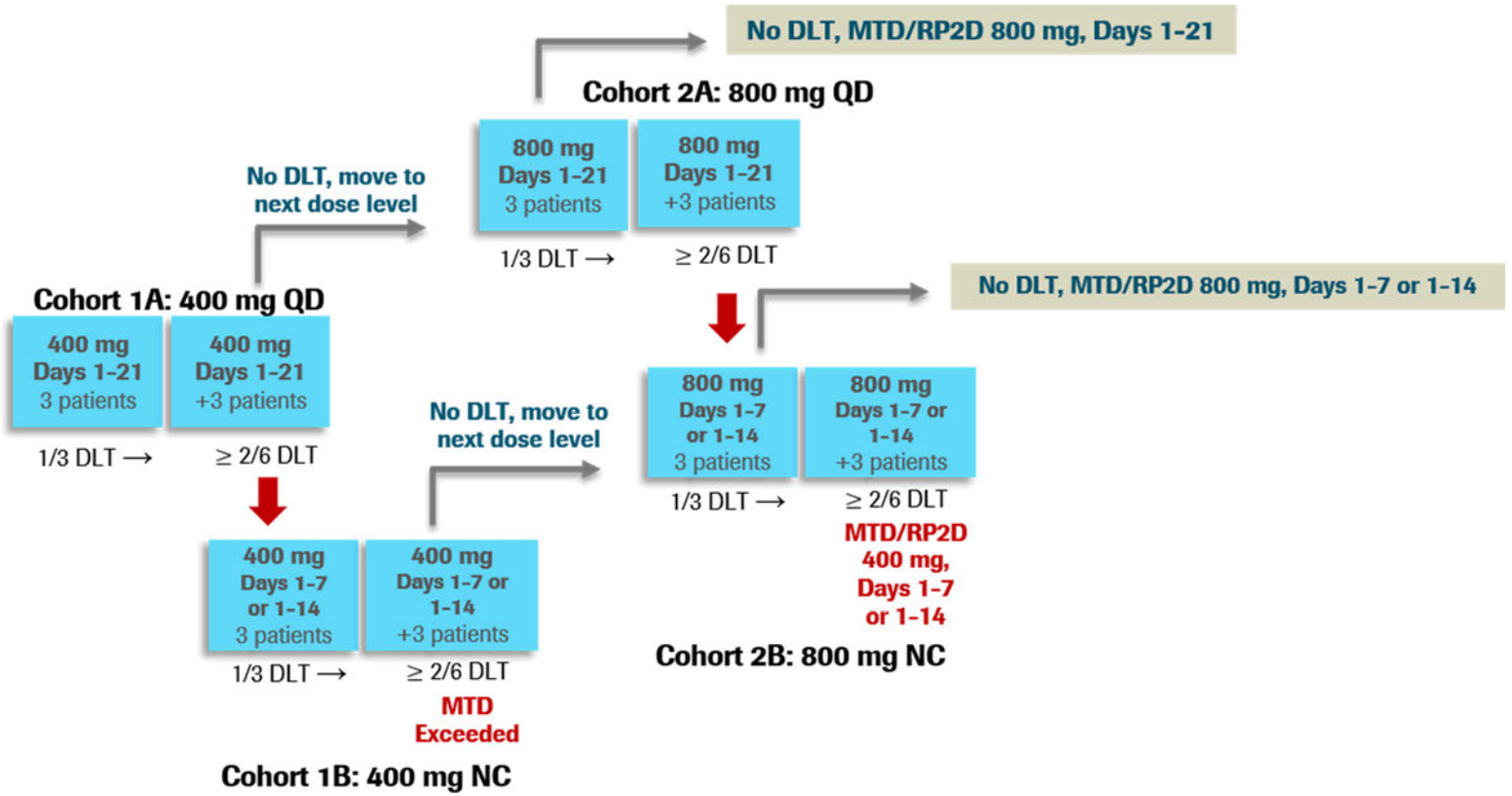
The dose-escalation phase will enroll 6–24 patients and will include 2–4 cohorts:

- Cohort 1A, 400 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 400 mg PO once a day (QD) continuous on Days 1–21 of each cycle.
- Cohort 1B, 400 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 400 mg PO QD non-continuous on either Days 1–7 or 1–14 of each cycle (see further description below).
- Cohort 2A, 800 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD continuous on Days 1–21 of each cycle.
- Cohort 2B, 800 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD non-continuous on either Days 1–7 or 1–14 of each cycle.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. The investigator will record reasons for screen failure within the interactive voice or web-based response system (IxRS) and electronic Case Report Form (eCRF [see Section 4.5.1]).

Figure 2 presents an overview of the dose-escalation phase design. A schedule of activities for dose-escalation and expansion phases are provided in Appendix 1 and Appendix 2, respectively.

Figure 2 Phase Ib Dose-Escalation Study Schema



DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NC=non-continuous; QD = once a day; RP2D = recommended Phase II dose.

The 400-mg and 800-mg cohorts for dose escalation will be run sequentially (i.e., the 400-mg cohort followed by the 800-mg cohort). Dose escalation will be performed based on a standard 3 + 3 design. Each cohort will consist of at least 3 patients, unless 1 of the 3 patients experiences DLTs (refer to Section 3.1.1.1 for DLT criteria), in which case 3 additional patients will be treated at the same dose level. The dose escalation will continue until 2 patients among a cohort of 6 patients experience a DLT (i.e., ≥33% of patients with a DLT at that dose level; refer to dose-escalation rules below). Patients who experience a DLT will continue at the same dose level.

Dose de-escalation may be explored by incorporating non-continuous (NC) dosing of venetoclax (e.g., less than 21 days of dosing, such as 7 days out of 21 days or 14 days out of 21 days) dependent on the severity and timing of DLTs as well as the specific adverse events encountered. For example, if DLTs such as a Grade 3 rash occurred between Day 8 and Day 14, an NC schedule of Days 1–7 would be tested. Alternatively, if DLTs are thought to be possibly mitigated by a 7-day break such as Grade 3 fatigue occurring near the end of the DLT window (e.g., Day 20), then an NC schedule of Days 1–14 could be chosen to be tested. Patients may be treated in up to two NC sub-cohorts (i.e., either 400 mg NC and/or 800 mg NC; refer to Figure 2). At each dose de-escalation level, either a Days 1–7 or Days 1–14 NC treatment schedule will be assessed.

3.1.1.1 Definition of Dose-Limiting Toxicity

Patients will be closely monitored for adverse events during the 21-day DLT assessment window. All adverse events, including DLTs, will be graded according to the NCI CTCAE v5.0 (Appendix 12) unless otherwise indicated. If a patient experiences a DLT, the patient will be treated according to clinical practice and will be monitored for resolution of the toxicity.

For dose-escalation purposes, a DLT will be defined as any one of the following events regardless of relationship to study treatment (unless otherwise specified below) occurring during the 21-day DLT assessment period, which runs from Days 1–21 of Cycle 1:

- Grade 4 neutropenia (ANC < 500/mm^3) lasting > 7 days
- Grade 4 thrombocytopenia (platelet count < 25,000/mm^3) or Grade 3 thrombocytopenia associated with severe bleeding
- Grade 4 anemia
- Grade 3 febrile neutropenia for > 7 days or Grade 4 febrile neutropenia of any duration
- Treatment related Grade ≥ 3 non-hematologic, non-hepatic, and non-cardiac major organ toxicity lasting for ≥ 72 hours
- Grade ≥ 3 serum bilirubin, hepatic transaminase (ALT or AST), or ALP lasting for ≥ 72 hours

For patients with Grade 2 hepatic transaminase or ALP levels at baseline as a result of liver metastases or bone metastases, a hepatic transaminase or ALP level ≥ 10 times the upper limit of normal (ULN) will be considered a DLT. For patients with abnormal TBILI at baseline an increase of >3.0–10.0 times baseline value will be considered a DLT.

- Grade ≥3 cardiac toxicity (resting ejection fraction [EF] 39%–20%; ≥20% drop from baseline; symptomatic heart failure)
- Treatment-related death

Adverse events meeting the criteria for DLT within the 21-day assessment period must be reported to the Sponsor within 24 hours.

3.1.1.2 Dose-Escalation Rules, Determination of Dose-Limiting Toxicities, and Recommended Phase II Dose

Dose escalation will occur in accordance with the rules listed below:

- A minimum of 3 DLT-evaluable patients will initially be enrolled into each cohort.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.
- If 2 or more of the first 6 DLT-evaluable patients in the continuous (QD) dose-escalation cohorts experience a DLT, an additional 3 patients will be evaluated for DLTs at the corresponding NC dose level. If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next NC dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the NC dose level cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.
- If 2 or more of the first 6 DLT-evaluable patients in the NC dose-escalation cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., ≥33%) experience a DLT will be declared the MTD.
- If the MTD is not exceeded at any dose level, the highest dose administered in this study will be declared the MTD.

Determination of whether a patient is evaluable for DLT assessment will be made in accordance with the following rules:

- Patients who receive study treatment (e.g., at least 66% of planned venetoclax doses and 1 dose of trastuzumab emtansine) and remain in the study through the DLT assessment window will be considered DLT evaluable.

- Patients who discontinue from treatment with trastuzumab emtansine or venetoclax treatment prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination and will be replaced by an additional patient at that same dose level.
- Patients who do not receive at least 66% of planned venetoclax doses (e.g., 14 out of 21 days for continuous [QD] dosing, 10 out of 14 days for Days 1–14 NC, or 5 out of 7 days for Days 1–7 NC) or 1 dose of trastuzumab emtansine during the DLT assessment period will be replaced, to ensure that at least 3 patients in each cohort have been assessed for the full DLT assessment period of 21 days prior to moving to the next dose level.

Patients exhibiting acceptable safety and evidence of clinical benefit (as determined by the investigator) may continue to receive study treatment until confirmed objective disease progression or unacceptable toxicity, whichever occurs first.

The Sponsor will review cumulative safety data and make recommendations regarding dose escalation and overall study conduct on the basis of study safety data to ensure patient safety while receiving study treatment. These include recommendations to open or suspend patient enrollment in a given dose-escalation cohort based on the overall benefit–risk profile of trastuzumab emtansine in combination with venetoclax.

Relevant demographic, adverse event, laboratory, dose administration, and PK data (if available) will be reviewed prior to the selection of the RP2D for the expansion and randomized phases of the study. The RP2D for both the expansion and randomized phases will be the same dose and schedule. The RP2D will be based on the MTD of venetoclax when combined with a fixed dose of trastuzumab emtansine and will integrate aggregate safety data during treatment. Decision making will be led by the Medical Monitor in consultation with the study investigators and a committee composed at a minimum of the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist. For example, based upon nonclinical data showing similar efficacy of NC versus continuous dosing, as well as the mechanism of action of combining venetoclax with a cytotoxic agent such as trastuzumab emtansine, NC dosing of 800 mg for 1–7 days or 1–14 days would be preferred over 400 mg QD. Aggregate clinical data would be integrated into the decision making, including safety and efficacy data.

3.1.2 Expansion Phase

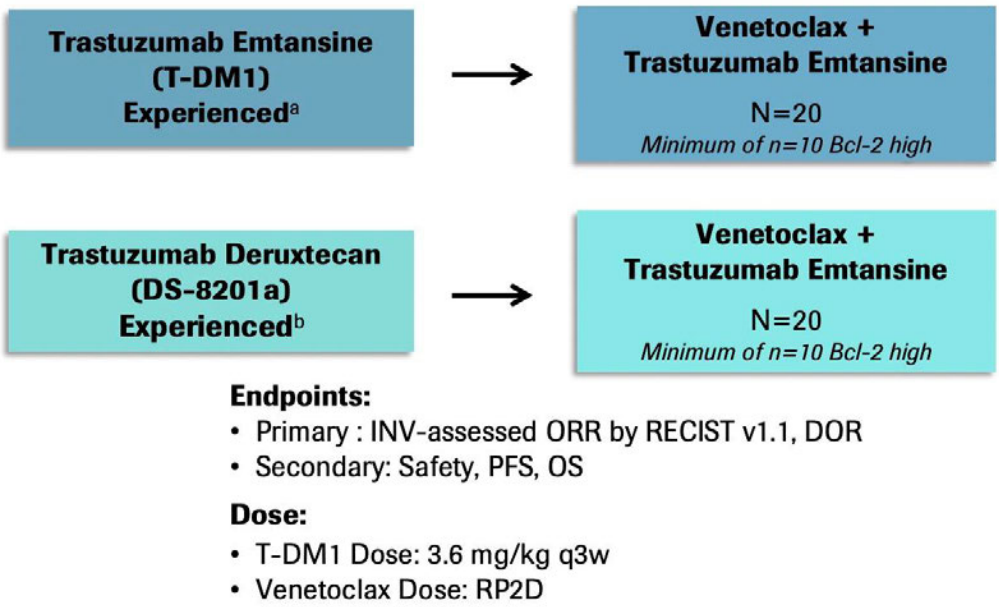
An expansion phase may be initiated to evaluate the safety, tolerability, and efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine in previously treated HER2-positive locally advanced or MBC patients who have received prior trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a).

The decision to open cohorts as part of an expansion phase will be data-driven and dependent on the observations made in the dose-escalation phase, emerging data with

trastuzumab deruxtecan, as well as other HER2-targeted therapies. The expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

Approximately 20 patients may be enrolled in each of the expansion cohorts (see Figure 3).

Figure 3 Phase Ib Expansion Cohorts Study Schema



Bcl-2 = B-cell lymphoma 2; DOR = duration of response; IHC = immunohistochemistry; INV = investigator; MBC = metastatic breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RP2D = recommended Phase II dose.

[a] Prior exposure to other HER2-targeted therapies (e.g., trastuzumab, pertuzumab, trastuzumab deruxtecan, margetuximab, pyrotinib, tucatinib and/or neratinib) is permitted.

[b] Eligibility for this cohort requires prior experience with trastuzumab deruxtecan (DS-8201a) in any setting.

3.1.3 Randomized Phase II Stage

The randomized Phase II stage will be initiated once the RP2D has been identified based on the cumulative data collected from the dose-escalation phase. It will consist of two interventional arms of trastuzumab emtansine plus placebo or trastuzumab emtansine plus venetoclax in patients with previously treated HER2-positive LABC or MBC, who have not received prior trastuzumab emtansine therapy.

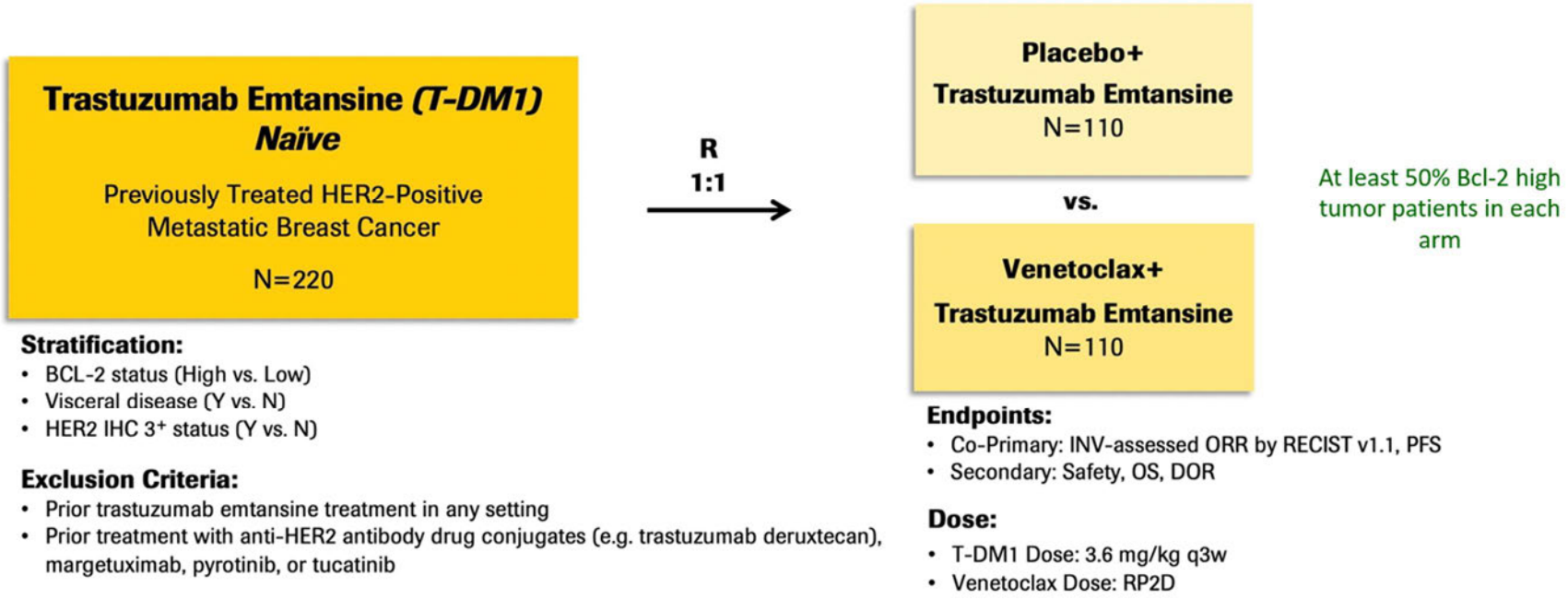
Approximately 220 patients will be randomized 1:1 to one of the following treatment arms:

- Control Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus placebo at the RP2D and schedule of venetoclax.

- Experimental Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus venetoclax at the RP2D and schedule.

Each arm will include at least 50% Bcl-2 high patients, and randomization will be based on the three stratification factors shown in Figure 4 (see also Section 4.2.1). Crossover between treatment arms will not be permitted. A schedule of activities for the randomized phase is provided in Appendix 2.

Figure 4 Phase II Randomized Study Schema



2L = second line; Bcl-2 = B-cell lymphoma 2; DOR = duration of response; IHC = immunohistochemistry; INV = investigator; N = no; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; R = randomization; RP2D = recommended Phase II dose; Y = yes.

3.1.4 Internal Monitoring Committee for the Randomized Phase II Stage

An IMC will be established to monitor patient safety as well as efficacy in the randomized Phase II stage of the study. The IMC will not be blinded, will help monitor safety of enrolled patients, and will conduct periodic interim reviews of safety data during the randomized Phase II stage of the study. The frequency of the reviews will be determined as needed. The IMC will be external to the study team and will be composed of at least one medical doctor and/or clinical science representative, with representatives from clinical safety, biostatistics, as well as statistical programming and analysis, who are not directly involved in the study. A separate IMC charter will outline the committee's composition, meeting timelines, and members' roles and responsibilities. The committee members will review all potential cases of serious adverse events, Grade 3 and 4 adverse events, adverse events of special interest, and deaths as specified in the IMC charter. The IMC will be apprised of all relevant efficacy and safety data from this study and other related clinical trials. Ad hoc meetings may be called as necessary in addition to scheduled meetings to provide recommendations on management of any new safety issues. The Sponsor will be the final decision maker regarding protocol procedures and modifications.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of study is planned to occur approximately 24 months after last patient in (LPI).

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Venetoclax Dose Selection in the Phase Ib Dose-Escalation Phase of the Study

Venetoclax has been investigated and shown to be well tolerated in multiple trials of hematopoietic malignancies at doses ranging from 200 mg to 1200 mg, both as a monotherapy and in combination with other agents including dexamethasone, rituximab, obinutuzumab, bortezomib, and chemotherapy. Venetoclax is approved in the U.S. and E.U. for the treatment of adult patients with CLL (or SLL in the U.S.), with or without 17p deletion, who have received at least one prior therapy. The recommended dose of venetoclax monotherapy in this setting is 400 mg QD in a ramp-up schedule (Venclexta® U.S. Package Insert) and this dosing is maintained during administration with rituximab. Venetoclax is also approved in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML, with 400 mg QD dosing when in

combination with azacitidine or decitabine and 600 mg QD dosing when in combination with LDAC in the U.S.

A Phase I dose-escalation trial investigating combinations of various doses of venetoclax (including 200 mg, 400 mg, 600 mg, and 800 mg) with tamoxifen assessed the safety and tolerability of venetoclax in combination with that ER modulator in patients with ER+, Bcl-2+ MBC (Lok et al. 2019). Venetoclax at the dose of 800 mg PO QD in combination with tamoxifen was well tolerated. The nature and frequencies of adverse events were consistent with the known safety profiles of venetoclax and tamoxifen, and no Grade 5 adverse events or DLTs occurred during the DLT observation period, based on the preliminary evidence of clinically relevant activity of venetoclax during the dose-escalation phase. Venetoclax dosing is further informed by the ongoing randomized Phase II VERONICA study (WO40181) evaluating venetoclax at 800 mg QD plus fulvestrant in patients with HR-positive MBC.

Based on the experience in hematologic malignancies as well as ER+ BC, and the expected limited overlapping toxicities and potential for drug–drug interactions (DDI) between venetoclax and trastuzumab emtansine (see Section 3.3.11), two dose levels have been selected for the dose-escalation phase of the study. This is based on population PK and saturation modeling to assess dose dependency of venetoclax exposure with the assumption that CLL/DLBCL modeling can adequately predict solid tumors. This modeling has shown limited value of studying a 600 mg dose of venetoclax as an intermediate step in a 400 mg to 800 mg dose escalation (internal Genentech data). Moreover, the toxicities are considered to be monitorable and manageable, and enabling a starting dose of 400 mg continuous QD and moving up to the second dose level of 800 mg continuous QD (refer to Section 3.1.1).

Patients with solid tumors may require a higher dose of venetoclax when compared with the 400 mg QD dose in hematologic malignancies such as CLL. This is reflected in the lower 50% effective concentration values of venetoclax for circulating lymphocyte counts (0.00863 μg/mL) compared with tumor size (0.146 μg/mL; Freise et al. 2017). Possible explanations for this observation include reduced blood flow and subsequent less efficient delivery of systemic venetoclax within a tumor, and altered signaling interactions between lymphoma cells and the cells of the tumor microenvironment. Therefore, a second dose level of 800 mg continuous QD is being evaluated, allowing for increased exposure of venetoclax in the tumor compartment.

3.3.2 Rationale for Venetoclax Dose Selection in the Phase II Randomized Portion of the Study

The dose-escalation phase will provide further information on the venetoclax dose that is considered safe and tolerable to be combined with trastuzumab emtansine. The venetoclax RP2D and MTD for the combination with trastuzumab emtansine, which will be the same for both the expansion and randomized phases, will be determined based on the dose-escalation phase of the study (see Section 3.1.1). The RP2D may be lower

than the MTD, dependent on the evaluation of the cumulative and aggregated data from the dose-escalation phase of the study. An IMC will conduct periodic reviews of safety data for all patients treated in the randomized Phase II stage of the study in order to confirm the safety and tolerability of the combination therapy at the RP2D (see Section 3.1.4).

3.3.3 Rationale for Trastuzumab Emtansine Dose and Schedule

The globally approved and standard-of-care regimen of trastuzumab emtansine is 3.6 mg/kg Q3W, as confirmed in Study TDM4370g/BO21977 (Verma et al. 2012), the pivotal Phase III trial comparing trastuzumab emtansine to lapatinib plus capecitabine in patients with HER2+ MBC who were previously treated with trastuzumab and a taxane.

3.3.4 Rationale for Dose-Finding Rules

The rules for dose escalation are designed to ensure patient safety while providing an opportunity to identify the optimal venetoclax dose and schedule in combination with trastuzumab emtansine to maximize the benefit–risk profile of the combination. Key elements of dose escalation based on a standard 3+3 design are described in Section 3.1 and depicted in Figure 2.

Rules based on the nature and timing of observed safety events have been implemented.

3.3.5 Rationale for Dosing Schedule

Given the anticipated limited overlapping toxicities between venetoclax and trastuzumab emtansine (Section 5), continuous dosing of venetoclax on a 21-day cycle based on the trastuzumab emtansine infusion schedule is being evaluated initially. NC 7- or 14-day schedules may be evaluated based on the severity and timing of occurrence of adverse events experienced.

3.3.6 Rationale for Patient Population

Clinical benefit with trastuzumab emtansine has been demonstrated in a randomized study to improve PFS and OS compared to lapatinib plus capecitabine, for patients with HER2-positive MBC who have received prior trastuzumab or taxane (Verma et al. 2012). Trastuzumab emtansine is the standard of care in this population; however, the PFS of approximately 8.6 months and OS of approximately 30 months for this patient population represent a continued unmet medical need. Despite advances in care for patients with HER2-positive MBC, it remains an incurable disease. Nearly all patients with HER2-positive MBC will eventually suffer disease progression and succumb to their disease. Thus, there is still a pressing need for more efficacious therapies with acceptable safety profiles in patients with HER2-positive disease.

3.3.7 Rationale for Control Group

This control arm treatment is recognized as the recommended standard of care for HER2-positive MBC based on the results from Study TDM4370g/BO21977 (see

Section 1.2) (Verma et al. 2012). Trastuzumab emtansine has become widely accepted as the standard of care in patients who have been previously exposed to trastuzumab alone or trastuzumab and a taxane, which is the patient population being studied in the current trial (Cardoso et al. 2018; NCCN 2019). The control arm data will be used to ascertain the individual contribution of venetoclax to efficacy with trastuzumab emtansine.

3.3.8 Rationale for Randomization and Blinding

Randomization will minimize differences between treatment groups at the outset of the trial and blinding will help prevent differential treatment of the groups later in the trial or the differential assessment of outcomes. Both randomization and blinding will mitigate bias and will aid to minimize the likelihood of differential treatment or assessments of outcomes.

3.3.9 Rationale for Objective Response Rate and Progression-Free Survival as Co-Primary Endpoints for the Randomized Phase II Stage

Investigator-assessed ORR by RECIST v1.1 and PFS are the co-primary endpoints for this study.

ORR (as defined in Section 2.1.1) is an increasingly important endpoint for accelerated development of highly active anticancer therapies. Investigator-assessed ORR by RECIST v1.1 has been shown to be a meaningful trial endpoint correlating well with PFS and OS endpoints (Oxnard et al. 2016). In this patient population, ORR has been used as an early signal of clinical benefit (Verma et al. 2012, Tamura et al. 2019). Therefore, for this study ORR will be used alongside PFS as a measure of the individual contribution of venetoclax to efficacy with trastuzumab emtansine. The clinical significance of the ORR will be assessed by the magnitude and duration of response.

PFS is the standard and accepted endpoint reflecting clinical benefit in HER2-positive MBC. PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends upon the magnitude of the effect and the benefit-risk of the new treatment compared with available therapies (FDA 2007; EMA 2017).

To ensure the validity of investigator-assessed PFS as the primary endpoint, a number of measures have been implemented: a substantial target magnitude of benefit and study assessments that will allow a robust evaluation of benefit–risk. This includes conventional criteria using RECIST v1.1 to define radiographic disease progression with fixed assessment intervals that are identical in both treatment arms, a robust definition of PFS as well as prospectively defined methods to assess, quantify, and analyze PFS, including sensitivity analyses.

3.3.10 Rationale for Pharmacokinetic Assessments

This is the first study for which venetoclax will be given in combination with trastuzumab emtansine to patients with MBC. Accordingly, PK plasma or serum samples will be taken to characterize the pharmacokinetics of venetoclax and trastuzumab emtansine when given in combination (see Section 4.5.7 for details).

3.3.11 Rationale for Assessments of Drug–Drug Interactions between Study Treatments

The potential for venetoclax to affect trastuzumab emtansine pharmacokinetics is considered to be low. The antibody component of trastuzumab emtansine is a therapeutic protein and therefore is not expected to interact with CYP450 or transporter pathways. The potential for DDIs between venetoclax and DM1, the small molecule component of trastuzumab emtansine, are also expected to be low based on knowledge of the metabolic and transporter pathways for each molecule. Although venetoclax (a P-glycoprotein [P-gp] inhibitor) could potentially affect the pharmacokinetics of DM1 (a P-gp substrate) through a transporter-mediated interaction, the potential for a clinically meaningful effect is considered to be low, given that the DM1 catabolite of IV administered T-DM1 is less likely to be impacted by P-gp inhibition by venetoclax in the gut. Additionally, trastuzumab emtansine will be dosed in the linear PK range for this study, and co-administration of other anticancer agents with trastuzumab emtansine has not impacted trastuzumab emtansine pharmacokinetics (see the Trastuzumab Emtansine Investigator's Brochure). These results suggest that target-mediated clearance does not significantly contribute to the overall systemic clearance of trastuzumab emtansine, suggesting a low potential for venetoclax to impact trastuzumab emtansine PK.

The risk of a clinically significant PK drug interaction for trastuzumab emtansine to alter venetoclax pharmacokinetics is expected to be low on the basis of their metabolic pathways. Venetoclax is primarily metabolized by CYP3A in vitro and is a reversible inhibitor of CYP2C8 and CYP2C9 in vitro. Trastuzumab emtansine is a biologic administered intravenously and is not expected to modulate CYP3A activity and affect venetoclax metabolism.

Based on the evidence provided above, limited blood samples will be collected to characterize the DDI interactions between venetoclax and trastuzumab emtansine when given in combination (see Section 4.5.7 for details).

3.3.12 Rationale for Biomarker Assessments

BC is a heterogeneous disease, and HER2 and Bcl-2 expression have been shown to vary among patients (unpublished data). All patients may not be equally likely to benefit from treatment with venetoclax and trastuzumab emtansine. Predictive biomarker samples (tissue and blood) collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond to venetoclax and trastuzumab

emtansine. PD biomarkers will be assessed to demonstrate evidence of biologic activity of venetoclax and trastuzumab emtansine in patients, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

Currently, there are limited data about the correlation of response to Bcl-2 inhibition in BC and Bcl-2 expression levels. Bcl-2 levels are elevated in ER-positive subgroups relative to the other molecular subgroups that comprise BC. Furthermore, nonclinical data have demonstrated increased antitumor activity in high Bcl-2 expressing BC cell lines (see Section 1.5). Therefore, predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with Bcl-2-driven pathogenesis who are most likely to respond to venetoclax. The study aims to prospectively explore if Bcl-2 expression might have predictive or prognostic value or may be associated with disease progression in the studied population.

Fresh tissue acquisition in some patients with MBC may not be feasible; consequently, assessment of more easily accessible biomarkers in circulation is of high interest. In addition to identification of disease-specific, potentially prognostic, or predictive biomarkers in predose, baseline blood specimens, on-treatment collection of blood to evaluate circulating tumor DNA (ctDNA) may enable identification of biomarkers informing the relationship with established clinical response assessments, the monitoring of disease progression, and the identification of markers of resistance.

Tumor tissue samples will be analyzed through use of IHC to assess protein expression, and/or RNA sequencing to assess gene expression levels. Both tissue and blood samples will be analyzed by next-generation sequencing (NGS) to identify somatic alterations that are predictive of response to study drug, are associated with progression, are associated with acquired resistance to study drug, or can increase the knowledge and understanding of disease biology.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.13 Rationale for Stratification and Enrichment by B-Cell Lymphoma-2 (Bcl-2) Status

Bcl-2 levels are elevated in ER-positive tumors; however, there are scant clinical data demonstrating a pathogenic role for Bcl-2 in HER2-positive BC. Venetoclax specifically inhibits Bcl-2 activity and there is potential that Bcl-2 target-expression levels may

correlate with activity. The role of Bcl-2 in pathogenesis is confounded by the prognostic profile associated with the ER-positive subtype. To distinguish the potential for predictive value of Bcl-2 expression levels with targeted Bcl-2 inhibition, patients will be 1) randomized into venetoclax plus trastuzumab emtansine versus trastuzumab emtansine plus placebo arms to distinguish prognostic effects; and 2) stratified into Bcl-2 high and Bcl-2 low populations (as defined in Section 4.1.1.1).

In nonclinical analyses, elevated Bcl-2 expression levels in NHL cell lines correlate with venetoclax activity using this high versus low cutoff. Stratification will ensure that the relative populations of Bcl-2 high and low are well balanced between both arms and therefore enable evaluation of the correlation between Bcl-2 expression and venetoclax activity in BC. In addition, specifying a minimum number of Bcl-2 high tumor patients will enable evaluation of Bcl-2 status as a potential predictive biomarker. Responses will be evaluated by comparing the two stratified subgroups.

Since a cutoff for Bcl-2 levels in BC has not been established, retrospective analyses may also be performed to evaluate alternative cutoffs.

3.3.14 Rationale for Stratification by Visceral Metastases

The site(s) and degree of metastatic dissemination are among the principal prognostic factors for patients with MBC. Patients with visceral metastases to the liver and/or lung in HER2-positive MBC have been shown to have poor prognosis (Verma et al. 2012; Perez et al. 2017; Emens et al. 2019b). In the KATE2 study (Emens et al. 2019b), patients treated with trastuzumab emtansine plus placebo harboring visceral disease as compared to patients with no evidence of visceral disease performed worse (median PFS 4.3 months vs. NE). Visceral disease was defined as the presence of disease in the lung, liver, adrenal gland, central nervous system, pleural cavity or peritoneal cavity. All locations that included tumors in the breast, bone, bone marrow, lymph nodes, skin and soft tissue were classified as non-visceral disease. Moreover, the proportion of patients with visceral involvement is expected to be higher than those with non-visceral disease (70.8% vs. 29.2%, respectively) in KATE2, further justifying use of visceral disease as a stratification factor.

3.3.15 Rationale for Stratification by HER2 Expression Status

HER2 overexpression is an important prognostic and predictive biomarker in MBC (Pauletti et al. 2000). Specifically, in the recent KATE2 study (Emens et al. 2019b) evaluating trastuzumab emtansine in combination with atezolizumab or atezolizumab and placebo, higher HER2 expression (IHC 3+) and lower HER2 expression (IHC 2+/ISH+) demonstrated different prognosis for trastuzumab emtansine outcome (median PFS: 8 months. vs 3.2 months, respectively). The majority of patients were IHC 3+ (74%) as compared to IHC 2+ (19%). Given the association with variable prognosis as well as differences in prevalence, HER2 expression status by IHC has been selected as a

stratification factor in the current study. Patients will be stratified based on HER2 IHC 3+ status and responses will be evaluated by comparing these two stratified subgroups.

3.3.16 Rationale for Patient-Reported Outcome Assessments

As MBC is not curable with currently approved and available therapies, the main goals of treatment are to prolong survival and maintain or improve quality of life (Cardoso et al. 2018). Examining and measuring patients' symptoms and their impact of functioning and quality of life is important, particularly to inform how delays in radiographic progression and PFS might be associated with delays in clinical progression of symptoms and their interference with functioning, including maintenance of low disease burden. In addition, patients' reporting of their experience with treatment burden will complement the evaluation of treatment tolerability.

Symptoms, their impact on functioning and quality of life, and treatment burden will be assessed using validated patient reported outcome (PRO) measures. The EORTC QLQ-C30 will be administered to patients to assess symptoms and their impacts on functioning and quality of life (see Section 4.5.9 and Appendix 6), while the EORTC IL46 will be administered to assess treatment burden.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 226–284 patients with previously treated, HER2-positive LABC or MBC will be enrolled on this study.

4.1.1 Inclusion Criteria (All Study Phases)

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed invasive MBC or LABC that is incurable, unresectable, and previously treated with multimodality therapy:
  - Prior treatment for BC in the adjuvant, unresectable locally advanced, or metastatic settings, which must include both a taxane and trastuzumab (alone or in combination with another agent)
  - Progression must have occurred during or after most recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy
- Measurable disease that is evaluable per RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Willing to provide tumor biopsy sample at the time of screening

A tumor biopsy sample (either archival or fresh) must be collected from all patients from either the primary tumor or a metastatic site (preferred and within 6 months of enrollment, if clinically feasible) for determination of HER2 status by central laboratory testing for patient eligibility purposes, for Bcl-2 expression, and for research on biomarkers.

The tumor specimen must contain adequate evaluable tumor cells ($\geq$20% tumor cells) to enable Bcl-2, HER2, and other relevant biomarker analysis. Samples can be a tissue block (preferred) or at least 20 unstained freshly cut serial slides, and should be accompanied by an associated pathology report. If fewer than 20 slides are available, the Sponsor should be consulted. If a tumor sample is not available, a fresh biopsy must be collected.

The specimen must be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration samples are not acceptable.

- Local histological or cytological confirmation of ER and/or progesterone receptor status as defined by using IHC per American Society of Clinical Oncology/College of American Pathologists criteria (Hammond et al. 2010)
- Percentage of ER and/or progesterone receptor positivity, if available
- Willing to provide blood samples at the time of screening, on-study, and at progression for exploratory research on biomarkers
- HER2-positive BC as defined by an IHC score of 3+ or gene amplified by ISH as defined by a ratio of $\geq$2.0 for the number of HER2 gene copies to the number of chromosome 17 copies

  For the expansion phase and randomized Phase II stage: Centrally confirmed HER2-positive status prospectively tested by a Sponsor-designated central laboratory prior to enrollment.

  For the dose-escalation phase: Enrollment can be based upon prospective central testing or local IHC or ISH results; however, for local IHC or ISH results, the same tissue sample must be sent for central HER2 confirmation and the testing platform documented in the eCRF.

  Both IHC and ISH assays can be performed; however, unless reflex testing is necessary, only one positive result is required for eligibility.

  If multiple tumor specimens are submitted, the HER2 IHC score and or ISH amplification ratio will first be assessed on the most recently obtained specimen for the purpose of determining eligibility. For patients with bilateral BC, HER2 positivity must be demonstrated in both locations for archival tissue or in a metastatic biopsy.

  Centrally confirmed HER2 results (either IHC or ISH) from a current or previous Sponsor study can be used to determine eligibility for this study. Approval must be obtained from the Medical Monitor prior to randomization.

- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):
  - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte-colony stimulating factor support within 7 days prior to Cycle 1, Day 1)
  - Platelet count $\geq 100{,}000/\mu$L (without transfusion within 7 days prior to Cycle 1, Day 1)
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - Albumin > 2.5 g/dL
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exceptions:

    Patients with previously documented Gilbert syndrome who may have bilirubin $< 5 \times$ ULN

    Patients with documented liver metastases may have bilirubin $\leq 2.5 \times$ ULN
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases may have ALP $\leq 5 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of either 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

  - INR or aPTT $\leq 1.5 \times$ ULN

    For patients requiring anticoagulation therapy with warfarin or other coumarins, a stable INR between 2 and 3 is required. If anti-coagulation is required for a prosthetic heart valve, then INR should be between 2.5 and 3.5.
- Screening left ventricular ejection fraction (LVEF) $\geq 50\%$ on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan

  LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of

venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.1 Inclusion Criteria for Expansion Phase Only

In addition to the general inclusion criteria, patients in the expansion phase of the study must also meet the following criteria for study entry:

- Trastuzumab emtansine experienced cohort:
  - Disease progression during or after trastuzumab emtansine in the advanced/metastatic setting or disease recurrence in the neoadjuvant/adjuvant setting
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high.

    Bcl-2 high is defined as ≥50% of tumor cells stained with an intensity of IHC 2+ or 3+, and Bcl-2 low is defined as IHC 0 or 1+ or < 50% of tumor cells stained with an intensity of IHC 2+ or 3+.
- Trastuzumab deruxtecan (DS-8201a) experienced cohort:
  - Disease progression during or after trastuzumab deruxtecan in the advanced/ metastatic setting
  - Prior trastuzumab emtansine in any setting is allowed
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high (as defined above).

4.1.1.2 Inclusion Criteria for Randomized Phase II Stage

In addition to the general inclusion criteria, patients in the randomized Phase II stage of the study must also meet the following criteria for study entry:

- Bcl-2 expression status by IHC either from fresh tissue or the most recent archival tissue (see criteria in Section 4.1.1) by a central laboratory using the Ventana Bcl-2 IHC assay prior to randomization.

  At least 50% of patients in the randomized Phase II (e.g., 110 out of 220 patients) must be Bcl-2 high (as defined in Section 4.1.1.1).

4.1.2 Exclusion Criteria

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

- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1
- Radiation therapy within 2 weeks prior to Cycle 1, Day 1

  The patient must have recovered from any resulting acute toxicity (to Grade <1) prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin >500 mg/m^2
  - Liposomal doxorubicin >500 mg/m^2
  - Epirubucin >720 mg/m^2
  - Mitoxantrone >120 mg/m^2
  - Idarubicin >90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence
- Cardiopulmonary dysfunction as defined by:
  - Uncontrolled hypertension (systolic >150 mm Hg and/or diastolic >100 mm Hg with or without medication)
  - Inadequate LVEF at baseline, $<50\%$ by either ECHO or MUGA
  - History of symptomatic congestive heart failure (CHF)-Grade ≥ 3 per NCI CTCAE version 5.0 or Class $\geq$ II New York Heart Association
  - History of a decrease in LVEF to $<40\%$ or symptomatic CHF with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of randomization
  - Concurrent dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade ≥ 2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia

  - High-risk uncontrolled arrhythmias (i.e., supraventricular tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 (Mobitz 2) or third-degree AV-block])
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis, or active infection with HBV or HCV)
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Known HIV infection or human T-cell leukemia virus 1 infection
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $>$ 2 weeks prior to randomization
- Known central nervous system (CNS) disease, except for patients treated and currently with asymptomatic CNS metastases, provided that all of the following criteria are met:
  - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
  - No ongoing requirement for corticosteroids as therapy for CNS disease
  - No stereotactic radiation within 14 days prior to randomization
  - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

    Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.

- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade ≥ 3 peripheral neuropathy (according to the NCI CTCAE v 5.0)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Prior allogeneic stem cell or solid organ transplantation
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine after the final dose of study treatment, whichever is later

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Strong or moderate CYP3A inhibitors (see Appendix 14 for examples)
  - Strong or moderate CYP3A inducers (see Appendix 14 for examples)

  Additional restrictions for on-study use of CYP3A inhibitors/inducers are outlined in Section 4.4.2.
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade-containing Seville oranges), or starfruit (carambola) within 3 days before anticipated first dose of study drug until the last dose of study drug (see Section 4.4.2)
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History of active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) requiring specific medication in the 12 months prior to randomization, or active and uncontrolled bowel inflammation (e.g., diverticulitis) at time of randomization

- Inability or unwillingness to swallow a large number of tablets
- Known hypersensitivity to venetoclax or trastuzumab emtansine or to any of their excipients
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Other medical or psychiatric conditions that, in the opinion of the investigator, may interfere with the patient's participation in the study
- Blood transfusions if performed within 2 weeks prior to screening

4.1.2.1 Exclusion Criteria for Randomized Phase II Stage

In addition to the general exclusion criteria, patients in the randomized Phase II stage of this study who meet the following criteria will be excluded:

- Prior treatment with trastuzumab emtansine in any setting (neoadjuvant/adjuvant or advanced/metastatic setting)
- Prior treatment with venetoclax in any setting
- Prior treatment with anti-HER2 antibody drug conjugates (e.g. trastuzumab deruxtecan [DS-8201a]), margetuximab, pyrotinib, or tucatinib

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING (APPLICABLE TO RANDOMIZED PHASE II STAGE ONLY)

4.2.1 Treatment Assignment

The Phase II randomized portion of this study is randomized and double-blind. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS.

Patients in the randomized Phase II stage will be randomly assigned to one of two treatment arms: venetoclax in combination with trastuzumab emtansine or trastuzumab emtansine plus placebo. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm with respect to pre-specified stratification factors. Randomization will be stratified according to the following criteria:

- Bcl-2 status (Bcl-2 high vs. Bcl-2 low; as defined in Section 4.1.1.1)
- Visceral disease (Yes vs. No; as defined below)
- HER2 status IHC 3+ (Yes vs. No; as defined in Section 4.1.1)

Visceral disease will be defined as the presence of disease in the lung, liver, adrenal gland, central nervous system, pleural cavity, or peritoneal cavity. All locations that include tumors in the breast, bone, bone marrow, lymph nodes, skin, and soft tissue will be classified as non-visceral disease. Patients with tumors in multiple locations that

cover both visceral and non-visceral disease (e.g., a patient with a tumor in the liver and bone lesions) will be designated as having visceral disease for the purposes of the analysis.

Patients who are randomized into this study will not be allowed to be re-randomized to receive a second course of study treatment. Once a patient has been randomized into the study, the IxRS will be used to assign the kit numbers for study drugs to be dispensed at each treatment visit. It is important that the study drugs dispensed for each visit are the correct kit number, as assigned by the IxRS. This will ensure that drug use by dates and automatic study drug resupply to sites are managed appropriately via the IxRS.

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

While PK and immunogenicity samples will be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct of the study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for venetoclax PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to

study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above) will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are venetoclax, trastuzumab emtansine, and placebo.

Rescue medications and pre-medications are considered non-investigational medicinal products (NIMPs). In this study, diphenhydramine is considered a NIMP.

4.3.1.1 Venetoclax and Placebo

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength. Venetoclax tablets will be packaged in high-density polyethylene (PE) plastic bottles to accommodate the study design. Venetoclax tablets must be stored at 15°C–25°C (59°F–77°F).

For information on the formulation and handling of venetoclax, see the pharmacy manual and the Venetoclax Investigator's Brochure.

The formulation of placebo is equivalent to venetoclax but without the active agent. The handling of placebo is described in the pharmacy manual.

If unblinding occurs, the treatment assignment placebo will no longer be administered to patients randomized to Arm A (trastuzumab emtansine and placebo).

4.3.1.2 Trastuzumab Emtansine

Trastuzumab emtansine will serve as the comparator/active control and will not be blinded. Trastuzumab emtansine will be provided as a lyophilized formulation in a single-use 20 mL glass vial. Each 20 mL vial contains enough product to deliver approximately 160 mg of trastuzumab emtansine. Trastuzumab emtansine vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until use. Do not freeze vials. Trastuzumab emtansine vials should not be used beyond the expiration date provided by the manufacturer.

For information on the packaging, reconstitution, and handling of trastuzumab emtansine, refer to the pharmacy manual and the Trastuzumab Emtansine Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens for the dose-escalation phase, dose-expansion phase, and randomized Phase II stage are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

If trastuzumab emtansine is held, then venetoclax/placebo should continue, provided the dosing selected in the dose-escalation phase of this study is continuous. In the case of NC dosing of venetoclax/placebo, when trastuzumab emtansine is held, then venetoclax placebo should be held as well and restart concomitantly to preserve treatment synchronization. If trastuzumab emtansine is permanently discontinued for toxicity, then venetoclax/placebo can continue, provided that the patient is deriving clinical benefit from venetoclax/placebo, in the opinion of the investigator. Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Venetoclax and Placebo

At the start of each cycle, patients will be supplied with sufficient venetoclax and placebo tablets for that cycle. A drug diary will be provided to the patient to record oral administration of doses, including the date and time of dosing. Patients will be instructed to return empty bottles or unused tablets.

The investigator is responsible for monitoring patient compliance by monitoring the patient diary and counting unused tablets. Patient compliance with the assigned daily dose of study medication will be assessed by standard pill counts. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Each dose of venetoclax or placebo will be taken orally once daily with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or patient's first meal of the day. Patients should self-administer venetoclax at approximately the same time each morning. On days that PK sampling is required, the patient's first meal of the day and all study treatment doses should occur in the clinic to ensure accurate timing of the PK sampling. On those days, the time of each dose of venetoclax will be recorded to the nearest minute.

A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax. The following is an

example of a breakfast that contains approximately 520 Kcal and has 30% of the total caloric content of the meal from fat that is, approximately 17 grams of fat: one box cereal (30–40 g), skim milk (240 mL), one boiled egg, one slice of toast (15 g) with 1 tablespoon of margarine (14 g). The toast and margarine may be replaced with one medium croissant or two large pancakes. If there is a substantial period of time between the patient's regular time of breakfast and their venetoclax dosing in the clinic on PK sampling days, patients may have a low-fat snack in the morning. Patients must be instructed not to take their study treatment with the snack and to take their study treatments in the clinic after a meal.

Venetoclax tablets should be swallowed whole and never be chewed, cut, or crushed. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another venetoclax dose should be taken, and the second dose should be noted in the drug diary. If tablets are not intact or if vomiting occurs more than 15 minutes after taking venetoclax, no replacement dose is to be taken. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose with food as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose. Otherwise, the dose should not be taken.

4.3.2.2 Trastuzumab Emtansine

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W. The initial dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes ≥10% compared to the previous visit or baseline, whichever is most recent. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed, following the dose reduction levels provided in Table 11. Once a dose has been reduced for adverse event(s), it must not be re-escalated. If trastuzumab emtansine is discontinued because of toxicity, it should not be re-administered. Guidelines for dosage discontinuation for patients who experience adverse events are provided in Section 5.1.3.

If the timing of a protocol-mandated procedure, such as administration 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.

Refer to Table 1 for guidelines on administration of first and subsequent infusions of trastuzumab emtansine.

Table 1 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs as indicated in Appendix 1 and Appendix 2. • Administer the initial dose as a 90-minute IV infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms. • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Record patient's vital signs as indicated in Appendix 1 and Appendix 2. • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute infusions. • Patient should be observed during the infusions and for at least 30 minutes after infusion.

4.3.2.3 Sequence of Study Drug Administration

The oral dose of venetoclax should be administered first, followed by infusion of trastuzumab emtansine.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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.

4.3.3.1 Continued Access to Venetoclax and Trastuzumab Emtansine

The Sponsor will offer continued access to Roche IMPs venetoclax and trastuzumab emtansine free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs venetoclax and trastuzumab emtansine after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMPs venetoclax and trastuzumab emtansine after completing the study if any of the following conditions are met:

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

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) to non-target sites is allowed as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Study drug treatment may be continued during palliative radiotherapy.
- Pain medications administered per standard clinical practice
- Inactive influenza vaccinations during influenza season
- Bisphosphonates for prevention of skeletal related events

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

The use of anti-emetics and anti-diarrhea prophylaxis is permitted and should be administered per protocol guidelines (see Table 9 and Section 5.1.3 for more details). The use of anti-emetics must be documented in the eCRF. Use of prophylactic anti-microbial agents, TLS prophylaxis and/or treatment, and/or growth factors is also recommended according to standard institutional practice and should be documented in the eCRF.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion associated- events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Prohibited Food

Use of the following foods is prohibited for at least 3 days prior to initiation of treatment, throughout venetoclax administration, and for 28 days after the last dose of study treatment:

- Constituents of these foods have been shown to inhibit CYP3A4, the major enzyme responsible for the metabolism of venetoclax. Consumption of these foods could lead to increased venetoclax exposure:
  - Grapefruit
  - Grapefruit products
  - Seville oranges (including marmalade containing Seville oranges)
  - Star fruit (carambola)

4.4.3 Prohibited and Cautionary Therapy

Use of the following concomitant therapies are prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment, depending on the agent , and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details).
- The administration of live, attenuated influenza vaccine (e.g., FluMist®) is prohibited during treatment and within 28 days following the last dose of venetoclax.

Some additional therapies are prohibited only for specific study phases, or are allowed with caution, restrictions, and/or dose adjustments. These are described in Table 7 and are to be implemented after relevant exclusion criteria for these medications are met (see Section 4.1.1).

Venetoclax is a substrate of CYP3A and therefore venetoclax exposure can be impacted by concomitant strong and moderate of CYP3A inducers and inhibitors. DM1, the cytotoxic component of trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. Relevant restrictions and dosing recommendations for concurrent CYP3A inhibitors/inducers are described in Table 2. Medications that should be avoided are listed in Appendix 14.

After discontinuation of a moderate or strong CYP3A inhibitor that led to a venetoclax dose reduction as per the following guidelines, the investigator should wait for 3 days before increasing the venetoclax dose back to the original maintenance/target dose.

Table 2 Therapies Prohibited for Specific Study Phases, or Allowed with Caution, Restrictions, and/or Dose Adjustments

Therapy	Phase Ib: Dose-Escalation		Phase Ib: Expansions and Phase II: Randomized
	DLT Window [a]	Post DLT Window [a] at Cohort-Designated Dose	Cohort-Designated Dose
Strong CYP3A inhibitors	Prohibited	Avoid and consider alternative medications. Consult with the medical monitor if considering use. If usage is approved by the medical monitor, reduce venetoclax dose by at least 4-fold (see Table 3) and follow applicable local prescribing information. Consider delaying T-DM1 treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If T-DM1 treatment cannot be delayed, patients should be closely monitored for adverse reactions.	
Moderate CYP3A inhibitors	Prohibited	Avoid and consider alternative medications. Consult with the medical monitor if considering use. If usage is approved by the medical monitor, reduce venetoclax dose by 2-fold (see Table 3).	
Strong CYP3A inducer	Prohibited		
Moderate CYP3A inducer	Prohibited		Exclude through completion of the first cycle of venetoclax. After the first cycle, avoid and consider alternative medications with less induction. If used, contact the Medical Monitor for guidance.
P-gp inhibitors	If P-gp inhibitor must be used, monitor closely for toxicities and follow the applicable local prescribing information		
P-gp substrates	Concomitant use of narrow therapeutic index P-gp substrates should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.		
Warfarin and coumarin derivatives (e.g., phenprocoumon)	Use with caution with close monitoring of the international normalized ratio (INR).		
Excessive alcohol intake	Should be avoided (occasional to moderate use is permitted).		

DLT = dose-limiting toxicity; P-gp = P-glycoprotein.
Note: See Appendix 14 for examples of CYP3A4 inhibitors/inducers and P-gp substrates/inhibitors.
[a] DLT window applicable to dose-escalation stage only.

Table 3 Venetoclax Dose Reductions for Strong and Moderate CYP3A Inhibitors

Venetoclax Assigned Dose (mg)	Venetoclax Reduced Dose (mg)	
	Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors
100	Consult with Medical Monitor.	Consult with Medical Monitor.
200	Consult with Medical Monitor.	100
400	100 (70 for posaconazole in U.S. and countries with USPI-based approval)	200
600		300
800	200	400

U.S. = United States; USPI = United States Prescribing Information.

Appendix 14 contains examples of CYP3A4 inhibitors/inducers and P-gp substrates/inhibitors. Additional examples of these classes of medications are provided at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The above lists are not necessarily comprehensive; the investigator should also consult the prescribing information for any concomitant medication when determining the drug-drug interaction potential.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed. A decision may be made to allow the use of prohibited medications on a case by case basis, following discussion with the Medical Monitor and assessment of the benefit-risk ratio.

Patients who require the use of any therapies when they are prohibited (unless an allowance is made after consultation with the medical monitor) will be discontinued from study treatment and followed for safety outcomes and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anticancer therapy, whichever comes first.

4.4.3.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.2) may be used during the study at the discretion of the investigator.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. 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.

4.5.1 Informed Consent Forms and Screening Log

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

Prior to signing the main Informed Consent Form for the study, patients may consent to the collection of tumor tissue (archival or newly obtained via biopsy) for determination of Bcl-2 expression by signing a Prescreening Informed Consent Form.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, and foods that have been shown to inhibit CYP3A4 [Section 4.4.2]) used by the patient within 28 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Breast cancer history includes prior cancer therapies and procedures.

Demographic data will include age, sex, and self-reported race/ethnicity. Local HER2 testing information will also be collected, if available.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Tumor and Response Evaluations

All sites of measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in Appendix 1 and Appendix 2; a time window of ±7 days is allowed for all timepoints regardless of drug delays or interruptions. Tumor assessments will continue until disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Initial screening assessments must include CT scans (with oral or IV contrast unless contraindicated) or MRI scans of the chest, abdomen, and pelvis. A bone scan or positron emission tomography (PET) scan should also be performed to evaluate for bone metastases. MRI scans of the chest, abdomen, and pelvis or non-contrast CT scan may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast) or MRI scan with contrast (if CT contrast is contraindicated) of the head must be done at screening to evaluate CNS metastasis in all patients. If CT with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline. Patients with active or untreated symptomatic CNS metastases are not eligible for the study (see Section 4.1.1). Patients with untreated asymptomatic CNS metastasis at screening may be eligible. For untreated patients, brain MRI scan with contrast at screening is required, and needs to meet all eligibility criteria as specified in Section 4.1.

If a CT scan for tumor assessment is performed as part of a PET/CT, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Further investigations such as bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease according to RECIST v1.1 may be used.

Evaluation of tumor response conforming to RECIST v1.1 (Appendix 11) will be performed every 6 weeks (±7 days) following randomization until the primary PFS analysis, with additional scans performed as clinically indicated. The same radiographic procedures used to assess measurable disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT and/or MRI scans). Following the primary PFS analysis, tumor assessments will be conducted as per standard of care and recorded in the eCRF until disease progression.

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of the following assessments every 6 weeks until the primary PFS analysis:

1. CT and/or MRI of the chest/abdomen/pelvis, as well as other known sites of disease, including brain
2. If a patient has only bone as a site of involvement at screening, which is determined to be measurable disease as per RECIST v1.1, then a bone scan or PET scan is mandated at every tumor assessment, or a bone scan or PET scan is to be performed as clinically indicated (e.g., suspicion of disease progression)
3. In cases where patients demonstrate control of their systemic disease but who newly develop isolated brain metastases and are eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments
4. Any other imaging studies felt to be clinically indicated by the treating physician

Response will be assessed by the investigator using RECIST v1.1 (Appendix 11) at each tumor assessment. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if PD is suspected. If the initial screening bone scan or PET scan indicates bone metastases and this is the only site of involvement and is determined to be measurable disease per RECIST v1.1, then a bone scan or PET scan needs to be performed every 6 weeks. If the screening scan shows evidence of either non-measurable bone metastases or no bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion. If the brain is not identified as a site of involvement at screening, then brain CT or MRI only needs to be repeated beyond screening, if clinically indicated. In cases where a patient demonstrates control of their systemic disease but who newly develops isolated brain metastases and is eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments (Section 3.1).

If study drug treatment is discontinued prior to disease progression according to RECIST v1.1, tumor response assessment should continue to be performed as per the schedule specified in Appendix 1 and Appendix 2.

4.5.6 Left Ventricular Ejection Fraction Assessment

LVEF will be assessed by ECHO or MUGA. LVEF will be monitored at baseline and every fourth cycle thereafter. Additional LVEF measurements may be performed if LVEF declines are clinically suspected at the discretion of the investigator.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Chemistry panel (serum): glucose, BUN or urea, sodium, magnesium, chloride, bicarbonate, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin

  TLS laboratory assessments include serum creatinine, uric acid, potassium, calcium, phosphorous, and LDH.
- Coagulation: aPTT and INR
- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood)
- Thyroid function test (thyroid-stimulating hormone [TSH], free T3, and free T4)

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis.

- Blood samples for exploratory research on biomarkers and biomarker assay development

  Blood samples will be processed to obtain plasma, and serum for the determination of baseline level changes in surrogate PD biomarkers.

- C-reactive protein
- Blood samples for auto-antibody testing

  For patients who show evidence of immune-mediated toxicity, additional samples may be collected and will be analyzed centrally:

  - Anti-nuclear antibody
  - Anti–double-stranded DNA
  - Circulating anti-neutrophil cytoplasmic antibody
  - Perinuclear anti-neutrophil cytoplasmic antibody

- Plasma samples for venetoclax PK analysis
- Serum samples for trastuzumab emtansine PK analysis
- Serum samples for total trastuzumab analysis
- Serum samples for trastuzumab emtansine immunogenicity analysis

  Note: Alternative PK and ADA assessments may be explored if there is substantial difficulty in obtaining the timepoints listed in Appendix 3. Depending on the results from interim PK and ADA analyses, the frequency of PK and ADA sampling may be reduced or halted later in the study.

- Archival or newly collected tumor tissue sample obtained at baseline for determination of protein expression of Bcl-2 and HER2 by central laboratory testing for patient eligibility purposes and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10–19 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of $\geq$ 20% viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Exploratory biomarker research may include, but will not be limited to, analysis of tissue and ctDNA (i.e., mutation profiles associated with disease) and genes or gene signatures associated with apoptosis (i.e., BCL-2 family). Research may involve extraction of DNA, ctDNA, or RNA; analysis of somatic mutations; and use of NGS of a comprehensive panel of genes. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11.3), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum and plasma samples collected for PK or immunogenicity analysis may be needed for additional pharmacokinetics (e.g., PK biomarkers or relevant analytes/catabolites/metabolites) and immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.
- Tumor tissue and blood samples collected for biomarker research and biomarker assay development will be destroyed no later than no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the

samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings may be stored at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study

drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.9 Patient-Reported Outcome Assessments

PRO instruments will be completed during the randomized Phase II stage of the study to assess the treatment benefit and/or more fully characterize the safety profile of venetoclax in combination with trastuzumab emtansine compared to trastuzumab emtansine plus placebo. In addition, PRO instruments will enable the capture of each patient's direct experience with venetoclax in combination with trastuzumab emtansine compared to trastuzumab emtansine alone.

PRO data will be collected through use of the following instruments: the EORTC QLQ-C30 and the EORTC IL46.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments, translated into the local language as appropriate, will be self-administered via paper questionnaires and/or through use of an electronic device provided by the Sponsor. Instructions for completing the questionnaires will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor or entered into the study database by site personnel as appropriate. The data will be available for access by appropriate study personnel.

The EORTC QLQ-C30 and IL46 assessments will occur as outlined in the schedule of activities (Appendix 2).

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to receiving any information on disease status, prior to the performance of non-PRO assessments that could bias patients' answers, and prior to the administration of study treatment, unless otherwise specified.

During clinic visits, PROs should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.

- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- If completed on paper, site staff should review and ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

The questionnaires (EORTC QLQ-C30 and EORTC IL46) will be completed during the randomized Phase II stage only: at Cycle 1, Day 1 (baseline) prior to administration of study drug; then at every study treatment cycle prior to administration of study drug (i.e., on Cycle 2, Day 1; Cycle 3, Day 1; and Cycle 4, Day 1, etc.) and at the study treatment discontinuation visit (see Appendix 2). The EORTC QLQ-C30 will be collected at the first survival follow-up at 3 months (±30 days) and the second survival follow-up at 6 months (±30 days) following conclusion of treatment or disease progression per RECIST v1.1.

Patients who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will complete the EORTC QLQ-C30 at each tumor assessment visit until radiographic disease progression per RECIST v1.1, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first.

Patients whose native language is not available with the questionnaires are exempted from completing all PRO assessments.

The Sponsor will not derive adverse event reports from PRO data.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ-C30 (see Appendix 6) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 15 minutes to complete.

EORTC IL46

The EORTC IL46 is a validated single-item question assesses overall impact of study drug side effects (see Appendix 6). Specifically, the single-item EORTC IL46 assessment of patient experience with treatment-related side effects will be collected.

4.5.10 Optional Tumor Biopsies

Consenting patients will undergo an optional tumor biopsy (if deemed clinically feasible by the investigator) at Cycle 1, Day 1 and/or Cycle 2, Day 1 (see Appendix 1 and Appendix 2) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Where fresh biopsy is possible, samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are acceptable. Biopsies collected via fine-needle aspirations are not acceptable.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to venetoclax, trastuzumab emtansine, disease, or drug safety:

- Blood samples collected at baseline
- Additional archival tumor tissue samples (e.g., from an earlier biopsy) collected at screening
- Tumor tissue samples from biopsies performed at the investigator's discretion during the study
- Leftover blood, serum, plasma, peripheral blood mononuclear cell (PBMC), and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides).

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC approved- Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

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

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

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

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical

Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anticancer therapy not required per protocol
- Radiographic disease progression according to RECIST v1.1

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

Patients who discontinue treatment prematurely during the DLT-evaluation period during the dose-escalation phase will be replaced. Patients who discontinue study treatment prematurely during the randomized portion of the study will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit 28 days (+14 days) after the last dose of study drug (see Appendix 1 and Appendix 2 for additional details). After treatment discontinuation due to disease progression, information on survival follow-up and new anticancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are discontinued from study treatment for reasons including disease progression and have started follow-on treatment/s will be followed for survival approximately every 6 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Patients who are discontinued from study treatments for reasons other than disease progression and have not started follow-on treatment/s will be followed for disease status every 8 weeks (± 5 days) from the date of randomization until Week 24 (± 5) days and every 12 weeks (± 5 days), thereafter, until disease progression, loss to follow-up, withdrawal of consent, death or study termination by the Sponsor, whichever occurs first (see Appendix 1 and Appendix 2 for additional details).

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Venetoclax has been granted approval in the U.S. (Venclexta® U.S. Prescribing Information) and by the European Medicines Agency (Venclyxto® E.U. SmPC) for the treatment of patients with CLL, with or without 17p deletion, who have received at least one prior therapy. Venetoclax has also received accelerated approval in the U.S. in combination with azacitidine, decitabine, or LDAC to treat adults with newly diagnosed AML.

Venetoclax, however, is not approved for the treatment of BC, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with venetoclax in completed and ongoing studies. The anticipated important safety risks for venetoclax are outlined below. Please refer to the most recent version of Venetoclax Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Venetoclax

Clinical experience gained thus far with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the current Venetoclax Investigator's Brochure for more information.

On the basis of clinical data to date, the following known and potential risks with venetoclax are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.3.

5.1.1.1 Tumor Lysis Syndrome

Available data suggest that in patients with cancers other than CLL, with the exception of those with mantle cell lymphoma, the risk of TLS is low. Due to different biology between HER2-positive BC and hematological malignancies, the risk of TLS is considered to be very low in patients with HER2-positive BC. Therefore, TLS prophylaxis is not recommended by any of the international guidelines for patients with HER2-positive BC, even in those patients who have developed visceral crisis and are receiving chemotherapy.

The target population in this trial is considered to have low disease burden compared with patients who have visceral crisis; therefore, TLS risk is negligible (Lok et al. 2019). Nevertheless, patients should be advised to remain well hydrated for the first week of study drug administration. Although not mandatory, at the discretion of the investigator, a prophylactic oral agent (e.g., allopurinol 300 mg QD) may be initiated in patients who are deemed to be at risk of TLS in order to reduce the uric acid level. In the dose-escalation phase, TLS laboratory values obtained before the dose of venetoclax will be used to determine whether a patient developed a change related to TLS. Laboratory results from 24 hours post-dose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 7.

Patients with TLS should be treated as per institutional practice and local guidelines, including correction of electrolyte abnormalities and monitoring of renal function and fluid balance. Recommendations for initial management of electrolyte imbalances and prevention of TLS are provided in Appendix 7. In some cases, dialysis may be indicated. Guidelines for defining TLS are provided in Appendix 8.

To evaluate any possible risk of TLS with venetoclax in patients with HER2-positive BC, patients enrolled in the dose-escalation phase of the study will each have a sample collected for a serum chemistry panel 24 hours after the first dose of study drug. The Sponsor will review the chemistry panel results and establish a management plan for TLS if an increased risk is identified, if needed.

5.1.1.2 Neutropenia

Neutropenia is an important identified risk for venetoclax. Clinical data from oncology studies suggest that neutropenia adverse events are observed among patients who receive venetoclax as a single agent or in combination with other therapeutic agents, with higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in Table 6. Granulocyte colony stimulating factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infection.

5.1.1.3 Serious Infections

Serious infection is an important identified risk for venetoclax. Infections have been reported in oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated patients with hematologic malignancies and are similar across all indications. Infections are closely monitored in venetoclax program across all indications. Patients should be advised to report fever or symptoms suggestive of serious infection and should be assessed for further management as per standard medical practice. In the oncology studies, recommendations are included in the protocol regarding the need for anti-infective prophylaxis per standard of care (e.g., NCCN guidelines for oncology subjects).

5.1.1.4 Other Hematological Effects

Anemia has been reported across oncology studies investigating venetoclax, with a higher frequency in some studies in which venetoclax is combined with other reference therapies; however, most of the events were non-serious and confounded by disease factors and prior therapies.

Thrombocytopenia adverse events have been reported in oncology studies investigating venetoclax, with a higher frequency in those studies in which venetoclax was combined with other chemotherapeutic agents. However, most of the events were non-serious and assessment of these events is confounded by the patients' underlying hematologic malignancy disease state, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several patients.

Lymphopenia has been observed in nonclinical studies and in the Phase I clinical study conducted in heavily pretreated patients with CLL and NHL. While opportunistic infections have been reported in the clinical program, data are confounded by the patients' underlying disease and prior therapies. Patients in this study who develop lymphopenia are potentially at risk for atypical infections. As such, prophylaxis against varicella zoster virus and *Pneumocystis jiroveci* pneumonia should be considered and

implemented (if applicable) as per local institutional practice, although some guidance is provided in Appendix 8.

5.1.1.5 Effects on Reproductive System and Pregnancy

This study is open to enrollment of both male and female patients. The effect of Bcl-2 inhibition on pregnancy has not been fully characterized. In animal studies, venetoclax resulted in increased post-implantation loss, and decreased fetal body weights were observed in the mouse embryo-fetal development study at the highest dosage administered. Venetoclax was not teratogenic. Six human pregnancies have been reported in the clinical program with venetoclax so far, including two pregnancies reported in a partner; in four out of six cases, a live infant with no neonatal complication, congenital anomalies, or birth defects was delivered. One out of six cases ended in therapeutic abortion in a patient with CLL who experienced progressive disease. One out of six cases was reported in a partner of a patient who had not received any study drug and for which the projected due date is pending.

In nonclinical studies, both venetoclax and trastuzumab emtansine have shown a potential to cause reproductive and embryo-fetal developmental toxicities as single agents. Therefore, there is the potential for this combination to cause overlapping or additional reproductive and embryo-fetal toxicities compared with the individual molecules. Consequently, both venetoclax and trastuzumab emtansine should not be administered to pregnant women, and both drugs must be discontinued if a patient becomes pregnant. Additionally, patients are advised to remain abstinent (i.e., refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 28 days after the last dose of study drug. Please refer to Section 4.1.1 for further details on study eligibility and contraceptive requirements for patients.

5.1.1.6 Treatment-Emergent Malignancies (Second Primary Malignancies)

Second primary malignancies are important potential risk for venetoclax. Events of second primary malignancies have been reported across the venetoclax hematologic oncology program. However, no causal association with the venetoclax administration has been confirmed, and no pattern has been observed. The overall observed incidence rate of malignancy in the venetoclax clinical trial programs were comparable to that reported in the general population. Second primary malignancies will be closely monitored in this study.

5.1.1.7 Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal as described in Section 4.3.2.1.

5.1.1.8 Concomitant Use with Other Medications

Specific recommendations are provided for co-administration of venetoclax with other medications, including inhibitors and inducers of CYP3A (see Section 4.4).

Live, attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live, attenuated vaccines during or following venetoclax therapy have not been studied. Patients should be advised that vaccinations may be less effective.

Due to possible CYP3A mediated metabolic interaction, certain food items (e.g., grapefruit and Seville oranges) should not be consumed during treatment with venetoclax. Further details of excluded food items are provided in Section 4.4.

5.1.2 Risks Associated with Trastuzumab Emtansine

5.1.2.1 Pulmonary Toxicity

Cases of ILD, including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving trastuzumab emtansine. Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at risk of pulmonary events.

Patients who have experienced a pulmonary event should be carefully evaluated before commencing trastuzumab emtansine treatment.

Guidelines for management of trastuzumab emtansine in patients who develop ILD or pneumonitis are provided in Appendix 10.

5.1.2.2 Hepatotoxicity

The following events have been reported with administration of trastuzumab emtansine:

- Serious hepatobiliary disorders

  Serious hepatobiliary disorders, including NRH of the liver and hepatobiliary disorders with a fatal outcome due to drug-induced liver injury, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases may have been confounded by concomitant medications with known hepatotoxic potential.

- Increased serum transaminases

  Asymptomatic increases in serum transaminase concentration (transaminitis) have been observed. Grade 1 and 2 events have been observed frequently; Grade 3 and 4 events have been observed less commonly. The incidence of increased AST was substantially higher than that for increased ALT. Increases in AST and ALT were commonly observed by Day 8 of each cycle and generally improved or returned to baseline by Day 21. A cumulative effect of trastuzumab emtansine, that is, an increase in the proportion of patients with

Grade 1 or 2 elevations in transaminases with successive cycles has been observed; however, there was no increase in the proportion of patients with Grade 3 abnormalities over time.

- NRH

  NRH is a form of noncirrhotic portal hypertension that can be caused by chronic use of medications. NRH typically presents with the insidious or unexpected onset of signs or symptoms of portal hypertension (weakness, ascites, splenomegaly, esophageal varices) in a patient with little evidence of chronic liver disease.

  Cases of NRH have been identified from liver biopsies in patients treated with trastuzumab emtansine who presented with signs and symptoms of portal hypertension. 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. Biopsy-confirmed NRH leading to fatal hepatic failure has been reported (refer to Appendix 13).

  NRH should be considered in all patients with clinical symptoms of portal hypertension, even with normal transaminases, and no other manifestations of cirrhosis; in patients with a cirrhosis-like pattern seen on a CT scan of the liver; and/or in patients with liver failure following long-term treatment with trastuzumab emtansine.

Patients must meet specified hepatic laboratory test requirements to be included in this study (Section 4.1.1).

Hepatic laboratory parameters will be monitored as described in the schedule of assessments (Appendix 1 and Appendix 2).

Guidelines for management of trastuzumab emtansine in patients who develop increased serum transaminases, increased serum bilirubin, or NRH are provided in (Appendix 10).

5.1.2.3 Left Ventricular Dysfunction

Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. To date, significant cardiac events, including LVEF of $<40\%$, have been observed (infrequently) in clinical trials of trastuzumab emtansine; therefore, symptomatic CHF is a potential risk.

Patients must meet specified LVEF requirements to be included in this study (Section 4.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO) or MUGA scans as described in Section 4.5 and the schedule of assessments (Appendix 1 and Appendix 2).

Guidelines for patient monitoring and management of trastuzumab emtansine in patients who develop left ventricular dysfunction are provided in (Appendix 10).

5.1.2.4 Infusion-Related Reactions and Hypersensitivity Reactions

Infusion-related reactions (IRRs) and hypersensitivity reactions have been reported with administration of trastuzumab emtansine. Despite the different pathophysiology of IRRs (reactions involving cytokine release) and hypersensitivity (allergic) reactions, the clinical manifestations are the same. In general, IRRs are expected to be more frequent and severe with the first infusion and to decrease in number and severity over time. The severity of true hypersensitivity reactions would be expected to increase with subsequent infusions.

IRRs, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of 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.

Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine. Patients with a history of intolerance to trastuzumab will be excluded from this study (Section 4.1).

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 should be closely monitored for IRRs during and after each infusion of trastuzumab emtansine, as described in Section 4.3.2.1.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in (Appendix 10).

5.1.2.5 Hematologic Toxicity

Thrombocytopenia has been reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (platelet count $\geq$50,000/μL), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (platelet count $\geq$75,000/μL) by the next scheduled dose (i.e., within 3 weeks). In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

Patients with thrombocytopenia ($\leq$100,000/mm^3) and patients on anticoagulant treatment should be monitored closely during treatment with trastuzumab emtansine. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Trastuzumab emtansine has not been studied in patients with platelet counts $\leq$100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater ($<$50,000/mm^3), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 ($\geq$75,000/mm^3).

Declines in other hematopoietic lineages, for example, leukopenia, neutropenia, and anemia, were less frequent than that observed for platelets.

Patients must meet specified hematologic laboratory test requirements to be included in this study (Section 4.1).

Hematologic laboratory parameters will be monitored as described in Section 4.5 and the schedule of assessments (Appendix 1 and Appendix 2). Patients on anticoagulant or antiplatelet treatment should be monitored closely.

Guidelines for management of trastuzumab emtansine in patients who develop hematologic toxicity are provided in (Table 6).

5.1.2.6 Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with trastuzumab emtansine. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Caution should be used with these agents, and additional monitoring should be considered when concomitant use with trastuzumab emtansine is medically necessary.

5.1.2.7 Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine.

Patients with Grade ≥3 peripheral neuropathy will be excluded from this study (Section 4.1).

Patients will be clinically monitored on an ongoing basis for signs or symptoms of peripheral neuropathy as described in Section 4.5 and the schedule of assessments (Appendix 1 and Appendix 2).

Guidelines for management of trastuzumab emtansine in patients who develop peripheral neuropathy are provided in (Appendix 10).

5.1.2.8 Extravasation

In trastuzumab emtansine clinical studies, 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. These reactions have been observed more frequently within 24 hours of infusion.

The infusion site will be closely monitored for possible subcutaneous infiltration during drug administration, as described in Table 1). Specific treatment for trastuzumab

emtansine extravasation is unknown at this time. Patients should be managed symptomatically per local institutional guidelines.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.
The severity of adverse events will be graded according to the NCI CTCAE v5.0.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

If, in the opinion of the investigator, a toxicity is considered to be attributable solely to one component of the study treatment (i.e., trastuzumab emtansine, venetoclax or placebo, then the dose of that component should be delayed or modified in accordance with the guidelines below. If trastuzumab emtansine is held, then venetoclax/placebo should continue provided the dosing selected in the dose-escalation phase of this study is continuous. In the case of NC dosing of venetoclax/placebo, when trastuzumab emtansine is held, then venetoclax placebo should be held as well and restart concomitantly to preserve treatment synchronization. If trastuzumab emtansine is permanently discontinued for toxicity, then venetoclax/placebo can continue provided that the patient is deriving clinical benefit from venetoclax/placebo, in the opinion of the investigator. Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Venetoclax Dose Modifications

Although patients with adverse events are to be managed according to the particular clinical circumstances based on the investigator's medical judgement, dose reduction of venetoclax by one and, if needed, two dose levels will be allowed depending on the type and severity of the toxicity encountered (refer to Table 6 and Appendix 9). The dose reduction of venetoclax will occur per Table 4 below. Patients requiring clarification regarding management of adverse events and dosing and all patients who received starting dose of 800 mg requiring more than three dose reductions should be discussed with the Medical Monitor. All dose modifications/adjustments must be clearly documented in the patient's source notes and eCRF. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at the reduced dose level, unless further dose reduction is allowed. Dose re-escalation is not allowed.

Table 4 Dose Modification Scheme for Venetoclax/Placebo

Dose Reduction Schedule	Dose Level (mg)	Dose Level (mg)
Starting dose	800 mg	400 mg
First dose reduction	600 mg	200 mg
Second dose reduction	400 mg	100 mg
Third dose reduction	200 mg	Not Applicable
Requirement for further dose reduction	Discuss with Medical Monitor	Not Applicable

Trastuzumab Emtansine Dose Modifications

The dose of trastuzumab emtansine can be reduced by two dose levels for management of drug-related toxicities (i.e., from 3.6 mg/kg to 3.0 mg/kg and then from 3.0 mg/kg to 2.4 mg/kg). If further dose reduction is indicated after two dose reductions, the patient must discontinue trastuzumab emtansine. No dose re-escalation of trastuzumab emtansine is permitted in the study.

If significant trastuzumab emtansine-related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days after the last dose was 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, an adverse event of alopecia—even if considered related to trastuzumab emtansine—would most likely not be considered significant. Fatigue may or may not be considered either related to trastuzumab emtansine or significant. In general, when the significant 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 is not $>$42 days from the last dose received. In exceptional situations, patients may resume treatment after more than 42 days delay with the approval of the Medical Monitor or his delegate.

Patients should be re-evaluated weekly during the delay, whenever possible. If dosing resumes, the patient may receive trastuzumab emtansine either at the same dose level as before or at one lower dose level, at the discretion of the investigator. Subsequent cycles should remain Q3W, and patients should be assessed for toxicity as described in Section 5.1.3. If a patient requires a dose reduction, dosing will be reduced by one dose level as per Table 5.

Table 5 Dose Modification Scheme for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level (mg/kg, Q3W)
Starting dose	3.6
First dose reduction	3.0
Second dose reduction	2.4
Requirement for further dose reduction	Discontinue treatment

Q3W = every 3 weeks.

Note: The dose of trastuzumab emtansine, once reduced, may not be re-escalated. A maximum of two dose reductions is allowed; patients with any further requirement for dose reduction will discontinue treatment with trastuzumab emtansine.

No dose re-escalation is permitted. A patient treated with 2.4 mg/kg of trastuzumab emtansine who develops an adverse event requiring a dose reduction must discontinue study treatment and will be followed for safety, disease progression, and survival (Appendix 1 and Appendix 2).

Patients who experience a Grade 3 or 4 hematologic events, other than thrombocytopenia, 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 trastuzumab emtansine. Patients who discontinue trastuzumab emtansine can continue venetoclax/placebo provided that, in the opinion of the investigator, the patient is deriving clinical benefit from venetoclax/placebo. Patients who discontinue both study drugs will be followed for safety, disease progression, and survival (Appendix 1 and Appendix 2).

5.1.3.2 Treatment Interruption

Patients who interrupt venetoclax secondary to treatment-related adverse events for longer than 28 days from the last dose should discontinue venetoclax. However, patients who are deriving benefit from the treatment should continue trastuzumab emtansine treatment.

If significant trastuzumab emtansine–related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for >42 days after the last dose was received. Patients who discontinue trastuzumab emtansine can continue venetoclax/placebo provided that, in the opinion of the investigator, the patient is deriving clinical benefit from venetoclax/placebo and they are to continue evaluation per protocol.

5.1.3.3 Management Guidelines

Guidelines for management of adverse events associated with study treatment are provided in Appendix 9 (venetoclax) and in Appendix 10 (trastuzumab emtansine).

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 9, Appendix 10, and Table 6 below and prescribing information, as outlined below:

Table 6 below provides guidelines for the management of patients who experience the following potential overlapping toxicities for venetoclax and trastuzumab emtansine: hematologic, gastrointestinal, and hepatic events. It is recommended that study treatments be withheld or discontinued per the guidelines below. For these potential overlapping toxicities, refer to guidelines in Table 6.

Appendix 9 provides guidelines for the management of patients who experience venetoclax-specific non-hematologic toxicity that is not specifically described in Table 6. It is recommended that venetoclax be withheld or discontinued per the guidelines in Appendix 9.

Appendix 10 provides guidelines for the management of patients who experience trastuzumab emtansine-associated adverse events such as left ventricular dysfunction, pulmonary toxicity, infusion-related reactions, hypersensitivity, and NRH reactions. It is recommended that trastuzumab emtansine be withheld or discontinued per the guidelines in Appendix 10.

For cases in which management guidelines are not covered in Table 6, Appendix 9, and Appendix 10, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Venetoclax and Trastuzumab Emtansine

NCT CTCAE Category	Dose delay or dose modification

Grade ≥3 febrile neutropenia	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	• Administer treatment including G-CSF or growth factors for neutropenia as indicated and per institutional guidelines.
	  ○ When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo and trastuzumab emtansine.
	• For subsequent episodes of Grade ≥3 febrile neutropenia:
	  ○ Withhold venetoclax/placebo and trastuzumab emtansine.
	  When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo at one dose level reduction (refer to Table 4) and trastuzumab emtansine at previous dose.

Grades 3 and 4 neutropenia	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo and trastuzumab emtansine.
	• For subsequent episodes of Grade 4 neutropenia:
	  ○ Withhold venetoclax/placebo and trastuzumab emtansine.
	  ○ Consider secondary prophylaxis with G-CSF as indicated or per institutional guidelines.
	  When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo at one dose level reduction (refer to Table 4) and trastuzumab emtansine at previous dose.

Grade 3 thrombocytopenia (25,000 to < 50,000/mm^3)	• Withhold venetoclax/placebo. • Withhold trastuzumab emtansine. ○ When platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), resume venetoclax/placebo and trastuzumab emtansine at the previous dose level.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Venetoclax and Trastuzumab Emtansine (cont.)

NCT CTCAE Category	Dose delay or dose modification

Grade 3 thrombocytopenia (platelets 50,000 to 25,000/μL) with clinically significant bleeding; or
 	
Grade 4 thrombocytopenia (platelets < 25,000/μL)
	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ Platelets may be transfused if Grade 4 thrombocytopenia is associated with symptomatic bleeding or in the case of platelet count < 10,000/μL, or per institutional guidelines.
	  ○ When platelet level rises to > 75,000/μL, resume venetoclax/placebo at previous dose. The dose of trastuzumab emtansine should be reduced by one dose level (refer to Table 5).
	• For a subsequent episode of Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia:
	  ○ Withhold both venetoclax/placebo and trastuzumab emtansine.
	  ○ Platelets may be transfused if Grade 4 thrombocytopenia is associated with symptomatic bleeding or in the case of platelet count < 10,000/μL, or per institutional guidelines
	  ○ When platelet level rises to > 75, 000/μL, resume venetoclax/placebo at one dose level reduction (refer to Table 4). The dose of trastuzumab emtansine should be reduced by one dose level (refer to Table 5).
	• For recurrent Grade 4 thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, consult the Medical Monitor regarding continuation on study treatment.

Non-hematologic toxicity	

Grade 1–2 Diarrhea	• Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, antacids), infection by *C. difficile*, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber.
	• Dietary modifications:
	  ○ Stop all lactose-containing products and eat small meals.
	  ○ The BRAT (banana, rice, apples, toast) diet may be helpful.
	  ○ Encourage adequate hydration.
	• Loperamide treatment:
	  ○ Suggested dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool, up to a maximum of 16 mg/day.
	  ○ Recommend to continue loperamide treatment until diarrhea-free for 24 hours.
	  ○ If Grade ≤ 2 diarrhea persists after 48 hours total treatment with loperamide, consider second-line agents (diphenoxylate and atropine or tincture of opium).
	No change in study drug dosing will be implemented for Grade ≤2 diarrhea; patients should receive maximal supportive care as described above.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Venetoclax and Trastuzumab Emtansine (cont.)

NCT CTCAE Category	Dose delay or dose modification

Grade ≥ 3 Diarrhea	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ When diarrhea has improved to Grade ≤ 1, restart venetoclax/placebo and trastuzumab emtansine at the previous dose level.
	• If Grade ≥ 3 diarrhea recurs:
	  ○ Withhold venetoclax/placebo.
	  ○ Withhold trastuzumab emtansine.
	  When diarrhea has improved to Grade ≤ 1, resume venetoclax/placebo at one dose level reduction (refer to Table 4). Resume trastuzumab emtansine at the previous dose level.

Grade ≥ 3 increased transaminase (AST/ALT) (> 5 to ≤ 20× ULN)	• Withhold venetoclax/placebo. • Withhold trastuzumab emtansine. ○ When AST/ALT recovers to Grade ≤2, resume trastuzumab emtansine reduced by one dose level (refer to Table 5). Resume venetoclax/placebo at previous dose.
Grade 4 increased transaminase (AST/ALT) (> 20× ULN)	• Discontinue both trastuzumab emtansine and venetoclax/placebo. ○ Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.
TBILI increase > 1.5 × ULN to ≤ 3 × ULN (Grade 2)	• Withhold both venetoclax/placebo. • Withhold trastuzumab emtansine. When TBILI recovers to ≤ 1.5 × ULN, resume venetoclax/placebo and trastuzumab emtansine at the previous dose level.

TBILI increase > 3 × ULN to ≤ 10 × ULN (Grade 3)	• Withhold both venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ When TBILI recovers to ≤ 1.5 × ULN, resume venetoclax at the previous dose level and trastuzumab emtansine with one dose level reduction (refer Table 5).
	  ○ Discontinue trastuzumab emtansine if the event has not resolved to ≤ 1.5 × ULN within 42 days after the last dose received.

TBILI increase > 10 × ULN (Grade 4)	• Discontinue venetoclax/placebo and trastuzumab emtansine.

TBILI = total bilirubin; ULN = upper limit of normal.

Recommendations for the initial management of electrolyte imbalances and prevention of TLS are provided in Appendix 7. Additional guidelines are provided in the subsections below.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.10 and Section 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- TLS
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with symptomatic bleeding
- Grade ≥3 diarrhea
- Pneumonitis

- Grade ≥3 infusion-related reaction or hypersensitivity reaction
- Grade 4 febrile neutropenia

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of the 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 adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.2.3 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug or initiation of another anticancer therapy (whichever occurs first).

Serious adverse events and adverse events of special interest will continue to be reported (independent of causality) until 90 days after the last dose of study drug or until initiation of new systemic anticancer therapy, whichever occurs first.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that occur after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug), if the event is believed to be related to prior treatment with study drug, regardless if the patient has initiated another anticancer therapy treatment (Section 5.2.3).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of HER2-positive MBC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An IMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Metastatic Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on both clinical and laboratory findings (physical exam, biopsy, breast imaging, radiologic evidence, etc.). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying MBC

An event that leads to hospitalization under the following circumstances is not considered to be serious adverse event, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

- Hospitalization for a minor condition for which the patient suffers an adverse event, but does not meet the definition of an overnight admission (e.g., tooth extraction)

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose}
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For trastuzumab emtansine, venetoclax or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with trastuzumab emtansine, venetoclax or matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D., Ph.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), 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, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug after the final dose of study drug or until initiation of another anticancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 30 days after the final dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever

occurs last. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In 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 trastuzumab emtansine. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. 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.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Trastuzumab emtansine	Trastuzumab Emtansine Investigator's Brochure
Venetoclax	Venetoclax Investigator's Brochure

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

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

An IMC will monitor efficacy and safety data 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 analysis populations are defined as follows:

- The ITT population for the Phase II portion of the study is defined as all randomized patients, whether or not they were assigned to the arm where the study drug was administered.
- The ITT population for the non-randomized cohorts is defined as all enrolled patients who received any drug.
- The Bcl-2 high population consists of patients within the ITT population with $\geq$ 50% of tumor cells stained with an intensity of IHC 2+ or 3+.
- The safety-evaluable population is defined as patients who received any amount of any component of the investigational or non-investigational study treatments.

The ITT population is the primary analysis population for efficacy for the study, and efficacy analyses will be analyzed according to the intended treatment. Efficacy analyses will also be performed in the Bcl-2 high population. Safety analyses will be performed in the safety population according to treatment received.

Analyses will be performed separately for the dose-escalation phase, expansion phase, and randomized Phase II stage of the study.

The primary efficacy analysis will be performed in the ITT population of the randomized Phase II stage, which will be based on the co-primary endpoints of ORR and PFS. A key secondary efficacy analysis will be efficacy analyses in the Bcl-2 high population of the randomized Phase II stage. Descriptive efficacy analyses will also be performed on the non-randomized cohorts.

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Dose-Escalation Phase

The sample size for the dose-escalation phase is based on the dose-escalation rules described in the protocol. The planned enrollment for the dose-escalation phase is approximately 6–24 patients enrolled across 2–4 dose-escalation treatment groups.

6.1.2 Expansion Phase

Approximately 20 patients each may be enrolled in the expansion phase (trastuzumab emtansine-experienced cohort and trastuzumab deruxtecan-experienced cohort).

With 20 patients per cohort and an observed ORR of 60%, the exact 90% Clopper-Pearson confidence interval for the ORR would be 39%–78%, which would rule out an ORR of 35% or less.

Table 8 provides exact 90% confidence intervals for a range of observed proportions of ORR based on a sample size of 20 patients.

Table 8 Potential 90% Confidence Interval Estimated for the True ORR

Observed ORR	Exact 90% Confidence Interval for the True ORR
40%	(22%, 61%)
50%	(30%, 70%)
55%	(34%, 74%)
60%	(39%, 78%)
65%	(44%, 82%)
70%	(50%, 70%)

ORR = objective response rate.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such event in a cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively. Table 9 describes exact 90% confidence intervals for a range of observed proportions of adverse events based on a sample size of 20 patients.

Table 9 Potential 90% Confidence Interval Estimates for Adverse Event Rates

Observed Event Rate	Exact 90% Confidence Interval for the True ORR
1%	(0%, 16%)
5%	(0%, 22%)
10%	(2%, 28%)
20%	(7%, 40%)
30%	(14%, 51%)

ORR = objective response rate.

6.1.3 Randomized Phase II Stage

After the RP2D has been determined for venetoclax when given in combination with a fixed dose of trastuzumab emtansine, a total of 220 patients will be enrolled in the randomized Phase II stage of the study. The purpose of the randomized Phase II stage is estimation and hypothesis generation regarding the effect of venetoclax in combination with trastuzumab emtansine on ORR and duration of PFS relative to trastuzumab emtansine plus placebo. The point and interval estimates of the true underlying HR will be obtained.

For the co-primary endpoints of ORR and PFS in the primary efficacy analysis population, the trial will have:

- 85% power ($\alpha = 0.05$) to detect a 20% improvement in ORR (i.e., ORR Δ) (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm). In the meantime, a 20% improvement in ORR will have a 95% CI of (7%, 33%).
- 90% power ($\alpha = 0.05$) to detect a PFS HR of 0.6 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 161 total PFS events have occurred. In the meantime, a PFS HR of 0.6 will have a 95% CI of (0.44, 0.82). The assumptions of the sample size calculation are that the median PFS in the control arm is 6.8 months and that enrollment would occur non-uniformly over 24 months. Enrollment is anticipated to be lower during the second half of the enrolment period because it will be restricted to the Bcl-2 high population.

Within the Bcl-2 high population the study will have:

- 85% power ($\alpha = 0.05$) to detect a PFS HR of 0.5 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 75 total PFS events have occurred. In the meantime, a PFS HR of 0.5 will have a 95% CI of (0.32, 0.79).

The study will not, however, have adequate power to detect all potentially clinically meaningful differences in ORR and PFS. For example, within the entire ITT population:

- With 110 patients in each arm, there is only 60% power ($\alpha = 0.05$) to detect a 15% improvement in ORR (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm), and
- With approximately 161 total PFS events, only 62% power ($\alpha = 0.05$) to detect an HR of 0.70, in venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm.

Thus, a statistically negative outcome in any of the co-primary endpoints does not necessarily rule out a clinically meaningful outcome. The below tables show the power and CIs for several possible true underlying improvements in ORR and PFS in favor of the venetoclax plus trastuzumab emtansine arm.

Due to the smaller sample size of the Bcl-2 high population the power to detect a HR of 0.60 in the Bcl-2 population is 60% compared to 90% for the entire ITT population. The study has adequate power (85%) to detect a HR of 0.5 in the Bcl-2 high population.

Table 10 Operating Characteristics for Proposed Study Design for Possible True Underlying ORR Δ Values

	True Underlying ORR $\underline{\Delta}$		
	15%	20%	25%
Power to detect ORR Δ [a]	60%	85%	96%
95% confidence interval for true ORR Δ [b]	(2%, 28%)	(7%, 33%)	(12%, 38%)

ORR = objective response rate.

Note: trastuzumab emtansine plus placebo arm is assumed to have an ORR of 44%. Results are based on 110 patients in each arm.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the ORR $\underline{\Delta}$ in each column.

Table 11 Operating Characteristics for Proposed Study Design for Possible True Underlying PFS Hazard Ratio Values

	True Underlying Hazard Ratio			
	0.60	0.65	0.70	0.75
Power of log-rank test [a]	90%	78%	62%	44%
95% confidence interval for true hazard ratio [b]	(0.44, 0.82)	(0.48, 0.89)	(0.51, 0.95)	(0.55, 1.00)

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, median PFS in the trastuzumab emtansine plus placebo arm is 6.8 months, 161 total PFS events.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

Table 12 Operating Characteristics in the Bcl-2 High Group for Proposed Study Design for Possible True Underlying PFS Hazard Ratio Values

	True Underlying Hazard Ratio			
	0.50	0.55	0.60	0.65
Power of log-rank test [a]	85%	73%	60%	46%
95% confidence interval for true hazard ratio [b]	(0.32, 0.79)	(0.35, 0.86)	(0.38, 0.94)	(0.41, 1.00)

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, median PFS in the trastuzumab emtansine plus placebo arm is 6.8 months, 75 total PFS events.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized by treatment arm and for all randomized patients within each phase of the study. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, lines of prior therapy, rapid disease progression to first-line therapy, Bcl-2 status, ER status, site of disease, and presence of visceral/liver metastases) will be summarized using means,

standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES (RANDOMIZED PHASE II STAGE ONLY)

The primary efficacy analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment (the ITT population).

The primary efficacy analysis will occur when 161 patients have experienced a PFS event. It is anticipated that this will occur six months after the last patient enters treatment.

6.4.1 Co-Primary Efficacy Endpoints

6.4.1.1 Objective Response Rate

The co-primary endpoint ORR is defined as the proportion of patients with CR or PR as assessed by the investigator on two consecutive assessments at least 28 days apart using the criteria in RECIST v1.1. Patients with no disease assessments for any reason will be classified as non-responders. An estimate of ORR with 95% CI will be calculated for each treatment arm using the normal approximation to the binomial distribution. An estimate and 95% CI for the difference in ORR between the two treatment groups will be presented based on the normal approximation to the binomial distribution.

6.4.1.2 Progression-Free Survival

The co-primary efficacy endpoint PFS is defined as the time from randomization to the first occurrence of disease progression (as defined by the investigator according to RECIST v1.1) or death from any cause, whichever comes first. Data for patients without the occurrence of disease progression or death as of the clinical data cut-off date will be censored at the time of last tumor assessment (or the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Kaplan-Meier curves of time to PFS for each treatment group will be provided. The Cox proportional hazards model stratified by the randomization stratification factors (Bcl-2 status [high, low], visceral disease [yes, no], and HER2 status IHC 3+ [yes, no] will be used to provide an estimate of the hazard ratio of venetoclax plus trastuzumab emtansine to placebo plus trastuzumab emtansine with associated 95% CI and p-value. The unstratified hazard ratio estimate and 95% CI will also be presented.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Duration of Objective Response

DOR is defined as the time from the first documented objective response (CR or PR) to the time of first documented disease progression (as determined by the investigator using RECIST v1.1) or death from any cause, whichever occurs first. Data for patients

without the occurrence of disease progression or death as of the clinical data cut-off will be censored at the time of the last tumor assessment.

DOR will be estimated using the Kaplan-Meier methodology. Only patients achieving a CR or PR will be included in the assessment of DOR. No formal hypothesis testing will be performed due to the non-randomized population.

6.4.2.2 Overall Survival

OS is defined as time from randomization to death from any cause. Data for patients who are alive at the time of the analysis data cut-off will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day.

OS will be analyzed using the same methodology as PFS (see Section 6.4.1).

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Clinical Benefit Rate

CBR is defined as CR or PR (as defined in Section 6.4.1) or achieving SD lasting ≥6 months from randomization as assessed by the investigator using RECIST v1.1. Patients with no disease assessments for any reason will be classified as non-responders.

CBR will be analyzed using the same methodology as ORR (see Section 6.4.1).

6.4.3.2 Patient-Reported Outcomes Data

Summary statistics and the mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of the EORTC QLQ-C30 and EORTC IL46 (an item for trouble with side effects) questionnaires at each timepoint, at the end of treatment, at the time of progression, and at the time of clinical progression (if different from time to progression). In addition, mean scores for global health status, physical functioning, and selected symptom scales will be presented. The scores will be derived according to the EORTC scoring manual guidelines.

Completion and compliance rates will be summarized at each timepoint by treatment arm. The analysis populations for PRO changes will be all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

Safety will be assessed separately for each study phase through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Individual pharmacokinetic concentration data will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, and maximum) after appropriate grouping. Pharmacokinetic parameters may also be calculated as data allow (e.g., C_{max}, AUC, clearance, volume of distribution, half-life, etc.) and tabulated and/or summarized after appropriate grouping. Population PK analyses of concentration data (with or without the PK data from other studies) may be conducted as appropriate. Potential PK DDIs may be assessed by comparison with relevant historical data for venetoclax and/or trastuzumab emtansine. Potential correlations between exposure and response (e.g., PD, efficacy, ECG, and safety endpoints) may also be explored, if warranted.

The results of population PK analyses and exploratory exposure-response analyses may be reported separately from the clinical study report. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of venetoclax and/or trastuzumab emtansine.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients for trastuzumab emtansine at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if: 1) they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response) or 2) they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies to better understand disease pathobiology and guide the development of new therapeutic approaches. Exploratory biomarker analyses may be performed in an effort to understand the association of these biomarkers with study treatment response. Results will be presented in a separate report.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses (Randomized Phase II Stage Only)

Periodic analyses of cumulative safety data and one interim analysis is planned for this study. Given the hypothesis-generating nature of this study, the Sponsor considers the interim efficacy analysis as exploratory.

The planned interim efficacy analysis of cumulative safety, ORR, and PFS will occur when approximately 56 PFS events have occurred. This is expected to occur after the enrollment of the first 110 patients who have been followed up for at least 6 months.

If the interim analysis coincides within approximately 1 month of a planned safety review, the safety review may be combined with the efficacy interim analyses. Outcomes from these reviews that may affect study conduct will be communicated in a timely manner to the investigators, and IRBs/ECs will be notified.

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 through use of eCRFs. 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 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.

Where PRO data (EORTC QLQ-C30 and IL46) are captured via paper questionnaires, data will be entered into the EDC system by site staff. Otherwise, PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC PATIENT REPORTED OUTCOME DATA

Where an electronic device is be used to capture PRO data, the device will be designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

Where a device-based system is employed, the electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the

data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

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

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

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry

of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or 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 applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

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 (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

In the U.S., this trial will be sponsored and managed by Genentech. F. Hoffmann-La Roche Ltd will sponsor this trial outside of the U.S. with management responsibilities being shared by Genentech and Roche. Genentech and Roche have authorized Roche Registrations, a company formed under the laws of England, to act as their legally authorized representative for the purposes of Article 19 of Directive 2001/20/EC relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use. Reference to “Sponsor” in this protocol will mean Genentech for the United States and F. Hoffmann−La Roche Ltd for all countries outside of the United States.

Approximately 145 sites globally will participate in this study to enroll approximately 284 patients. Data will be recorded via an EDC system from Medidata Solutions (New York, NY, with use of eCRFs; see Section 7.2). Central laboratories will be used for the analyses of and/or management of PK, PD, genotyping, and tissue samples. An IxRS will be used for patient registration, patient number, and dose assignment.

An IMC will review data on a regular basis at predefined timepoints during the study. The IMC will review results from the analyses of unblinded safety data and make recommendations to the Sponsor regarding continuation and/or modification of the study. The final decision on the IMC recommendation will be made by the Sponsor. The details of the composition, roles, and responsibilities of the IMC will be documented in detail in the IMC charter and submitted to Health Authorities as applicable.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application

has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.7 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 Activities: Dose Escalation

Assessment or Procedure	Screening Period	Treatment Period (Cycle 1)				Treatment Period (Cycle 2 through Study Treatment Discontinuation) [a]	Study Treatment Completion/Early Discontinuation [b]	3 Month Follow-Up (±14 Days) [c]
	Days −28 to −1	Day 1	Day 2	Day 8	Day 15	Day 1 (± 3 Days)	≤30 Days after Last Dose of Study Treatment	
Informed consent [d]	x							
Demographics [e]	x							
General medical history [f]	x							
Central HER2 and Bcl-2 testing [g]	x							
Complete physical examination [h]	x							
Limited symptom-directed physical examination [i]		x	x	x	x	x	x	
ECOG performance status	x	x				x	x	
Weight and BSA [j]	x					x		
Vital signs [k]	x	x	x	x	x	x		
Hematology [l]	7 days prior to C1D1	x		x	x	x	x	
Serum chemistry [m]	7 days prior to C1D1	x		x	x	x	x	
TLS laboratory assessments [n]	within 3 days of C1D1 or prior to C1D1 dose	x	x					
Thyroid function test (TSH/free T3/free T4)	x	x				Every 4th cycle	x	
C-reactive protein	x							
INR or aPTT	x	x				As clinically indicated		
HIV, HCV, and HBV serology [o]	x	x						
Urinalysis [p]	x					As clinically indicated		
Pregnancy test [q]	x					x	x	x
Tumor response assessment [r]	x	x				x		

Appendix 1: Schedule of Activities: Dose Escalation (cont.)

Assessment or Procedure	Screening Period	Treatment Period (Cycle 1)				Treatment Period (Cycle 2 through Study Treatment Discontinuation) [a]	Study Treatment Completion/Early Discontinuation [b]	3 Month Follow-Up (±14 Days) [c]
	Days −28 to −1	Day 1	Day 2	Day 8	Day 15	Day 1 (± 3 Days)	≤30 Days after Last Dose of Study Treatment	
Bone scan [s]	x	Perform as clinically indicated or as scheduled tumor assessment if only bone involvement at baseline						
CT or MRI of brain [t]	Mandatory at screening	Perform as clinically indicated or as scheduled tumor assessment [r]						
12-Lead electrocardiogram [u]	x	Perform as clinically indicated						
NYHA classification	x							
ECHO or MUGA scan [v]	x	Every Fourth Cycle Additional LVEF measurements may be performed at the discretion of the investigator if LVEF declines are clinically suspected.					If not performed within 6 weeks of this visit	
Venetoclax administration		x [w]						
Trastuzumab emtansine administration		x [x] (on Day 1 of each cycle)						
Serum and plasma samples for PK analysis		x		x (NC)		C2D1, C4D1, C4D7 (NC) (see Appendix 3)	x	
Blood sample for biomarker analysis		x				C2D1, C3D1, every odd cycle D1 (see Appendix 4)	x	
Blood sample for auto-antibodies [y]	x							
Tissue sample for biomarker analysis [z]	x	x				x (see Appendix 4)	x	
Concomitant medications	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x
Survival follow-up								x [b]

Appendix 1: Schedule of Activities: Dose Escalation (cont.)

Assessment or Procedure	Screening Period	Treatment Period (Cycle 1)				Treatment Period (Cycle 2 through Study Treatment Discontinuation) [a]	Study Treatment Completion/Early Discontinuation [b]	3 Month Follow-Up (±14 Days) [c]
	Days −28 to −1	Day 1	Day 2	Day 8	Day 15	Day 1 (± 3 Days)	≤30 Days after Last Dose of Study Treatment	
Initiation of anticancer treatments								x [b]

ADA = anti-drug antibody; Bcl-2 = B-cell lymphoma 2; BSA = body surface area; C = cycle; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NC = non-continuous; NYHA = New York Heart Association; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Notes: With the exception of Day 1 of Cycle 1, all assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used; such tests do not need to be repeated for screening.

[a] Visit dates for Cycle 2 and subsequent cycles must be calculated utilizing the previous visit date ±3 days.

[b] The treatment completion/discontinuation visit will optimally be scheduled for ≤30 days after last dose of study treatment.

[c] Patients will be followed for survival, serious adverse events, and adverse events of special interest considered as related to study drug (Section 5.4.2). Subsequent anticancer therapies (not all concomitant medications) need to be reported approximately every 3 months starting from the study drug completion visit until death, loss to follow-up, withdrawal of consent, or study discontinuation by the Sponsor. Survival follow-up information will be collected every 6 months via telephone calls, patient medical records, and/or clinic visits. Study staff may use a public information source (e.g., county records) to obtain information about survival status only where permitted.

[d] Written informed consent must be obtained before any study-specific screening assessments are performed.

[e] Demographics include age, sex, and self-reported race/ethnicity.

[f] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements, and foods that have been shown to inhibit CYP3A4 [Section 4.4.2]) used by the patient within 28 days prior initiation of study treatment. Breast cancer history includes prior cancer therapies and procedures.

[g] Refer to Appendix 4 for tissue requirements related to eligibility. HER2 and Bcl-2 status may be determined outside of the screening window of 28 days.

[h] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[j] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline and/or previous cycle.

[k] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Hematology includes CBC, with RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Hematologic evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[m] Serum chemistry includes glucose, BUN or urea, sodium, magnesium, chloride, bicarbonate, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[n] TLS laboratory assessments collected during dose escalation include serum creatinine, uric acid, potassium, calcium, phosphorous and LDH. If the screening assessments were done within 3 days prior to Cycle 1, Day 1, there is no need to repeat the TLS panel at Cycle 1, Day 1. Refer to Appendix 8 for further instructions.

[o] All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV serology includes HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA. HBV DNA must be collected on or before Cycle 1, Day 1, in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc. HCV serology includes HCV antibody and (if HCV antibody test is positive) HCV RNA.

[p] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

[q] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. During the treatment period, a urine pregnancy test in women of childbearing potential in all treatment arms must be performed within 3 days prior study drug administration of every 3rd cycle of protocol-mandated therapy. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For patients who discontinue therapy before end of planned therapy, a pregnancy test must be done at the completion/early termination visit (within 28 days after the last dose of HER2-targeted therapy), at 3 months, and additionally at 6 months after the discontinuation of study treatment.

[r] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. See Section 4.5.5 for details on imaging and tumor assessments. Tumor response will be evaluated using RECIST v1.1 (Appendix 11). In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first. Results must be reviewed by the investigator before dosing at the next cycle. All tumor assessments should be documented in the eCRF before and after the primary PFS analysis.

[s] A bone scan is to be performed within 28 days prior to Cycle 1, Day 1 (see Section 4.5.5 for further instructions).

[t] CT/MRI scan of the brain is mandatory at screening and should be performed 1) with scheduled tumor assessments when identified as a site of involvement at baseline, 2) as clinically indicated, or 3) if a patient demonstrates control of systemic disease but has a newly developed isolated brain metastases and is eligible to remain on study treatment, a brain MRI or CT will be performed along with regularly scheduled tumor assessments.

[u] A 12-lead ECG is required at screening. Subsequent ECGs may be performed as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[v] LVEF assessment by ECHO is preferred, but LVEF may also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

[w] Venetoclax will be administered on a once daily dosing schedule.

[x] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Cycle 1 Day 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[y] Auto-antibody testing includes anti-nuclear antibody, anti-double-stranded DNA, and circulating and perinuclear anti-neutrophil cytoplasmic antibody. The baseline sample will be obtained pre-treatment at Cycle 1, Day 1, before the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally.

[z] At screening, the FFPE archival tumor block from the most recently collected, available tumor tissue or fresh core biopsy (3 cores) is mandated. If more than one FFPE block exists from different timepoints (e.g., initial diagnosis vs. metastatic disease tissue), the most recent block is mandatory to be sent. If the FFPE block from the earlier timepoint is available, then this would be requested to also be sent. In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided. At least 20 freshly serial cut, unstained slides will be acceptable in lieu of the FFPE block. Optional core biopsies will be obtained at Cycle 1, Day 1 and on Day 1 of any subsequent on treatment cycle (± 3 days) if patient consented. At the study drug discontinuation/early study completion visit, if reason for discontinuation is disease progression, a biopsy must be taken (if deemed clinically feasible) before next line of therapy begins, unless purely anti-hormonal therapy.

Appendix 2
Schedule of Activities: Expansion Cohorts/Randomized Phase II

Assessment or Procedure	Screening Period Days –28 to –1	Treatment Period (Cycle 1) Day 1	Treatment Period (Cycles 2 through Study Treatment Discontinuation) [a] Day 1 (± 3 Days)	Study Treatment Completion/Early Discontinuation [b] ≤ 30 Days after Last Dose of Study Treatment	3 Month Follow-Up (±14 Days) [c]
Informed consent [e]	x				
Demographics [e]	x				
General Medical history [f]	x				
Central HER2 and Bcl-2 testing [g]	x				
Complete physical examination [h]	x				
Limited symptom-directed physical examination [i]		x	x	x	
ECOG performance status	x	x	x	x	
Weight and BSA [j]	x		x		
Vital signs [k]	x	x	x		
Hematology [l]	7 days prior to C1D1	x	x	x	
Serum chemistry [m]	7 days prior to C1D1	x	x	x	
TLS laboratory assessments [n]	within 3 days of C1D1 or prior to C1D1 dose	x			
Thyroid function test (TSH/free T3/free T4)	x	x	Every 4th cycle	x	
C-reactive protein	x				
INR or aPTT	x	x	As clinically indicated		
HIV, HCV, and HBV serology [o]	x	x			
Urinalysis [p]	x		As clinically indicated		
Pregnancy test [q]	x		x	x	x

Appendix 2: Schedule of Activities: Expansion Cohorts/Randomized Phase II (cont.)

Assessment or Procedure	Screening Period Days –28 to –1	Treatment Period (Cycle 1) Day 1	Treatment Period (Cycles 2 through Study Treatment Discontinuation) [a] Day 1 (± 3 Days)	Study Treatment Completion/Early Discontinuation [b] ≤ 30 Days after Last Dose of Study Treatment	3 Month Follow-Up (±14 Days) [c]
Tumor and response assessment [r]	x	x	x		
CT or MRI of brain [s]	Mandatory at screening	Perform as clinically indicated or as scheduled tumor assessment [t]			
12-Lead electrocardiogram [u]	x	Perform as clinically indicated			
NYHA classification	x				
ECHO or MUGA scan [v]	x	x[w]		If not performed within 6 weeks of this visit	
Venetoclax/placebo administration		x [x]			
Trastuzumab emtansine administration		x [y] (on Day 1 of each cycle)			
Serum and plasma samples for PK/ADA analysis		x [z]	C2D1, C4D1, C4D8 (NC) (See Appendix 3)	x	
Blood sample for biomarker analysis		x [aa]	C2D1, C3D1, Every Odd Cycle D1 (See Appendix 4)	x	
Blood sample for auto-antibodies [bb]	x				
Tissue sample for biomarker analysis [cc]	x	x	x (See Appendix 4)	x	
Concomitant medications	x	x	x	x	
Adverse events	x	x	x	x	x
Survival follow-up					x [b]
Initiation of anticancer treatments					x [b]

ADA = anti-drug antibody; Bcl-2 = B-cell lymphoma 2; BSA = body surface area; C = cycle; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NC = non-continuous; NYHA = New York Heart Association; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Notes: With the exception of Day 1 of Cycle 1, all assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used; such tests do not need to be repeated for screening.

[a] Visit Dates for Cycle 2 and subsequent cycles must be calculated utilizing the previous visit date ±3 days.

[b] The treatment completion/discontinuation visit will optimally be scheduled for ≤30 days after last dose of study treatment.

[c] Patients will be followed for survival, serious adverse events, and adverse events of special interest considered as related to study drug (Section 5.4.2). Subsequent anticancer therapies (not all concomitant medications) need to be reported approximately every 3 months starting from the study drug completion visit until death, loss to follow-up, withdrawal of consent, or study discontinuation by the Sponsor. Survival follow-up information will be collected every 6 months via telephone calls, patient medical records, and/or clinic visits. Study staff may use a public information source (e.g., county records) to obtain information about survival status only where permitted.

[d] Written informed consent must be obtained before any study-specific screening assessments are performed.

[e] Demographics include age, sex, and self-reported race/ethnicity.

[f] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements, and foods that have been shown to inhibit CYP3A4 [Section 4.4.2]) used by the patient within 28 days prior to the Cycle 1, Day 1 visit. Breast cancer history includes prior cancer therapies and procedures.

[g] Refer to Appendix 4 or tissue requirements related to eligibility. HER2 and or Bcl-2 status are required and must be centrally confirmed prior to treatment.

[h] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[j] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline and/or previous cycle.

[k] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Hematology includes CBC, with RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Hematologic evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[m] Serum chemistry includes glucose, BUN or urea, sodium, magnesium, chloride, bicarbonate, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[n] TLS assessment frequency during the dose-expansion and randomized phases will be determined based on a comprehensive review of data in the dose-escalation phase. TLS laboratory assessments include serum creatinine, uric acid, potassium, calcium, phosphorous and LDH. If the screening assessments were done within 3 days prior to Cycle 1 Day 1, there is no need to repeat the TLS panel at Cycle 1 Day 1. Refer to Appendix 8 for further instructions.

[o] All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV DNA must be collected on or before Cycle 1, Day 1, in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

[p] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

[q] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. During the treatment period, a urine pregnancy test in women of childbearing potential in all treatment arms must be performed within 3 days prior study drug administration of every 3rd cycle of protocol-mandated therapy. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For patients who discontinue therapy before end of planned therapy, a pregnancy test must be done at the completion/early termination visit (within 28 days after the last dose of HER2-targeted therapy), at 3 months, and additionally at 6 months after the discontinuation of study treatment.

[r] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. See Section 4.5.5 for details on imaging and tumor assessments. Tumor response will be evaluated using RECIST v1.1 (Appendix 11). In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first. Results must be reviewed by the investigator before dosing at the next cycle. All tumor assessments should be documented in the eCRF before and after the primary PFS analysis.

[s] CT/MRI scan of the brain is mandatory at screening and should be performed 1) with scheduled tumor assessments when identified as a site of involvement at baseline, 2) as clinically indicated, or 3) if a patient demonstrates control of systemic disease but has a newly developed isolated brain metastases and is eligible to remain on study treatment, a brain MRI or CT will be performed along with regularly scheduled tumor assessments.

[t] A bone scan is to be performed within 28 days prior to Cycle 1, Day 1 (see Section 4.5.5 for further instructions).

[u] A 12-lead ECG is required at screening. Subsequent ECGs may be performed as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[v] LVEF assessment by ECHO is preferred, but LVEF may also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

[w] ECHO or MUGA assessments will be performed every fourth cycle. Additional LVEF or MUGA measurements may be performed at the discretion of the investigator if LVEF declines are clinically suspected.

[x] Venetoclax/placebo will be administered on a once daily dosing schedule.

[y] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Cycle 1 Day 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[z] Serum and plasma samples for PK/ADA analysis will take place on Cycle 1, Day 1 for all patients and on Cycle 1, Day 8 for NC patients.

[aa] Blood for biomarker analysis will take place on Cycle 1, Day 1.

[bb] Auto-antibody testing includes anti-nuclear antibody, anti-double-stranded DNA, and circulating and perinuclear anti-neutrophil cytoplasmic antibody. The baseline sample will be obtained pre-treatment at Cycle 1, Day 1, before the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally.

[cc] At screening, the FFPE archival tumor block from the most recently collected, available tumor tissue or fresh core biopsy (3 cores) is mandated. If more than one FFPE block exists from different timepoints (e.g., initial diagnosis vs. metastatic disease tissue), the most recent block is mandatory to be sent. If the FFPE block from the earlier timepoint is available, then this would be requested to also be sent. In cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided. At least 20 freshly serial cut, unstained slides will be acceptable in lieu of the FFPE block. Optional core biopsies will be obtained at Cycle 1, Day 1 and on Day 1 of any subsequent on treatment cycle (±3 days) if patient consented. At the study drug discontinuation/early study completion visit, if reason for discontinuation is disease progression, a biopsy must be taken (if deemed clinically feasible) before next line of therapy begins, unless purely anti-hormonal therapy.

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Samples

Table 1 Continuous Daily Venetoclax Dosing

Study Visit	Venetoclax (Plasma PK Sample) [a]	Total Trastuzumab (Serum PK Sample) [b]	Trastuzumab Emstansine (Serum PK Sample) [c]	ADA to Trastuzumab Emstansine (Serum ADA Sample) [c]
Cycle 1, Day 1		Pre-infusion of trastuzumab emtansine (Within 24 hr prior to dosing)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 min after end of trastuzumab emtansine infusion	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
Cycle 2, Day 1	Predose (within 1 hr before dosing) 4 hr postdose (±20 min)	------	Pre-infusion of trastuzumab emtansine (within 24 hours prior to dosing)	------
Cycle 4, Day 1	Predose (within 1 hr before dosing) 4 hr postdose (±20 min)	------	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 minutes after end of trastuzumab emtansine infusion (±10 min)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
120 days (±28 days) after treatment completion or discontinuation	------	------	------	Anytime during visit

ADA = anti-therapeutic antibody; hr = hour; min = minute; PK = pharmacokinetic.

Notes: PK and ADA samples are to be collected, prepared, and shipped according to procedures outlined in the separate laboratory manual. Record exact date and time of venetoclax dosing on the day of and the day prior to the date of PK sampling. Patients should record venetoclax doses taken at home in a dosing diary. Record exact date and time of all PK and ADA sample collections. Sample collection times are relative to the administration of the study drug being measured.

[a] Venetoclax should be administered in the clinic on days that venetoclax PK sample is to be taken. Venetoclax PK will be collected for patients enrolled in all study phases.

[b] Total trastuzumab PK will be collected for patients enrolled in all study phases.

[c] Trastuzumab emtansine PK and ADA to trastuzumab emtansine samples will only be collected for patients enrolled in the randomized Phase II stage.

Table 2 Schedule of Pharmacokinetic and ADA Assessments for Non-Continuous 7/21 or 14/21 Venetoclax Dosing

Study Visit	Venetoclax (Plasma Sample) [a]	Total Trastuzumab (Serum Sample) [b]	Trastuzumab Emstansine (Serum Sample)[c]	ADA to Trastuzumab Emtansine (Serum Sample) [c]
Cycle 1, Day 1		Pre-infusion of trastuzumab emtansine (Within 24 hr prior to dosing)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 min after end of trastuzumab emtansine infusion	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
Cycle 1, Day 8 [d]	Predose (within 1 hr before dosing) 4 hr postdose (±20 minutes)	------	------	------
Cycle 2, Day 1	------	------	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)	------
Cycle 4, Day 1	------	------	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 minutes after end of trastuzumab emtansine infusion (±10 min)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
Cycle 4, Day 8 [d]	Predose (within 1 hour before dosing) 4 hours postdose (±20 min)	------	------	------
120 days (±28 days) after treatment completion or discon.	------	------	------	Anytime during visit

ADA = anti-therapeutic antibody; discon = discontinuation; hr = hour; min = minute; PK = pharmacokinetic.

Notes: PK and ADA samples are to be collected, prepared, and shipped according to procedures outlined in the separate laboratory manual.

Record exact date and time of venetoclax dosing on the day of and the day prior to the date of PK sampling. Patients should record venetoclax doses taken at home in a dosing diary. Record exact date and time of all PK and ADA sample collections. Sample collection times are relative to the administration of the study drug being measured.

[a] Venetoclax should be administered in the clinic on days that venetoclax PK sample is to be taken. Venetoclax PK will be collected for patients enrolled in all study phases.

[b] Total trastuzumab PK will be collected for patients enrolled in all study phases.

[c] Trastuzumab emtansine PK and ADA to trastuzumab emtansine samples will only be collected for patients enrolled in the randomized Phase II stage.

[d] For a 7 out of 21 day venetoclax dosing schedule, where no dose is scheduled on Day 8 of each cycle, samples should be drawn on Day 7 of the cycle, with allowance to collect on Day 5 or 6 to avoid a weekend or holiday.

Appendix 4
Biomarker Assessments

Table 1 Blood Samples for Biomarker Analysis

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pre-infusion	Whole blood sample [a]
		Blood for plasma
Cycle 2, Day 1	Pre-infusion	Blood for plasma
Cycle 3, Day 1	Pre-infusion	Blood for plasma
Every Odd Cycle, Day 1	Pre-infusion	Blood for plasma
Study Treatment/Early Discontinuation Visit	At any time during visit	Blood for plasma

[a] Whole blood sample will be taken from all patients enrolled in the study.

Table 2 Tissue Sample for Biomarker Analysis

Visit	Timepoint	Requirement	Sample Type
Screening	Pre-infusion	Mandatory	○ FFPE archival tumor block or partial block most recently collected, available tumor tissue or Fresh core biopsy (3 cores) ○ If more than 1 FFPE blocks exists from different time points e.g. initial diagnosis vs. metastatic disease tissue, the most recent block or partial block is mandatory to be sent. If the FFPE block from the earlier timepoint is available then this would be requested to also be sent. ○ In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided ○ Upon discussion with the Medical Monitor (in case of site regulations that prevent sending a block), at least 20 freshly serial cut, unstained slides will be acceptable in lieu of FFPE block. ○ If fewer than unstained slides are available at baseline, discuss with the Medical Monitor to decide on eligibility.
Cycle 1 Day 1	Pre-infusion (within 28 days of C1D1)	Optional	Fresh Core Biopsy (3 cores) FFPE block or partial block preferred or freshly serial cut, at least 20 freshly serial cut slides
Any Subsequent on-treatment Cycle Day 1	Pre-infusion	Optional	Fresh Core Biopsy (3 cores) FFPE block or partial block preferred or freshly serial cut, at least 20 freshly serial cut slides
Study Treatment/ Early Discontinuation Visit	At time of Study treatment/early discontinuation visit (if the reason for discontinuation was PD) Must be taken before next line of therapy begins. In case new line therapy is purely anti-hormonal, biopsy could be taken after it is started.	Mandatory (if deemed clinically feasible)	Fresh Core Biopsy (3 cores) at site of progression if accessible or from any other lesion FFPE block preferred or freshly serial cut, at least 20 freshly serial cut slides

Appendix 5
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
- Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 6
Patient-Reported Outcomes Questionnaires

Figure 1 EORTC QLQ-30 (Version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

Figure 1 EORTC QLQ-30 (Version 3) (cont.)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Figure 2 EORTC IL46

EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 7
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

FIRST DOSE OF VENETOCLAX

- Within the first 24 hours after the first dose, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150–200 mL/hr; not $<$ 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS) (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

In addition to the recommendations for patients receiving first dose of venetoclax:

- For potassium increase $\geq$ 0.5 mmol/L from baseline, or any value $>$ 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of $>$ 0.5 mg/dL AND $>$ 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

The Sponsor may explore a different TLS lab schedule in the randomized Phase II expansion portion of the study based on findings in dose-escalation phase.

Appendix 8
Guidelines for Defining Tumor Lysis Syndrome

All tumor lysis syndrome events should be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 criteria.

Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days after the start of therapy. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (±alkalinization) and a hypouricemic agent(s).

Table 1 Howard Definition of Laboratory Tumor Lysis Syndrome

Laboratory Assessment	Range
Uric acid	>476 μmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/L (<7.0 mg/dL) or ionized calcium <1.12 (0.3 mmol/L) [a]

Note: Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

[a] The corrected calcium level in mg/dL is the measured calcium in mg/dL + (0.8 × [4-albumin in g/dL]).

Table 2 Howard Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory TLS and one or more of the following criteria:
Creatinine [a]: An increase in serum creatinine level of 0.3 mg/dL (26.5 µmol/L); a single value >1.5 times the ULN of the age appropriate normal range if no baseline creatinine measurement is available; or the presence of oliguria, defined as average urine output of <0.5 mL/kg/hour for 6 hours
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia[b]

TLS=tumor lysis syndrome; ULN=upper limit of normal.

[a] Acute kidney injury is defined as an increase in the creatinine level of ≥0.3 mg/dL (26.5 umol/L) or a period of oliguria lasting ≥6 hours. By definition, if acute kidney injury is present, the patient has clinical TLS.

[b] Not directly attributable to a therapeutic agent.

REFERENCE

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New Engl J Med 2011;364:1844–54.

Appendix 9
Management of Venetoclax-Specific Adverse Events

Event	Action to Be Taken
Non-hematologic toxicity (Not specifically described in Table 6)	
Grade 3 or 4 non-hematologic events	• Delay venetoclax for a maximum of 28 days. First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose level reduction. • Certain treatment emergent non-hematologic adverse events (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases, if a patient is clinically stable, resumption of study drug may be possible after consultation with the Medical Monitor.
Grade 2 related non-hematologic toxicity	• Delay treatment with venetoclax until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. • After resolution, resume full dose of venetoclax.
Grade 1 non-hematologic toxicity	• No dose reduction or delay.

Appendix 10
Management of Trastuzumab Emtansine-Specific Adverse Events

Event	Action to Be Taken
Left ventricular dysfunction	
Symptomatic congestive heart failure	Discontinue trastuzumab emtansine.
Asymptomatic LVEF decrease	
LVEF $>45\%$	Continue trastuzumab emtansine at the same dose level.
LVEF 40% to $\leq 45\%$ and decrease from baseline of $\geq 10\%$ points	Withhold trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF decrease from baseline of $\geq 10\%$ points is confirmed, discontinue trastuzumab emtansine.
LVEF 40% to $\leq 45\%$ and decrease from baseline of $<10\%$ points	Continue trastuzumab emtansine at the same dose level. Repeat LVEF assessment within 3 weeks.
LVEF $<40\%$	Withhold trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF $<40\%$ is confirmed, discontinue trastuzumab emtansine.
Infusion-related reaction (caused by cytokine release) or hypersensitivity (allergic) reaction	
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may

Event	Action to Be Taken
	be given at the investigator's discretion.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.
Neurotoxicity	
Grade ≥3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤2 within 42 days after the last dose received.
Interstitial Lung Disease and Pneumonitis	
Grades 1–4	Discontinue trastuzumab emtansine treatment.
NRH	If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered. Discontinue trastuzumab emtansine treatment and have the patient evaluated by a hepatologist.

LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction; NRH = Nodular Regenerative Hyperplasia.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm 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.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and 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 measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation .

ASSESSMENT OF TUMOR BURDEN

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.

IDENTIFICATION 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 considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. 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").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring 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 node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) 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 measurement 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 "too small to measure" 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 "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. 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.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, 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 lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: 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 all 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.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

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.

REFERENCES

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.

Appendix 12
National Cancer Institute Common Terminology Criteria

In the present study, toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

A pdf of the NCI CTCAE v5.0 can be downloaded from the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Investigators who do not have access to Internet can contact the Data Center to receive a hard copy of this document by mail.

Appendix 13
Guidelines for Liver Biopsy

Because nodular regenerative hyperplasia (NRH) can be a very subtle diagnosis to make on liver biopsy, every attempt should be made to maximize the amount of tissue obtained.

The needle used should be at least 18 gauge, and percutaneous biopsies of length at least 1.5 cm are recommended, if clinically appropriate. In order to diagnose NRH, reticulin and trichrome stains are necessary.

Smaller biopsies obtained via a transjugular approach and smaller biopsy gun needle biopsies are discouraged. Small wedge biopsies should also be discouraged.

Appendix 14
Sample List of Excluded and Cautionary Medications

Examples of Strong and Moderate CYP3A Inhibitors and Inducers

CYP3A Inhibitors		CYP3A Inducers	
Strong	**Moderate**	**Strong**	**Moderate**
boceprevir	aprepitant	apalutamide	bosentan
clarithromycin	ciprofloxacin	carbamazepine	efavirenz
cobicistat	conivaptan	enzalutamide	etravirine
danoprevir	crizotinib	mitotane	phenobarbital
dasabuvir	cyclosporine	phenytoin	primidone
elvitegravir	diltiazem	rifampin	
idelalisib	dronedarone	St. John's Wort	
indinavir	erythromycin		
itraconazole	fluconazole		
ketoconazole	fluvoxamine		
lopinavir	imatinib		
nefazodone	tofisopam		
nelfinavir	verapamil		
ombitasvir			
paritaprevir			
posaconazole			
ritonavir			
saquinavir			
telaprevir			
telithromycin			
tipranavir			
troleandomycin			
voriconazole			

Refer to Section 4.4.3 for guidance related to prohibited and cautionary medications.

Examples of P-gp Substrates and Inhibitors

P-gp	
Substrates	**Inhibitors** [a]
dabigatran	amiodarone
digoxin	carvedilol
etexilate	clarithromycin
fexofenadine	dronedarone
	itraconazole
	lapatinib
	lopinavir
	propafenone
	quinidine
	ranolazine
	ritonavir
	saquinavir
	telaprevir
	tipranavir
	verapamil

P-gp=P-glycoprotein.

[a] These are anticancer agents; consult the Medical Monitor before use.

Refer to Section 4.4.3 for guidance related to prohibited and cautionary medications.

PROTOCOL

TITLE: **A PHASE Ib/II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH TRASTUZUMAB EMTANSINE IN PATIENTS WITH PREVIOUSLY TREATED HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**

PROTOCOL NUMBER: CO41863

VERSION NUMBER: 2 (VHP)

EUDRACT NUMBER: 2019-004200-35

IND NUMBER: 137088

NCT NUMBER: NCT04298918

TEST PRODUCT: Venetoclax (RO5537382)
Trastuzumab emtansine (RO5304020)

MEDICAL MONITOR: [redacted], M.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: See electronic date stamp below.

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
06-Apr-2020 20:30:50	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	19 December 2019

PROTOCOL AMENDMENT, VERSION 2 (VHP): RATIONALE

Protocol CO41863 has been amended to address a request from the Italian Health Authority, the reference competent authority in this Voluntary Harmonisation Procedure (VHP). Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 3.1.1 has been revised to clarify that the dose de-escalation decision will depend on the severity and timing of the DLTs as well as the specific adverse events, including those that result in dose interruption and modifications.
- Section 4.1.1 has been updated to add inclusion criteria requiring prior exposure to pertuzumab.
- Section 4.1.1.1 has been updated to add inclusion criteria specific to the dose-escalation phase requiring prior exposure to trastuzumab emtansine.
- Sections 4.5.9.1 and 7.3 have been amended to remove text relating to electronic collection of patient reported outcome data.
- Section 5.1.1.1 has been revised to include tumor lysis syndrome (TLS) language and literature references more appropriate for the target population in this trial.
- Section 5.1.1.1 has been updated to provide guidance on potential predisposing risk factors for TLS for the target population in this trial.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IB/II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH TRASTUZUMAB EMTANSINE IN PATIENTS WITH PREVIOUSLY TREATED HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	CO41863
VERSION NUMBER:	2 (VHP)
EUDRACT NUMBER:	2019-004200-35
IND NUMBER:	137088
NCT NUMBER:	NCT04298918
TEST PRODUCT:	Venetoclax (RO5537382) Trastuzumab emtansine (RO5304020)
MEDICAL MONITOR:	[redacted], M.D.
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 retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE: **A PHASE Ib/II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF VENETOCLAX IN COMBINATION WITH TRASTUZUMAB EMTANSINE IN PATIENTS WITH PREVIOUSLY TREATED HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**

PROTOCOL NUMBER:	CO41863
VERSION NUMBER:	2 (VHP)
EUDRACT NUMBER:	2019-004200-35
IND NUMBER:	137088
NCT NUMBER:	NCT04298918
TEST PRODUCT:	Venetoclax (RO5537382) Trastuzumab emtansine (RO5304020)
PHASE:	Ib/II
INDICATION:	Locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the "randomized Phase II stage").

The dose-escalation phase will assess safety and tolerability, determine the maximum tolerated dose (MTD) and the recommended Phase II dose (RP2D), and evaluate *the* preliminary efficacy of trastuzumab emtansine in combination with venetoclax in patients with previously treated HER2-positive unresectable locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) *who have received prior* trastuzumab emtansine in the metastatic setting.

Once the RP2D is established, additional patients may be enrolled in the expansion phase to evaluate the safety, tolerability, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D in patients with previously treated HER2-positive LABC or MBC who have previously received either trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a). The decision to open these cohorts will be data-driven and dependent on the observations made in the dose-escalation phase, as well as emerging data about trastuzumab deruxtecan and other HER 2-targeted therapies. Importantly, the expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

The randomized Phase II stage will aim to evaluate the safety, tolerability, pharmacokinetics, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D compared with trastuzumab emtansine plus placebo in patients with previously treated HER2-positive LABC or MBC who have not received prior trastuzumab emtansine therapy, either alone or in combination with other anticancer therapies. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Endpoints for Dose-Escalation Phase

Primary Safety Objective

The safety objective for the dose-escalation phase is to evaluate the safety and tolerability of trastuzumab emtansine in combination with venetoclax—including estimation of the MTD, determination of the RP2D, and characterization of dose-limiting toxicities (DLTs)—on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Exploratory Efficacy Objective

The exploratory efficacy objective for the dose-escalation phase is to make a preliminary assessment of the anti-tumor activity of trastuzumab emtansine and venetoclax on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with complete response (CR) or partial response (PR) on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for the dose-escalation phase of this study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Objectives and Endpoints for Expansion Phase

Primary Efficacy Objective

The primary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- ORR

Secondary Efficacy Objective

The secondary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- DOR

Safety Objective

The safety objective for the expansion phase is to evaluate the safety and tolerability of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The PK objective for the expansion phase of the study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Objectives and Endpoints for Randomized Phase II Stage

Primary Efficacy Objective

The primary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following co-primary endpoints:

- ORR
- Progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

Secondary Efficacy Objective

The secondary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- DOR
- Overall survival (OS) after randomization, defined as the time from randomization to death from any cause

Exploratory Efficacy Objective

The exploratory efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Clinical benefit rate (CBR), defined as the proportion of patients with CR, PR, or stable disease (SD) at 6 months after randomization, as determined by the investigator according to RECIST v1.1

Safety Objective

The safety objective for the randomized Phase II stage is to evaluate safety of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Incidence and severity of adverse events with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The PK objective for the randomized Phase II stage of this study is to characterize the pharmacokinetics of trastuzumab emtansine and venetoclax when given in combination on the basis of the following endpoints:

- Serum concentrations of trastuzumab emtansine at specified timepoints
- Plasma concentrations of venetoclax at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to trastuzumab emtansine when given with placebo or in combination with venetoclax on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Patient Reported Outcome Objective

The *patient-reported outcome* objective for the randomized Phase II stage is to evaluate *the efficacy* of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoint:

- Change from baseline in patient-reported symptoms and their impact on functioning and health-related quality of life*, and overall burden of side effects,* as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and EORTC Item List 46 (EORTC IL46) *item*

Study Design

Description of Study

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the "randomized Phase II stage"). The expansion phase may run concurrent to and *in* parallel with the randomized Phase II stage.

Dose-Escalation Phase

The dose-escalation phase will determine the RP2D and MTD for venetoclax when given in combination with a fixed dose of trastuzumab emtansine (3.6 mg/kg) in patients with previously treated, HER2-positive LABC or MBC *having received* prior trastuzumab emtansine in the metastatic setting.

The dose-escalation phase will enroll 6–24 patients and will include 2–4 cohorts:

- Cohort 1A, 400 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (every 3 weeks [Q3W]) and venetoclax 400 mg orally (PO) once a day (QD) continuous on Days 1–21 of each cycle.
- Cohort 1B, 400 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 400 mg PO QD non-continuous (NC) on either Days 1–7 or 1–14 of each cycle.
- Cohort 2A, 800 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD continuous on Days 1–21 of each cycle.
- Cohort 2B, 800 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD non-continuous on either Days 1–7 or 1–14 of each cycle.

The 400-mg and 800-mg cohorts for dose escalation will be run sequentially (i.e., the 400-mg cohort followed by the 800-mg cohort). Dose escalation will be performed based on a standard 3 + 3 design. Each cohort will consist of at least 3 patients, unless 1 of the 3 patients experiences DLTs (refer to the protocol for DLT criteria), in which case 3 additional patients will be treated at the same dose level. The dose escalation will continue until 2 patients among a cohort of 6 patients experience a DLT (i.e., ≥33% of patients with a DLT at that dose level; refer to dose-escalation rules in the protocol). Patients who experience a DLT will continue at the same dose level.

Dose de-escalation may be explored by incorporating non-continuous (NC) dosing of venetoclax (e.g., less than 21 days of dosing, such as 7 days out of 21 days or 14 days out of 21 days) dependent on the severity and timing of DLTs as well as the specific adverse events*, including those that result in dose interruptions or dose modifications*. For example, if DLTs such as a Grade 3 rash occurred between Day 8 and Day 14, an NC schedule of Days 1–7 would be tested. Alternatively, if DLTs are thought to be possibly mitigated by a 7-day break such as Grade 3 fatigue occurring near the end of the DLT window (e.g., Day 20), then an NC schedule of Days 1–14 could be chosen to be tested. Patients may be treated in up to two NC sub-cohorts (i.e., either 400 mg NC and/or 800 mg NC). At each dose de-escalation level, either a Days 1–7 or Days 1–14 NC treatment schedule will be assessed.

Refer to the protocol for definition of DLT, dose-escalation rules, and determination of DLTs and RP2D.

Expansion Phase

An expansion phase may be initiated to evaluate the safety, tolerability, and efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine in previously treated HER2-positive locally advanced or MBC patients who have received prior trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a).

The decision to open cohorts as part of an expansion phase will be data-driven and dependent on the observations made in the dose-escalation phase, emerging data with trastuzumab deruxtecan, as well as other HER2-targeted therapies. The expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

Randomized Phase II Stage

The randomized Phase II stage will be initiated once the RP2D has been identified based on the cumulative data collected from the dose-escalation phase. It will consist of two interventional arms of trastuzumab emtansine plus placebo or trastuzumab emtansine plus venetoclax in patients with previously treated HER2-positive LABC or MBC, who have not received prior trastuzumab emtansine therapy.

Approximately 220 patients will be randomized 1:1 to one of the following treatment arms:

- Control Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus placebo at the RP2D and schedule of venetoclax.
- Experimental Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus venetoclax at the RP2D and schedule.

Each arm will include at least 50% Bcl-2 high patients. Randomization will be stratified according to the following criteria:

- Bcl-2 status (Bcl-2 high vs. Bcl-2 low)
- Visceral disease (Yes vs. No)
- HER2 status IHC 3+ (Yes vs. No)

Number of Patients

Approximately 226–284 patients will be enrolled in this study across approximately 145 sites globally. The study will enroll 6–24 patients in Part 1 of the study and approximately 220 patients in Part 2. An additional approximately 20–40 patients may be enrolled in the expansion cohorts.

Target Population

Inclusion Criteria (All Study Phases)

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed invasive MBC or LABC that is incurable, unresectable, and previously treated with multimodality therapy:
  - Prior treatment for BC in the adjuvant, unresectable locally advanced, or metastatic settings, which must include a taxane, trastuzumab (alone or in combination with another agent), *and pertuzumab*
    - *For patients who have not received pertuzumab in early breast cancer setting, prior treatment with pertuzumab in the metastatic setting is required prior to enrollment*
  - Progression must have occurred during or after most recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy
- Measurable disease that is evaluable per RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Willing to provide tumor biopsy sample at the time of screening

  A tumor biopsy sample (either archival or fresh) must be collected from all patients from either the primary tumor or a metastatic site (preferred and within 6 months of enrollment, if clinically feasible) for determination of HER2 status by central laboratory testing for patient eligibility purposes, for Bcl-2 expression, and for research on biomarkers.

  The tumor specimen must contain adequate evaluable tumor cells (≥ 20% tumor cells) to enable Bcl-2, HER2, and other relevant biomarker analysis. Samples can be a tissue block (preferred) or at least 20 unstained freshly cut serial slides. If fewer than 20 slides are available, the Sponsor should be consulted. If a tumor sample is not available, a fresh biopsy must be collected.

The specimen must be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration samples are not acceptable.

- Local histological or cytological confirmation of estrogen receptor (ER) and/or progesterone receptor status as defined by using IHC per American Society of Clinical Oncology/College of American Pathologists criteria
- Percentage of ER and/or progesterone receptor positivity, if available
- Willing to provide blood samples at the time of screening, on-study, and at progression for exploratory research on biomarkers
- HER2-positive breast cancer (BC) as defined by an IHC score of 3+ or gene amplified by in situ hybridization (ISH) as defined by a ratio of ≥ 2.0 for the number of HER2 gene copies to the number of chromosome 17 copies

  For the expansion phase and randomized Phase II stage: Centrally confirmed HER2-positive status prospectively tested by a Sponsor-designated central laboratory prior to enrollment.

  For the dose-escalation phase: Enrollment can be based upon prospective central testing or local IHC or ISH results; however, for local IHC or ISH results, the same tissue sample must be sent for central HER2 confirmation and the testing platform documented in the eCRF.

  Both IHC and ISH assays can be performed; however, unless reflex testing is necessary, only one positive result is required for eligibility.

  If multiple tumor specimens are submitted, the HER2 IHC score and or ISH amplification ratio will first be assessed on the most recently obtained specimen for the purpose of determining eligibility. For patients with bilateral BC, HER2 positivity must be demonstrated in both locations for archival tissue or in a metastatic biopsy.

  Centrally confirmed HER2 results (either IHC or ISH) from a current or previous Sponsor study can be used to determine eligibility for this study. Approval must be obtained from the Medical Monitor prior to randomization.
- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):
  - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte-colony stimulating factor support within 7 days prior to Cycle 1, Day 1)
  - Platelet count $\geq 100{,}000/\mu$L (without transfusion within 7 days prior to Cycle 1, Day 1)
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - Albumin $\geq 25\ g/L\ (2.5\ g/dL)$
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exceptions:

    Patients with previously documented Gilbert syndrome who may have bilirubin $< 5 \times$ ULN

    Patients with documented liver metastases may have bilirubin $\leq 2.5 \times$ ULN
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases may have ALP $\leq 5 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of either 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

  - INR or aPTT $\leq 1.5 \times$ ULN

    For patients requiring anticoagulation therapy with warfarin or other coumarins, a stable INR between 2 and 3 is required. If anti-coagulation is required for a prosthetic heart valve, then INR should be between 2.5 and 3.5.

- Screening left ventricular ejection fraction (LVEF) $\geq 50\%$ on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan

  LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.

- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Inclusion Criteria for Dose-Escalation Phase Only

In addition to the general inclusion criteria, patients in the dose-escalation phase of the study must also meet the following criteria for study entry:

- *Prior exposure to trastuzumab emtansine in any setting (advanced/metastatic or early breast cancer) is required*

Inclusion Criteria for Expansion Phase Only

In addition to the general inclusion criteria, patients in the expansion phase of the study must also meet the following criteria for study entry:

- Trastuzumab emtansine experienced cohort:
  - Disease progression during or after trastuzumab emtansine *treatment* in the advanced/metastatic setting or disease recurrence in the neoadjuvant/adjuvant setting
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high.

    Bcl-2 high is defined as $\geq$ 50% of tumor cells stained with an intensity of IHC 2+ or 3+, and Bcl-2 low is defined as IHC 0 or 1+ or < 50% of tumor cells stained with an intensity of IHC 2+ or 3+.

- Trastuzumab deruxtecan (DS-8201a) experienced cohort:
  - Disease progression during or after trastuzumab deruxtecan in the advanced/metastatic setting
  - Prior trastuzumab emtansine in any setting is allowed
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high.

Inclusion Criteria for Randomized Phase II Stage

In addition to the general inclusion criteria, patients in the randomized Phase II stage of the study must also meet the following criteria for study entry:

- Bcl-2 expression status by IHC either from fresh tissue or the most recent archival tissue (see criteria for all study phases) by a central laboratory using the Ventana Bcl-2 IHC assay prior to randomization.

  At least 50% of patients in the randomized Phase II (e.g., 110 out of 220 patients) must be Bcl-2 high.

Exclusion Criteria

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

- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1
- Radiation therapy within 2 weeks prior to Cycle 1, Day 1
- The patient must have recovered from any resulting acute toxicity (to Grade $<$ 1) prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines as specified below:

- Doxorubicin $>$ 500 mg/m^2
- Liposomal doxorubicin $>$ 500 mg/m^2
- Epirubucin $>$ 720 mg/m^2
- Mitoxantrone $>$ 120 mg/m^2
- Idarubicin $>$ 90 mg/m^2

If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.

- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence
- Cardiopulmonary dysfunction as defined by:
    - Uncontrolled hypertension (systolic $>$ 150 mm Hg and/or diastolic $>$ 100 mm Hg with or without medication)
    - Inadequate LVEF at baseline, $<$ 50% by either ECHO or MUGA
    - History of symptomatic congestive heart failure (CHF)-Grade $\geq$ 3 per NCI CTCAE version 5.0 or Class $\geq$ II New York Heart Association
    - History of a decrease in LVEF to $<$ 40% or symptomatic CHF with prior trastuzumab treatment
    - Myocardial infarction or unstable angina within 6 months of randomization
    - Concurrent dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
    - Evidence of transmural infarction on ECG
    - Significant symptoms (Grade $\geq$ 2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia
    - High-risk uncontrolled arrhythmias (i.e., supraventricular tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 (Mobitz 2) or third-degree AV-block])
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis, or active infection with HBV or HCV)
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Known HIV infection or human T-cell leukemia virus 1 infection
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $>$ 2 weeks prior to randomization
- Known central nervous system (CNS) disease, except for patients treated and currently with asymptomatic CNS metastases, provided that all of the following criteria are met:
    - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
    - No ongoing requirement for corticosteroids as therapy for CNS disease

  - No stereotactic radiation within 14 days prior to randomization
  - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

    Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.
- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium or calcium $>$ 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade $\geq$ 3 peripheral neuropathy (according to the NCI CTCAE v 5.0)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Prior allogeneic stem cell or solid organ transplantation
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine after the final dose of study treatment, whichever is later

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Strong or moderate CYP3A inhibitors
  - Strong or moderate CYP3A inducers

  Additional restrictions for on-study use of CYP3A inhibitors/inducers are outlined in the protocol.
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade-containing Seville oranges), or starfruit (carambola) within 3 days before anticipated first dose of study drug until the last dose of study drug
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History of active inflammatory bowel disease (e.g., Crohn’s disease or ulcerative colitis) requiring specific medication in the 12 months prior to randomization, or active and uncontrolled bowel inflammation (e.g., diverticulitis) at time of randomization
- Inability or unwillingness to swallow a large number of tablets
- Known hypersensitivity to venetoclax or trastuzumab emtansine or to any of their excipients

- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Other medical or psychiatric conditions that, in the opinion of the investigator, may interfere with the patient's participation in the study
- Blood transfusions if performed within 2 weeks prior to screening

Exclusion Criteria for Randomized Phase II Stage

In addition to the general exclusion criteria, patients in the randomized Phase II stage of this study who meet the following criteria will be excluded:

- Prior treatment with trastuzumab emtansine in any setting (neoadjuvant/adjuvant or advanced/metastatic setting)
- Prior treatment with venetoclax in any setting
- Prior treatment with anti-HER2 antibody drug conjugates (e.g. trastuzumab deruxtecan [DS-8201a]), margetuximab, pyrotinib, or tucatinib.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of study is planned to occur approximately 24 months after last patient in (LPI). In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength. Each dose of venetoclax will be taken orally once daily. The venetoclax treatment regimens for the dose-escalation phase, dose-expansion phase, and randomized Phase II stage are summarized in the Description of Study above.

Comparator

The formulation of placebo is equivalent to venetoclax but without the active agent. Each dose of placebo will be taken orally once daily. The placebo treatment regimen for the randomized Phase II stage is summarized in the Description of Study above.

Trastuzumab emtansine will serve as the comparator/active control and will not be blinded. Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W.

The oral dose of venetoclax should be administered first, followed by infusion of trastuzumab emtansine.

Statistical Methods

Primary Analysis for Dose-Escalation Phase

The primary objective for the dose-escalation phase is to evaluate the safety and tolerability of trastuzumab emtansine in combination with venetoclax, including estimation of the MTD, determination of the RP2D, and characterization of DLTs. The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received. Safety will be assessed separately for each study phase through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI

CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

Primary Analysis for Randomized Phase II Stage

The co-primary endpoints for the randomized Phase II stage are ORR and PFS. The primary efficacy analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment (the intent-to-treat [ITT] population). The primary efficacy analysis will occur when 161 patients have experienced a PFS event. It is anticipated that this will occur six months after the last patient enters treatment. Patients with no disease assessments for any reason will be classified as non-responders. An estimate of ORR with 95% CI will be calculated for each treatment arm using the normal approximation to the binomial distribution. An estimate and 95% CI for the difference in ORR between the two treatment groups will be presented based on the normal approximation to the binomial distribution.

PFS is defined as the time from randomization to the first occurrence of disease progression (as defined by the investigator according to RECIST v1.1) or death from any cause, whichever comes first. Data for patients without the occurrence of disease progression or death as of the clinical data cut-off date will be censored at the time of last tumor assessment (or the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Kaplan-Meier curves of time to PFS for each treatment group will be provided. The Cox proportional hazards model stratified by the randomization stratification factors (Bcl-2 status [high, low], visceral disease [yes, no], and HER2 status IHC 3+ [yes, no] will be used to provide an estimate of the hazard ratio of venetoclax plus trastuzumab emtansine to placebo plus trastuzumab emtansine with associated 95% CI and p-value. The unstratified hazard ratio estimate and 95% CI will also be presented.

Determination of Sample Size

The sample size for the dose-escalation phase is based on the dose-escalation rules described in the protocol. The planned enrollment for the dose-escalation phase is approximately 6–24 patients enrolled across 2–4 dose-escalation treatment groups.

Approximately 20 patients each may be enrolled in the expansion phase (trastuzumab emtansine-experienced cohort and trastuzumab deruxtecan-experienced cohort).

With 20 patients per cohort and an observed ORR of 60%, the exact 90% Clopper-Pearson confidence interval for the ORR would be 39%–78%, which would rule out an ORR of 35% or less. The protocol provides exact 90% confidence intervals for a range of observed proportions of ORR based on a sample size of 20 patients. For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such event in a cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively. The protocol describes exact 90% confidence intervals for a range of observed proportions of adverse events based on a sample size of 20 patients.

After the RP2D has been determined for venetoclax when given in combination with a fixed dose of trastuzumab emtansine, a total of 220 patients will be enrolled in the randomized Phase II stage of the study. The purpose of the randomized Phase II stage is estimation and hypothesis generation regarding the effect of venetoclax in combination with trastuzumab emtansine on ORR and duration of PFS relative to trastuzumab emtansine plus placebo. The point and interval estimates of the true underlying HR will be obtained.

For the co-primary endpoints of ORR and PFS in the primary efficacy analysis population, the trial will have:

- 85% power ($\alpha = 0.05$) to detect a 20% improvement in ORR (i.e., ORR Δ) (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm). In the meantime, a 20% improvement in ORR will have a 95% CI of (7%, 33%).

- 90% power ($\alpha = 0.05$) to detect a PFS HR of 0.6 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 161 total PFS events have occurred. In the meantime, a PFS HR of 0.6 will have a 95% CI of (0.44, 0.82). The assumptions of the sample size calculation are that the median PFS in the control arm is 6.8 months and that enrollment would occur non-uniformly over 24 months. Enrollment is anticipated to be lower during the second half of the enrolment period because it will be restricted to the Bcl-2 high population.

Within the Bcl-2 high population the study will have:

- 85% power ($\alpha = 0.05$) to detect a PFS HR of 0.5 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 75 total PFS events have occurred. In the meantime, a PFS HR of 0.5 will have a 95% CI of (0.32, 0.79).

The study will not, however, have adequate power to detect all potentially clinically meaningful differences in ORR and PFS. For example, within the entire ITT population:

- With 110 patients in each arm, there is only 60% power ($\alpha = 0.05$) to detect a 15% improvement in ORR (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm), and
- With approximately 161 total PFS events, only 62% power ($\alpha = 0.05$) to detect an HR of 0.70, in venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm.

Thus, a statistically negative outcome in any of the co-primary endpoints does not necessarily rule out a clinically meaningful outcome. The protocol describes the power and CIs for several possible true underlying improvements in ORR and PFS in favor of the venetoclax plus trastuzumab emtansine arm.

Due to the smaller sample size of the Bcl-2 high population the power to detect a HR of 0.60 in the Bcl-2 population is 60% compared to 90% for the entire ITT population. The study has adequate power (85%) to detect a HR of 0.5 in the Bcl-2 high population.

Interim Analyses (Randomized Phase II Stage Only)

Periodic analyses of cumulative safety data and one interim analysis is planned for this study. Given the hypothesis-generating nature of this study, the Sponsor considers the interim efficacy analysis as exploratory.

The planned interim efficacy analysis of cumulative safety, ORR, and PFS will occur when approximately 56 PFS events have occurred. This is expected to occur after the enrollment of the first 110 patients who have been followed up for at least 6 months.

If the interim analysis coincides within approximately 1 month of a planned safety review, the safety review may be combined with the efficacy interim analyses. Outcomes from these reviews that may affect study conduct will be communicated in a timely manner to the investigators, and IRBs/ECs will be notified.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AML	acute myeloid leukemia
AV	atrioventricular
BC	breast cancer
Bcl-2	B-cell lymphoma 2
CBR	clinical benefit rate
CHF	congestive heart failure
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DDI	drug–drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
EBC	early breast cancer
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EORTC IL46	EORTC Item List 46
EORTC QLQ-C30	EORTC Quality of Life–Core 30 Questionnaire
ER	estrogen receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio

Abbreviation	Definition
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IL46	Item List 46
ILD	interstitial lung disease
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LABC	locally advanced breast cancer
LDAC	low-dose cytarabine
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition (scan)
NC	non-continuous (dose)
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal product
NRH	nodular regenerative hyperplasia
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PO	by mouth; orally

Abbreviation	Definition
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
QD	once a day
QLQ-C30	Quality of Life–Core 30 Questionnaire
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SD	stable disease
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
TGI	tumor growth inhibition
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
TPC	treatment of physician’s choice
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE BREAST CANCER

Breast cancer (BC) is the most common cancer among women in the world, with an estimated 2.09 million cases diagnosed globally per year and a mortality rate of approximately 627,000 deaths (Bray et al. 2018). While advances in early diagnosis and adjuvant therapy have led to a decrease in mortality rates from BC in developed countries, the prevalence of metastatic breast cancer (MBC) is still high and it is not curable, with the main goals of treatment being to prolong survival while maintaining or improving patients' quality of life (Cardoso et al. 2018).

BC risk assessment, prognosis, and treatment strategy rely on the status of key biomarkers: hormonal receptors (estrogen receptor [ER] and progesterone receptor) and HER2, also known as erbB2, neu, and p185HER2. Approximately 15%–20% of patients with primary invasive BC overexpress the HER2 receptor (Reese and Slamon 1997; Owens et al. 2004; Wolff et al. 2013; Zhang et al. 2015). Before HER2-targeted therapy became available, primary BCs that overexpressed HER2 were associated with a poorer prognosis, including a greater risk of relapse and shortened survival compared with that of HER2-negative tumors (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001). That changed with the introduction of trastuzumab, the first anti-HER2 therapy approved for HER2-positive BC, with HER2 positivity being designated as an immunohistochemistry (IHC) score of 3+ or HER2 gene amplification ratio of $\geq$ 2.0 by in situ hybridization (ISH).

Until recently, for patients with HER2-positive MBC, the combination of trastuzumab and a taxane was widely accepted as the first-line treatment option of choice on the basis of the survival advantage demonstrated in two large pivotal trials (Studies H0648g [Slamon et al. 2001] and M77001 [Marty et al. 2005]). More recently, the regimen of pertuzumab in combination with trastuzumab and docetaxel has shown clear superiority in terms of both progression-free survival (PFS) and overall survival (OS) with a generally similar safety profile (Study WO20698/TOC4129g [Baselga et al. 2012]), and became the new standard of care for first-line HER2-positive MBC.

In patients with HER2-positive advanced BC previously treated with trastuzumab and a taxane, trastuzumab emtansine has significantly prolonged PFS (up to 3 months improvement) and OS (up to 7 months increase) with a more favorable safety profile than lapatinib plus capecitabine (Study BO21977/TDM4370g, EMILIA [Verma et al. 2012]) or compared with a treatment of physicians' choice (TPC) in patients who previously received trastuzumab, taxane, and lapatinib (Wildiers et al. 2015). Trastuzumab emtansine is considered the standard of care in the aforementioned patient population (Cardoso et al. 2018; National Comprehensive Cancer Network [NCCN] 2019).

Based on the clinical data mentioned above, for patients with HER2-positive BC, the continuous blockage of HER2 through the initial lines of therapy in the metastatic setting is recommended (NCCN 2019). Even though the survival time of patients with HER2-positive BC has been prolonged in recent years, there remains a significant need for further outcome improvement. This could be achieved with the addition of new agents with novel mechanisms of action and acceptable toxicity, such as the pro-apoptotic molecule venetoclax, that can be combined with established HER2-targeted therapies.

1.2 BCL-2 SIGNALING PATHWAY AND HER2-POSITIVE BREAST CANCER

Cancer cells are characterized by their capacity for relentless growth, survival, and evasion of cell death (Adams and Cory 2007; Strasser et al. 2011). Apoptosis is the dominant mode of programmed cell death with two distinct pathways: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway (Strasser et al. 2011). Intrinsic apoptosis is regulated by the B-cell lymphoma 2 (Bcl-2) family of anti-apoptotic proteins of which key members are Bcl-2, Bcl-X_L, Bcl-w, A1, and MCL-1 (Cory et al. 2003). Bcl-2 family proteins have been described to be overexpressed in numerous cancer types. BCL-2 overexpression has been described in approximately 54%–75% of BC cases.

Bcl-2 is a relevant therapeutic target in hematologic malignancies, including chronic lymphocytic leukemia (CLL])/small lymphocytic lymphoma (SLL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), myelodysplastic syndrome, and acute myeloid leukemia (AML) (Perini et al. 2018), and may have an important role in the survival of solid tumors such as BC and lung cancer. For example, patient-derived xenograft (PDX) tumor models of luminal B BC have demonstrated significant improvement in tumor responses and OS when treated with the dual BCL-2/BCL-X_L inhibitor ABT-737 in combination with tamoxifen, compared with tamoxifen alone (Oakes et al. 2012; Vaillant et al. 2013). Similar efficacy was observed using the Bcl-2–specific inhibitor venetoclax (GDC-0199/ABT-199), suggesting that Bcl-2 may be a critical target (Vaillant et al. 2013; Lok et al. 2019) in patients with ER-positive, Bcl-2–positive MBC. The combination appears to show preliminary efficacy as well as a favorable toxicity profile when compared with other adjunctive therapies used with endocrine therapy, such as the mTOR, PIK3CA, and CDK4/6 inhibitors (Lok et al. 2019).

Bcl-2 is believed to be an important target in HER2-positive BC. Internal Genentech and Roche biomarker data in HER2-positive BC suggest that higher levels of Bcl-2 expression may be a poor prognostic factor in early breast cancer (EBC). Analysis of EBC tumor samples demonstrated that 24% of HER2-positive tumors were Bcl-2 high by IHC analysis (Genentech internal, unpublished). These data are consistent with previously reported data indicating that 21%–26% of HER2-positive samples are Bcl-2–positive (Honma et al. 2015; Eom et al. 2016).

1.3 BACKGROUND ON TRASTUZUMAB EMTANSINE

Trastuzumab emtansine (Kadcyla®) is a regulatory authority–approved antibody-drug conjugate. Linkage of a cytotoxic agent to highly specific monoclonal antibodies targeting unique and/or overexpressed cell-surface tumor antigens focuses the delivery of such agents to tumor cells, creating a more favorable therapeutic window than can be achieved by their administration as free drugs. Trastuzumab emtansine is specifically designed for the treatment of HER2-positive cancer. It is composed of the cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent; N2'deacetyl-N2'-[3-mercapto-1-oxopropyl]-maytansine) conjugated to trastuzumab via lysine side chains, with an average drug-to-antibody ratio of approximately 3.5:1.

Trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. After binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity.

Based on Phase I, II, and III studies in which trastuzumab emtansine demonstrated clinical activity, it is currently approved as a single agent for the treatment of patients with HER2-positive MBC who previously received trastuzumab and a taxane, separately or in combination (Kadcyla U.S. Package Insert; E.U. Summary of Product Characteristics [SmPC]). Trastuzumab emtansine is also approved for the adjuvant treatment of patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. Data from clinical trials of trastuzumab emtansine that are relevant to the design of the current trial are summarized in the following sections. Refer to the most recent version of the Trastuzumab Emtansine Investigator's Brochure for further information on all of the completed and ongoing trastuzumab emtansine studies.

1.3.1 Study TDM4370g/BO21977 (EMILIA)

Study TDM4370g/BO21977 was a randomized Phase III study of trastuzumab emtansine versus lapatinib plus capecitabine in patients with HER2-positive, unresectable locally advanced BC (LABC) or MBC previously treated with trastuzumab and a taxane (n = 991). Patients received trastuzumab emtansine (3.6 mg/kg IV every 3 weeks [Q3W]) or capecitabine (1000 mg/m^2 orally [PO] twice a day, Days 1–14 Q3W) plus lapatinib (1250 mg PO once a day [QD]) until progressive disease or unmanageable toxicity.

Primary endpoints were PFS by independent review, OS, and safety. A total of 991 patients were enrolled, and 978 patients received treatment. Baseline patient demographics, prior therapy, and disease characteristics were balanced. There was a significant improvement in PFS favoring trastuzumab emtansine (hazard ratio [HR] = 0.650; 95% CI: 0.549 to 0.771; p = 0.0001; median PFS: 9.6 vs. 6.4 months). Objective response rate (ORR) was 43.6% for the trastuzumab emtansine arm versus

30.8% for the lapatinib plus capecitabine arm, with a median duration of response (DOR) of 12.6 months versus 6.5 months, respectively. Final OS analysis showed a consistent survival benefit for trastuzumab emtansine compared with lapatinib plus capecitabine (median OS = 29.9 vs. 25.9 months; stratified HR = 0.75), despite 27% of patients crossing over from the control arm to trastuzumab emtansine (Diéras et al. 2017).

Trastuzumab emtansine was well tolerated, with no unexpected safety signals. The most common Grade ≥ 3 adverse events in the trastuzumab emtansine arm were thrombocytopenia (12.9% vs. 0.2%, respectively), increased AST (4.3% vs. 0.8%), and increased ALT (2.9% vs. 1.4%); the most common Grade ≥ 3 adverse events in the lapatinib plus capecitabine arm were diarrhea (20.7% vs. 1.6%), palmar plantar erythrodysesthesia (16.4% vs. 0%), and vomiting (4.5% vs. 0.8%). The incidence of Grade 3 adverse events in the trastuzumab emtansine arm was 40.8% versus 57.0% in the lapatinib plus capecitabine arm (Verma et al. 2012). Based on the results of the EMILIA study, trastuzumab emtansine was granted regulatory approval in the U.S. and E.U. for treatment-refractory HER2-positive LABC or MBC.

1.3.2 Study WO30085 (KATE2)

Study WO30085 (KATE2) is an ongoing, randomized, multicenter, double-blind, placebo-controlled Phase II study of the efficacy and safety of trastuzumab emtansine (3.6 mg/kg IV Q3W) in combination with atezolizumab (1200 mg IV Q3W) or trastuzumab emtansine plus placebo in patients with HER2-positive LABC or MBC who have received prior trastuzumab and taxane-based therapy. A total of 202 patients have been randomized to study treatment in a 2:1 ratio. Based on the primary efficacy endpoint of PFS, as determined by investigator-assessed Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), the study did not demonstrate a statistically significant benefit from the addition of atezolizumab to trastuzumab emtansine in the intent-to-treat (ITT) population. The stratified PFS HR was 0.82 (95% CI: 0.55 to 1.23), and p-value was 0.3332, with a median PFS of 8.2 months (95% CI: 5.8 to 10.7 months) for the treatment arm versus 6.8 months (95% CI: 4.0–11.1 months) for the control arm. However, in the exploratory analysis of the PD-L1 immune cell-positive subgroup, the stratified HR was 0.60 (95% CI: 0.32–1.11) with a median PFS of 8.5 months (95% CI: 5.7 months to non-evaluable) for the treatment arm versus 4.1 months (95% CI: 2.7 to 11.1 months) for the control arm, suggesting a potential benefit for this patient subgroup (Emens et al. 2019b).

The ORR as assessed by investigator using RECIST v1.1 was similar between the treatment arms (43.5% vs. 45.5%). Of the 69 patients with measurable disease at baseline in the trastuzumab emtansine plus placebo arm, 36.2% had a partial response (PR) and 7.2% had a complete response (CR). Of the 132 patients with measurable disease at baseline in the trastuzumab emtansine plus atezolizumab arm, 39.4% had a PR and 6.1% had a CR. The DOR data based on investigator assessment in both arms were immature at the primary cancer-related causes of death with low event rates in

each arm (26.7% in the trastuzumab emtansine plus placebo arm vs. 28.3% in the trastuzumab emtansine plus atezolizumab arm). The median DOR was not reached.

At a second planned analysis (Emens et al. 2019a) with at least 18 months of follow-up in the ITT population, the median OS was not reached in either arm, but numerically favored the trastuzumab emtansine plus atezolizumab arm. One-year survival was 89.1% versus 89.0% (stratified HR = 0.74; 95% CI: 0.42 to 1.30) in the trastuzumab emtansine plus atezolizumab and trastuzumab emtansine plus placebo arms, respectively. In PD-L1–selected patients, 1-year survival rates were higher with trastuzumab emtansine plus atezolizumab as compared with trastuzumab emtansine plus placebo (94.3% vs. 87.9%; stratified HR = 0.55; 95% CI: 0.22 to 1.38). All biomarkers of T-cell activation and quantity were enriched in the PD-L1–selected subgroup. This included higher expression of PD-L1, Teff signature, and CD8 RNA, as well as greater numbers of tumor-infiltrating lymphocytes (TILs) observed in PD-L1–positive tumors. Overall, the safety profile of the combination was consistent with the known safety profile of each drug. Rate of high-grade adverse events (≥ Grade 3) was 53% versus 45% in the trastuzumab emtansine plus atezolizumab as compared with trastuzumab emtansine plus placebo. Fatal Grade 5 events were similar in the two arms at 1.5% versus 1.5%. Adverse events leading to discontinuation of any study treatment was higher in the in the trastuzumab emtansine plus atezolizumab arm as compared with trastuzumab emtansine plus placebo arm (29% vs. 15%, respectively).

1.3.3 Study TDM4997g/BO25734 (TH3RESA)

Study TDM4997g/BO25734 was a Phase III, randomized, open-label trial to evaluate trastuzumab emtansine compared with TPC (these were approved or standard-of-care therapies based on frequently used regimens) in patients with HER2-positive MBC. Patients had received prior treatments with trastuzumab, lapatinib, and a taxane in any setting, and disease progression occurred after at least two regimens of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting.

The study demonstrated a statistically significant and clinically meaningful improvement in PFS for trastuzumab emtansine compared with TPC. The median PFS was 6.2 months for the trastuzumab emtansine arm and 3.3 months for the TPC arm, with a stratified HR of 0.528 (95% CI: 0.422, 0.661); p = 0.0001. The ORR was 31% for the trastuzumab emtansine arm versus 9% for the TPC arm, resulting in an ORR difference of 22.7% (95% CI: 16.2 to 29.2; p = 0·0001).

At the final OS analysis with a median 30.5 months of follow-up, trastuzumab emtansine demonstrated a clinically meaningful and statistically significant improvement in OS compared with TPC. The median OS improved from 15.8 months (95% CI: 13.5 to 18.7 months) with TPC to 22.7 months (95% CI: 19.4 to 27.5 months) with trastuzumab emtansine. The stratified HR was 0.68 (95% CI: 0.54 to 0.85; p = 0.0007). Despite the longer treatment duration relative to control (4.1 months; [0.03–31.2]), trastuzumab

emtansine (7.9 months [0.03–38]) had a favorable safety profile, which was consistent with prior studies (Krop et al. 2017).

In the updated safety analysis, fewer patients receiving trastuzumab emtansine than those receiving TPC had Grade ≥3 adverse events (40% vs. 47%). The most common Grade ≥3 adverse events (affecting ≥2% of patients in either group) that were more frequent with trastuzumab emtansine included thrombocytopenia (6% vs. 3%) and hemorrhage of any type (4% vs. <1%). Serious adverse events were reported in 25% of patients in the trastuzumab emtansine group and 22% in the TPC group. Deaths from adverse events were reported in 3 patients (2%) in the TPC group (of which 1 death was judged to be treatment related) and 9 patients (2%) in the trastuzumab emtansine group (of which 3 deaths were judged to be treatment related) (Krop et al. 2017).

1.3.4 Study BO27938 (KATHERINE)

Study BO27938 is a multicenter, Phase III, randomized, open-label trial to evaluate patients with HER2-positive EBC who had residual invasive disease after completion of neoadjuvant therapy. At the interim analysis, among 1486 randomly assigned patients (743 in the trastuzumab emtansine group and 743 in the trastuzumab group), invasive disease or death had occurred in 91 patients in the trastuzumab emtansine group (12.2%) and 165 patients in the trastuzumab group (22.2%). The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the trastuzumab emtansine group and 77.0% in the trastuzumab group. Invasive disease-free survival was significantly higher in the trastuzumab emtansine group than in the trastuzumab group (HR for invasive disease or death was 0.50; 95% CI: 0.39–0.64; p<0.001). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the trastuzumab emtansine group and 15.9% of those in the trastuzumab group. The safety data were consistent with the known safety profile of trastuzumab emtansine, with more adverse events associated with trastuzumab emtansine than with trastuzumab alone. As of December 2019, based on the results of the KATHERINE study, trastuzumab emtansine (Kadcyla) was approved in the U.S. and has received recommendation for approval in the E.U. from the Committee for Medicinal Products for Human Use for the adjuvant treatment of patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

1.4 BACKGROUND ON VENETOCLAX

Venetoclax (also referred to as GDC-0199, RO5537382, ABT-199, A-1195425.0, Venclexta®, and Venclyxto®) is an orally bioavailable, selective small-molecule inhibitor of Bcl-2 in the biaryl acylsulfonamide chemical class. Venetoclax binds with high affinity (Ki<0.01 nM) to the anti-apoptotic protein Bcl-2 and with lower affinity to other anti-apoptotic Bcl-2 family proteins such as Bcl-X_L and Bcl-w (>4,000-fold and >2,000- to >20,000-fold lower affinity than to Bcl-2, respectively; Souers et al. 2013). Survival of platelets depends on Bcl-X_L, and thrombocytopenia is therefore a major dose-limiting toxicity (DLT) caused by inhibition of BCL-X_L in the clinic. Venetoclax has an improved

therapeutic index by maintaining efficacy against tumor cells while avoiding dose-limiting thrombocytopenia.

Venetoclax has been extensively studied in oncology, particularly in hematologic malignancies but also in some solid tumors. Efficacy data indicate that venetoclax, both as a monotherapy and in combination with other therapeutic agents, shows promising safety, tolerability, pharmacokinetics, and efficacy. This includes combinations with rituximab; obinutuzumab; bendamustine plus rituximab; O6-benzylguanine; rituxan plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); obinutuzumab plus CHOP (G-CHOP); bortezomib plus dexamethasone, azacitidine, or decitabine; and cytarabine in patients with hematologic malignancies, including CLL/SLL, NHL, MM, myelodysplastic syndrome, and AML.

In the United States, venetoclax (Venclexta®) is indicated for the treatment of adult patients with CLL or SLL. In addition, it is approved in combination with azacitidine or decitabine or low-dose cytarabine (LDAC) for the treatment of adults with newly diagnosed AML who are age 75 years or older or who have comorbidities that preclude use of intensive induction chemotherapy. The AML indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

In the European Union, venetoclax (Venclyxto®) in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. Monotherapy is indicated for the treatment of CLL in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

In solid tumors, such as ER-positive, Bcl-2 positive MBC, venetoclax has shown promising activity (Lok et al. 2019). In a Phase Ib dose-escalation study, venetoclax administered at 200, 400, 600, or 800 mg QD in combination with tamoxifen at 20 mg QD was shown to be well tolerated. No DLTs, including Grade ≥3 toxicity, were observed in any of the cohorts and the maximum tolerated dose (MTD) was not reached. The 800 mg QD dose was selected as the recommended Phase II dose (RP2D). Efficacy was promising with 54% ORR and a clinical benefit rate (CBR) of 75% for the 800 mg QD cohort, comparing favorably with historical studies of patients treated with tamoxifen in the first-line relapse setting (e.g., ORR 17%–33% and CBR 38%–56%).

The combination of venetoclax plus hormonal therapy (fulvestrant) in ER-positive MBC is being further evaluated in the ongoing randomized Phase II Study WO40181 (VERONICA). Study results will be reported in the Venetoclax Investigator's Brochure(s) when available.

Refer to the Venetoclax Investigator's Brochure(s) for details on nonclinical and clinical studies.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Trastuzumab emtansine is an active regimen and the standard of care in second-line HER2-positive MBC (Verma et al. 2012). The safety of trastuzumab emtansine is well established, having been evaluated in over 2000 patients with BC in clinical studies. Trastuzumab emtansine is generally well tolerated, with the most common adverse events being nausea, fatigue, and headache. Adverse events of particular relevance include thrombocytopenia, hemorrhage, hepatotoxicity (increases in serum transaminases and nodular regenerative hyperplasia [NRH] of the liver), infusion related-reactions/hypersensitivity, cardiac dysfunction (left ventricular dysfunction), peripheral neuropathy, and pulmonary toxicity (interstitial lung disease [ILD].

Venetoclax has been evaluated in a variety of oncological indications, particularly in hematological malignancies, and has been generally well tolerated as a single agent as well as in combination with targeted therapies and chemotherapy (refer to the Venetoclax Investigator's Brochure for more details). Adverse events commonly observed with venetoclax include nausea, vomiting, diarrhea, and myelotoxicity (including anemia, thrombocytopenia, and leukopenia). To date, the majority of these adverse events have been manageable without requiring treatment discontinuation. Important identified risks for venetoclax include tumor lysis syndrome (TLS), particularly in CLL and mantle cell lymphoma, and neutropenia. Serious infection is also an identified risk. Of note, cytopenias and TLS are commonly observed in hematologic malignances and in some cases independently of treatment, and their prevalence in solid tumors remains to be elucidated.

Nonclinical data indicate a potential synergistic mechanism of action between venetoclax and trastuzumab emtansine. Microtubule inhibitors, such as taxanes and vinca alkaloids, have been described to promote degradation of the anti-apoptotic protein MCL-1 (Wertz et al. 2011), which can be a resistance factor for venetoclax monotherapy (Bose et al. 2017). The mechanism of DM1 inhibition of microtubules is similar to that of vinca alkaloids and, as such, DM1 also induces degradation of MCL-1 (Genentech unpublished data). Direct inhibition of MCL-1 in combination with venetoclax has been shown to be synergistic nonclinically across various hematologic and solid tumor malignancies (Phillips et al. 2015; Li et al. 2019; Moujalled et al. 2019). These nonclinical data support the investigation of venetoclax with combination partners that inhibit MCL-1, either directly or indirectly, and provide scientific rationale to test the combination of trastuzumab emtansine (via MCL-1 degradation) and venetoclax. Further, Bcl-2 upregulation has been associated with resistance to trastuzumab emtansine in various BC cell lines (unpublished data; Saatci et al. 2018). Combining venetoclax with trastuzumab emtansine was shown to enhance apoptosis in vitro compared to single agent treatments in these trastuzumab emtansine–resistant cell lines

(Genentech unpublished data). The combination of trastuzumab emtansine and venetoclax has been tested in vivo in trastuzumab emtansine naive and resistant models, and the results of the data are summarized as follows (Genentech unpublished data):

- In the MDA-MB-361 HER2-positive trastuzumab emtansine naive–BC xenografts grown orthotopically in NOD-SCID mice, trastuzumab emtansine administered intravenously once in combination with venetoclax administered PO QD for 21 days demonstrated enhanced tumor growth inhibition (TGI) compared to trastuzumab emtansine or venetoclax monotherapy. TGI on Day 21 of the dosing period was 38% for trastuzumab emtansine, 34% for venetoclax, and 70% for the combination of trastuzumab emtansine and venetoclax.
- KPL-4 trastuzumab emtansine–resistant cell line clones were generated to be trastuzumab emtansine resistant in vitro through long-term drug treatment. KPL-4 clones 8 and 17 demonstrated upregulation of Bcl-2 protein at resistance. The combination of trastuzumab emtansine and venetoclax showed enhanced anti-tumor efficacy for both clones when grown orthotopically as xenografts in NOD-SCID mice. Trastuzumab emtansine was administered once intravenously and venetoclax was administered PO QD for 21 days. For KPL-4 clone 17, TGI on Day 21 of the dosing period was 27% for trastuzumab emtansine, 3% for venetoclax, and 74% for the combination of trastuzumab emtansine and venetoclax. For KPL-4 clone 8, TGI 2 days after end of treatment (Study Day 23) was 93% for trastuzumab emtansine, 8% for venetoclax, and 143% for the combination of trastuzumab emtansine and venetoclax.

Importantly, in vivo assessment of altering venetoclax schedules dosed for either 10 or 21 consecutive days has demonstrated equivalent anti-tumor efficacy when administered in combination with trastuzumab emtansine (Genentech unpublished data). Furthermore, a shorter schedule of venetoclax dosing (5 continuous days) was also shown to improve responses in combination with trastuzumab emtansine in HER2-positive BC PDX models that are sensitive as well as resistant to trastuzumab emtansine (unpublished data). In separate studies using additional HER2-positive PDX models, inhibition of Bcl-2 and Bcl-X_L with navitoclax (ABT-263) significantly enhanced cytotoxicity of trastuzumab emtansine (Zoeller et al. 2019). The nonclinical data cited herein provide rationale for testing continuous and non-continuous schedules of venetoclax in combination with trastuzumab emtansine. Therefore, this study will offer an opportunity to evaluate the safety and activity of a promising novel approach combining venetoclax and trastuzumab emtansine for the treatment of HER2-positive MBC in the clinical setting.

The safety and tolerability of the combination of trastuzumab emtansine and venetoclax is currently unknown and will be evaluated in the Phase Ib portion of this study. Although the combination is expected to have limited overlapping toxicities, there remains the potential for unknown toxicities. Key overlapping toxicities for the combination include hematologic toxicities, such as neutropenia, febrile neutropenia, thrombocytopenia, and gastrointestinal toxicities (e.g., nausea, vomiting, diarrhea).

To minimize this risk, stringent inclusion and exclusion criteria (Sections 4.1.1 and 4.2.2) and close safety monitoring (Section 5.1), together with rules for dose modifications and safety management guidelines for known risks of single-agent trastuzumab emtansine and venetoclax, have been implemented in the current study. Furthermore, guidance on management of potential overlapping toxicities is described in Section 5.1.3.3. Specifically, during the Phase Ib portion of this study, safety review will be led by the Medical Monitor in consultation with the study investigators and a committee composed at a minimum of the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist. During the randomized Phase II stage of the study, an Internal Monitoring Committee (IMC; Section 3.1.4) has also been incorporated into the trial design to periodically review aggregate efficacy and safety data (refer to the IMC charter for a detailed monitoring plan).

HER2-positive MBC remains an incurable disease despite advances in patient care. Nearly all patients with HER2-positive MBC will eventually suffer disease progression and succumb to their disease. There continues to be a need for more efficacious therapies with acceptable safety profiles in patients with HER2-positive disease. Therefore, the addition of venetoclax based on its pro-apoptotic mechanism of action and potential to overcome resistance to trastuzumab emtansine, as well as a manageable safety profile, can represent a potential valuable treatment option and offers a favorable benefit–risk balance for patients in this study.

2. OBJECTIVES AND ENDPOINTS

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the “randomized Phase II stage”).

The dose-escalation phase will assess safety and tolerability, determine the MTD and the RP2D, and evaluate *the* preliminary efficacy of trastuzumab emtansine in combination with venetoclax in patients with previously treated HER2-positive LABC or MBC *who have received* prior trastuzumab emtansine in the metastatic setting.

Once the RP2D is established, additional patients may be enrolled in the expansion phase to evaluate the safety, tolerability, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D in patients with previously treated HER2-positive LABC or MBC who have previously received either trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a). The decision to open these cohorts will be data-driven and dependent on the observations made in the dose-escalation phase, as well as emerging data about trastuzumab deruxtecan and other HER2-targeted therapies. Importantly, the expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

The randomized Phase II stage will aim to evaluate the safety, tolerability, pharmacokinetics, and efficacy of trastuzumab emtansine in combination with venetoclax at the RP2D compared with trastuzumab emtansine plus placebo in patients with previously treated HER2-positive LABC or MBC who have not received prior trastuzumab emtansine therapy, either alone or in combination with other anticancer therapies.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 OBJECTIVES AND ENDPOINTS FOR DOSE-ESCALATION PHASE

2.1.1 Primary Safety Objective

The safety objective for the dose-escalation phase is to evaluate the safety and tolerability of trastuzumab emtansine in combination with venetoclax—including estimation of the MTD, determination of the RP2D, and characterization of DLTs (see Section 3.1.1.1)—on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.1.2 Exploratory Efficacy Objective

The exploratory efficacy objective for the dose-escalation phase is to make a preliminary assessment of the anti-tumor activity of trastuzumab emtansine and venetoclax on the basis of the following endpoints:

- ORR, defined as the proportion of patients with CR or PR on two consecutive assessments, at least 28 days apart, as determined by investigator assessment using RECIST v1.1 (see Appendix 11)
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first

2.1.3 Pharmacokinetic Objective

The PK objective for the dose-escalation phase of this study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

2.1.4 Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue (see Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.2 OBJECTIVES AND ENDPOINTS FOR EXPANSION PHASE

2.2.1 Primary Efficacy Objective

The primary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- ORR

2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for the expansion phase is to evaluate the efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoint:

- DOR

2.2.3 Safety Objective

The safety objective for the expansion phase is to evaluate the safety and tolerability of venetoclax at the RP2D in combination with trastuzumab emtansine on the basis of the following endpoints:

- Incidence and severity of adverse events, including DLTs, with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.2.4 Pharmacokinetic Objective

The PK objective for the expansion phase of the study is to characterize the pharmacokinetics of venetoclax when given in combination with trastuzumab emtansine on the basis of the following endpoint:

- Plasma concentrations of venetoclax at specified timepoints

2.2.5 Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- Relationship between biomarkers in blood, plasma, and tumor tissue (see Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.3 OBJECTIVES AND ENDPOINTS FOR RANDOMIZED PHASE II STAGE

2.3.1 Primary Efficacy Objective

The primary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following co-primary endpoints:

- ORR
- PFS after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

2.3.2 Secondary Efficacy Objective

The secondary efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- DOR

- OS after randomization, defined as the time from randomization to death from any cause

2.3.3 Exploratory Efficacy Objective

The exploratory efficacy objective for the randomized Phase II stage is to evaluate the efficacy of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- CBR, defined as the proportion of patients with CR, PR, or stable disease (SD) at 6 months after randomization, as determined by the investigator according to RECIST v1.1

2.3.4 Safety Objective

The safety objective for the randomized Phase II stage is to evaluate safety of trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoints:

- Incidence and severity of adverse events with severity determined according to NCI CTCAE v5.0
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3.5 Pharmacokinetic Objective

The PK objective for the randomized Phase II stage of this study is to characterize the pharmacokinetics of trastuzumab emtansine and venetoclax when given in combination on the basis of the following endpoints:

- Serum concentrations of trastuzumab emtansine at specified timepoints
- Plasma concentrations of venetoclax at specified timepoints

2.3.6 Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to trastuzumab emtansine when given with placebo or in combination with venetoclax on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.3.7 Biomarker Objective

The exploratory biomarker objective for all phases in this study is to identify and/or evaluate biomarkers that are predictive of response to venetoclax in combination with trastuzumab emtansine (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to trastuzumab emtansine and venetoclax, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of venetoclax and/or trastuzumab emtansine activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Changes in expression levels of biomarkers or biomarker panels during and after investigational treatment with venetoclax in combination with trastuzumab emtansine
- The relationship between biomarkers in blood, plasma, and tumor tissue (see Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.3.8 *Patient Reported Outcome* Objective

The *patient reported outcome* objective for the randomized Phase II stage is to evaluate *the efficacy of* trastuzumab emtansine in combination with venetoclax compared with trastuzumab emtansine plus placebo on the basis of the following endpoint:

- Change from baseline in patient-reported symptoms and their impact on functioning and health-related quality of life*, and the overall burden of side effects,* as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and EORTC Item List 46 (EORTC IL46) *item*

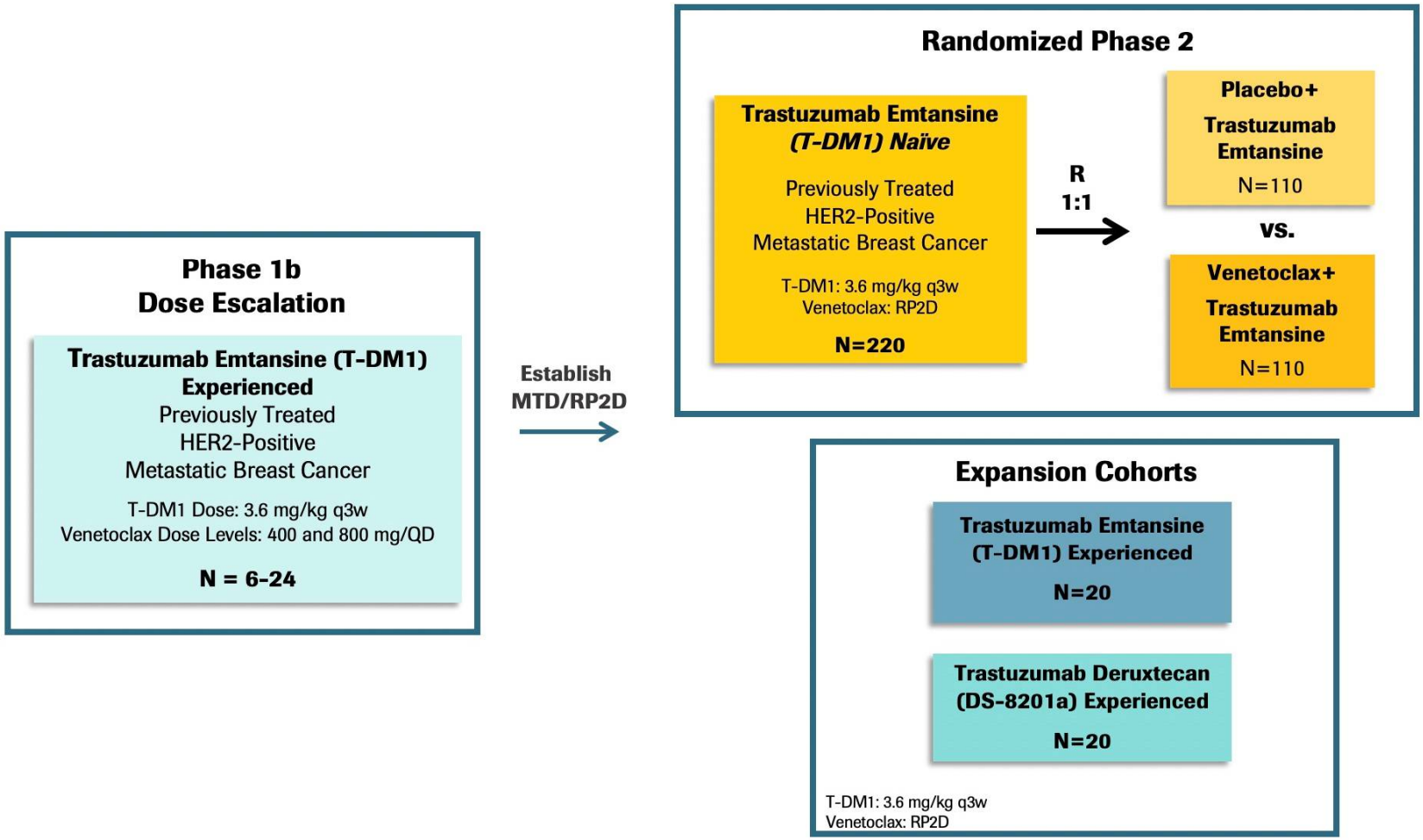
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This two-part study is composed of two stages: a Phase Ib stage consisting of a dose-escalation phase and an expansion phase; and a Phase II, randomized, placebo-controlled, double-blind, multicenter stage (hereafter referred to as the “randomized Phase II stage”). The expansion phase may run concurrent to and *in* parallel with the randomized Phase II stage.

Approximately 226–284 patients will be enrolled in this study across approximately 145 sites globally. The study will enroll 6–24 patients in the Phase Ib dose-escalation phase and approximately 220 patients in the Phase II stage. An additional approximately 20–40 patients may be enrolled in the Phase Ib expansion cohorts.

Figure 1 Overall Study Schema



MBC = metastatic breast cancer; MTD = maximum tolerated dose; Q3W = every 3 weeks; QD = once a day; RP2D = recommended Phase II dose.

3.1.1 Dose-Escalation Phase

The dose-escalation phase will determine the RP2D and MTD for venetoclax when given in combination with a fixed dose of trastuzumab emtansine (3.6 mg/kg) in patients with previously treated, HER2-positive LABC or MBC *who have received* prior trastuzumab emtansine in the metastatic setting.

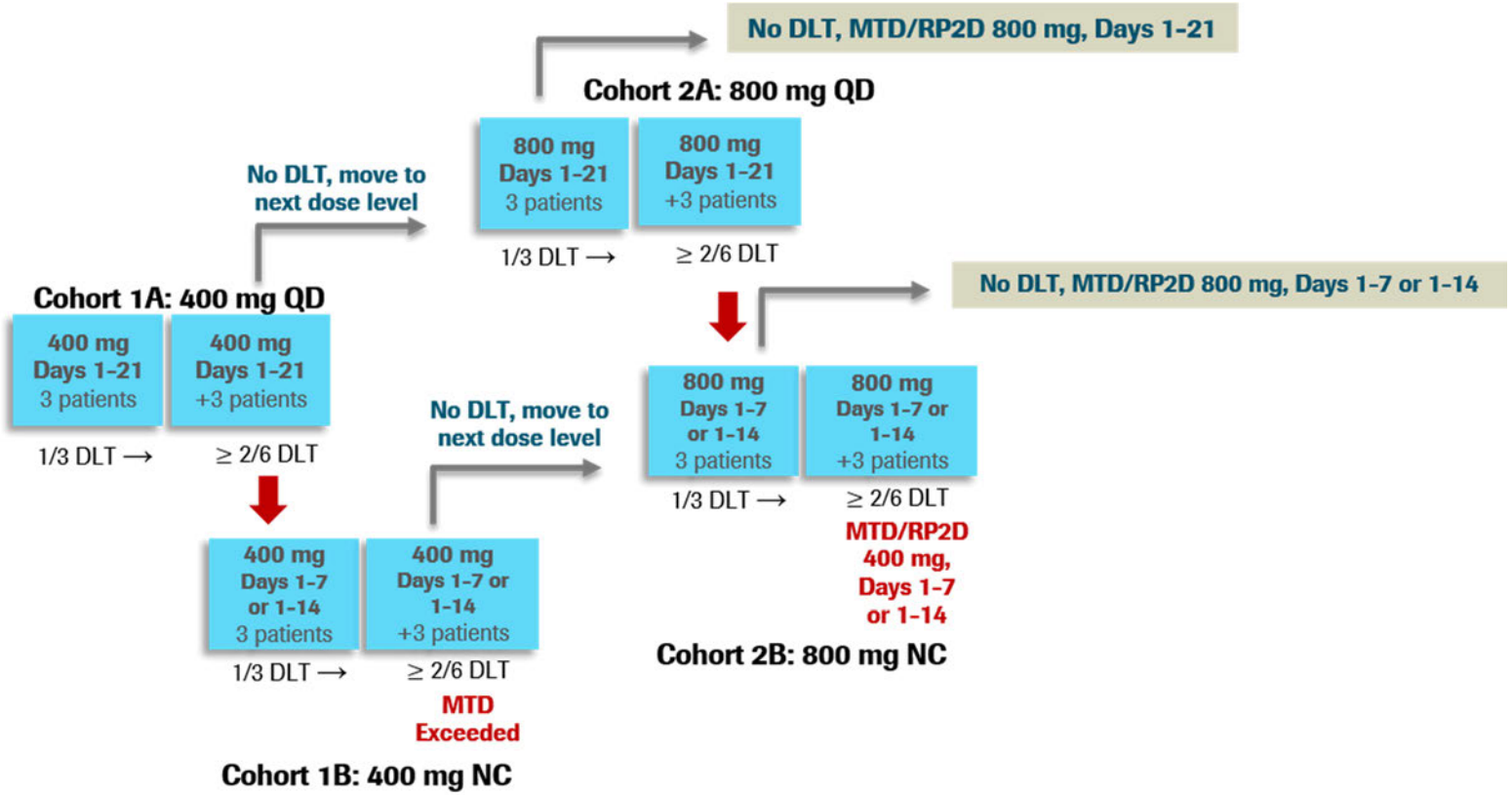
The dose-escalation phase will enroll 6–24 patients and will include 2–4 cohorts:

- Cohort 1A, 400 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 400 mg PO once a day (QD) continuous on Days 1–21 of each cycle.
- Cohort 1B, 400 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 400 mg PO QD non-continuous on either Days 1–7 or 1–14 of each cycle (see further description below).
- Cohort 2A, 800 mg QD Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD continuous on Days 1–21 of each cycle.
- Cohort 2B, 800 mg NC Cohort: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion on Day 1 of each 21-day cycle (Q3W) and venetoclax 800 mg PO QD non-continuous on either Days 1–7 or 1–14 of each cycle.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. The investigator will record reasons for screen failure within the interactive voice or web-based response system (IxRS) and electronic Case Report Form (eCRF [see Section 4.5.1]).

Figure 2 presents an overview of the dose-escalation phase design. A schedule of activities for dose-escalation and expansion phases are provided in Appendix 1 and Appendix 2, respectively.

Figure 2 Phase Ib Dose-Escalation Study Schema



DLT = dose-limiting toxicity; MTD = maximum tolerated dose; NC=non-continuous; QD = once a day; RP2D = recommended Phase II dose.

The 400-mg and 800-mg cohorts for dose escalation will be run sequentially (i.e., the 400-mg cohort followed by the 800-mg cohort). Dose escalation will be performed based on a standard 3 + 3 design. Each cohort will consist of at least 3 patients, unless 1 of the 3 patients experiences DLTs (refer to Section 3.1.1.1 for DLT criteria), in which case 3 additional patients will be treated at the same dose level. The dose escalation will continue until 2 patients among a cohort of 6 patients experience a DLT (i.e., ≥33% of patients with a DLT at that dose level; refer to dose-escalation rules below). Patients who experience a DLT will continue at the same dose level.

Dose de-escalation may be explored by incorporating non-continuous (NC) dosing of venetoclax (e.g., less than 21 days of dosing, such as 7 days out of 21 days or 14 days out of 21 days) dependent on the severity and timing of DLTs as well as the specific adverse events*, including those that result in dose interruptions or dose modifications*. For example, if DLTs such as a Grade 3 rash occurred between Day 8 and Day 14, an NC schedule of Days 1–7 would be tested. Alternatively, if DLTs are thought to be possibly mitigated by a 7-day break such as Grade 3 fatigue occurring near the end of the DLT window (e.g., Day 20), then an NC schedule of Days 1–14 could be chosen to be tested. Patients may be treated in up to two NC sub-cohorts (i.e., either 400 mg NC and/or 800 mg NC; refer to Figure 2). At each dose de-escalation level, either a Days 1–7 or Days 1–14 NC treatment schedule will be assessed.

3.1.1.1 Definition of Dose-Limiting Toxicity

Patients will be closely monitored for adverse events during the 21-day DLT assessment window. All adverse events, including DLTs, will be graded according to the NCI CTCAE v5.0 (Appendix 12) unless otherwise indicated. If a patient experiences a DLT, the patient will be treated according to clinical practice and will be monitored for resolution of the toxicity.

For dose-escalation purposes, a DLT will be defined as any one of the following events regardless of relationship to study treatment (unless otherwise specified below) occurring during the 21-day DLT assessment period, which runs from Days 1–21 of Cycle 1:

- Grade 4 neutropenia (ANC $<500/mm^3$) lasting >7 days
- Grade 4 thrombocytopenia (platelet count $<25,000/mm^3$) or Grade 3 thrombocytopenia associated with severe bleeding
- Grade 4 anemia
- Grade 3 febrile neutropenia for >7 days or Grade 4 febrile neutropenia of any duration
- Treatment related Grade ≥ 3 non-hematologic, non-hepatic, and non-cardiac major organ toxicity lasting for ≥ 72 hours
- Grade ≥3 serum bilirubin, hepatic transaminase (ALT or AST), or ALP lasting for ≥72 hours

For patients with Grade 2 hepatic transaminase or ALP levels at baseline as a result of liver metastases or bone metastases, a hepatic transaminase or ALP level ≥ 10 times the upper limit of normal (ULN) will be considered a DLT. For patients with abnormal TBILI at baseline an increase of >3.0–10.0 times baseline value will be considered a DLT.

- Grade ≥3 cardiac toxicity (resting ejection fraction [EF] 39%–20%; ≥20% drop from baseline; symptomatic heart failure)
- Treatment-related death

Adverse events meeting the criteria for DLT within the 21-day assessment period must be reported to the Sponsor within 24 hours.

3.1.1.2 Dose-Escalation Rules, Determination of Dose-Limiting Toxicities, and Recommended Phase II Dose

Dose escalation will occur in accordance with the rules listed below:

- A minimum of 3 DLT-evaluable patients will initially be enrolled into each cohort.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.
- If 2 or more of the first 6 DLT-evaluable patients in the continuous (QD) dose-escalation cohorts experience a DLT, an additional 3 patients will be evaluated for DLTs at the corresponding NC dose level. If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next NC dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the NC dose level cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next dose level may proceed.
- If 2 or more of the first 6 DLT-evaluable patients in the NC dose-escalation cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., ≥33%) experience a DLT will be declared the MTD.
- If the MTD is not exceeded at any dose level, the highest dose administered in this study will be declared the MTD.

Determination of whether a patient is evaluable for DLT assessment will be made in accordance with the following rules:

- Patients who receive study treatment (e.g., at least 66% of planned venetoclax doses and 1 dose of trastuzumab emtansine) and remain in the study through the DLT assessment window will be considered DLT evaluable.

- Patients who discontinue from treatment with trastuzumab emtansine or venetoclax treatment prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination and will be replaced by an additional patient at that same dose level.
- Patients who do not receive at least 66% of planned venetoclax doses (e.g., 14 out of 21 days for continuous [QD] dosing, 10 out of 14 days for Days 1–14 NC, or 5 out of 7 days for Days 1–7 NC) or 1 dose of trastuzumab emtansine during the DLT assessment period will be replaced, to ensure that at least 3 patients in each cohort have been assessed for the full DLT assessment period of 21 days prior to moving to the next dose level.

Patients exhibiting acceptable safety and evidence of clinical benefit (as determined by the investigator) may continue to receive study treatment until confirmed objective disease progression or unacceptable toxicity, whichever occurs first.

The Sponsor will review cumulative safety data and make recommendations regarding dose escalation and overall study conduct on the basis of study safety data to ensure patient safety while receiving study treatment. These include recommendations to open or suspend patient enrollment in a given dose-escalation cohort based on the overall benefit–risk profile of trastuzumab emtansine in combination with venetoclax.

Relevant demographic, adverse event, laboratory, dose administration, and PK data (if available) will be reviewed prior to the selection of the RP2D for the expansion and randomized phases of the study. The RP2D for both the expansion and randomized phases will be the same dose and schedule. The RP2D will be based on the MTD of venetoclax when combined with a fixed dose of trastuzumab emtansine and will integrate aggregate safety data during treatment. Decision making will be led by the Medical Monitor in consultation with the study investigators and a committee composed at a minimum of the following Sponsor representatives: statistician, safety scientist, PK scientist, and clinical scientist. For example, based upon nonclinical data showing similar efficacy of NC versus continuous dosing, as well as the mechanism of action of combining venetoclax with a cytotoxic agent such as trastuzumab emtansine, NC dosing of 800 mg for 1–7 days or 1–14 days would be preferred over 400 mg QD. Aggregate clinical data would be integrated into the decision making, including safety and efficacy data.

3.1.2 Expansion Phase

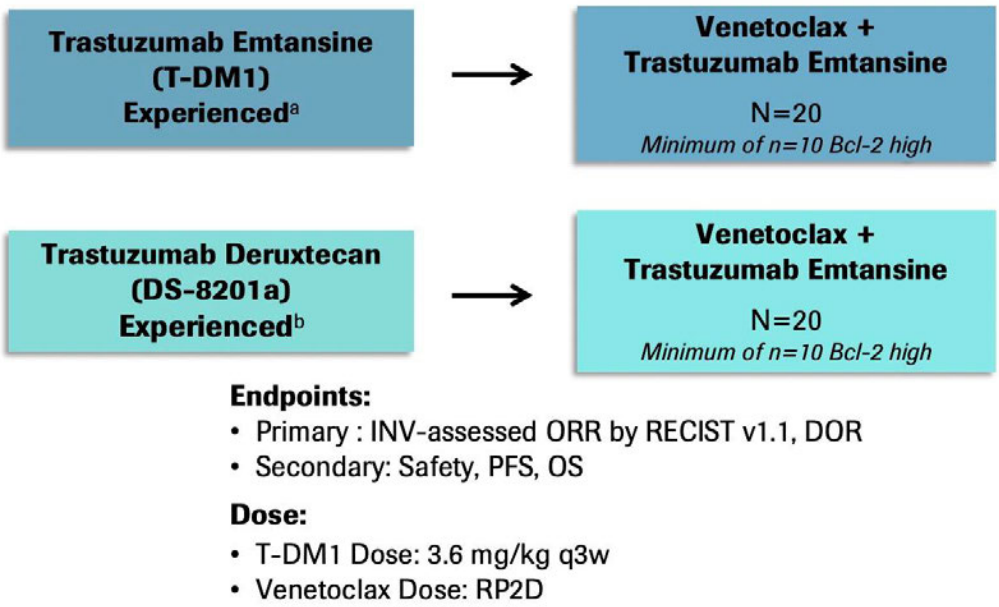
An expansion phase may be initiated to evaluate the safety, tolerability, and efficacy of venetoclax at the RP2D in combination with trastuzumab emtansine in previously treated HER2-positive locally advanced or MBC patients who have received prior trastuzumab emtansine or trastuzumab deruxtecan (DS-8201a).

The decision to open cohorts as part of an expansion phase will be data-driven and dependent on the observations made in the dose-escalation phase, emerging data with

trastuzumab deruxtecan, as well as other HER2-targeted therapies. The expansion phase may run concurrent to and in parallel with the randomized Phase II stage of the study.

Approximately 20 patients may be enrolled in each of the expansion cohorts (see Figure 3).

Figure 3 Phase Ib Expansion Cohorts Study Schema



Bcl-2 = B-cell lymphoma 2; DOR = duration of response; IHC = immunohistochemistry; INV = investigator; MBC = metastatic breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RP2D = recommended Phase II dose.

[a] Prior exposure to other HER2-targeted therapies (e.g., trastuzumab, pertuzumab, trastuzumab deruxtecan, margetuximab, pyrotinib, tucatinib and/or neratinib) is permitted.

[b] Eligibility for this cohort requires prior experience with trastuzumab deruxtecan (DS-8201a) in any setting.

3.1.3 Randomized Phase II Stage

The randomized Phase II stage will be initiated once the RP2D has been identified based on the cumulative data collected from the dose-escalation phase. It will consist of two interventional arms of trastuzumab emtansine plus placebo or trastuzumab emtansine plus venetoclax in patients with previously treated HER2-positive LABC or MBC, who have not received prior trastuzumab emtansine therapy.

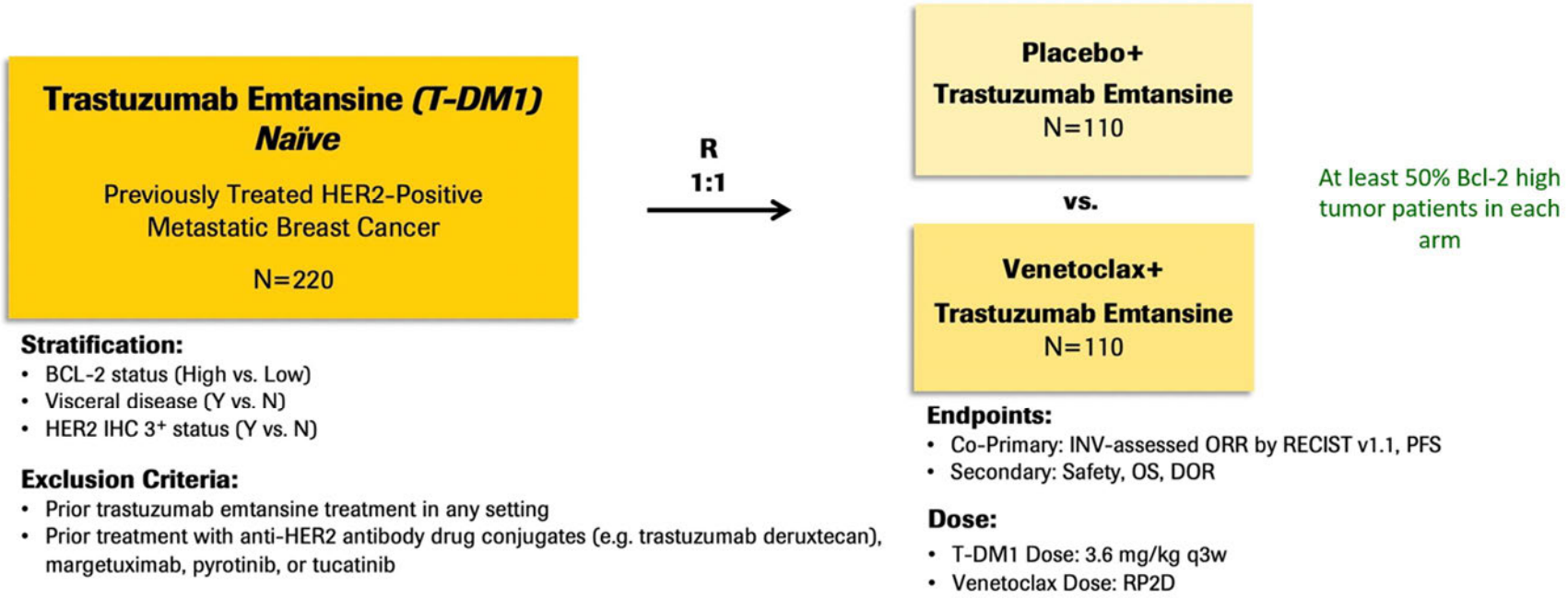
Approximately 220 patients will be randomized 1:1 to one of the following treatment arms:

- Control Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus placebo at the RP2D and schedule of venetoclax.

- Experimental Arm: Patients will receive trastuzumab emtansine 3.6 mg/kg by IV infusion Q3W plus venetoclax at the RP2D and schedule.

Each arm will include at least 50% Bcl-2 high patients, and randomization will be based on the three stratification factors shown in Figure 4 (see also Section 4.2.1). Crossover between treatment arms will not be permitted. A schedule of activities for the randomized phase is provided in Appendix 2.

Figure 4 Phase II Randomized Study Schema



Bcl-2 = B-cell lymphoma 2; DOR = duration of response; IHC = immunohistochemistry; INV = investigator; N = no; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; R = randomization; RP2D = recommended Phase II dose; Y = yes.

3.1.4 Internal Monitoring Committee for the Randomized Phase II Stage

An IMC will be established to monitor patient safety as well as efficacy in the randomized Phase II stage of the study. The IMC will not be blinded, will help monitor safety of enrolled patients, and will conduct periodic interim reviews of safety data during the randomized Phase II stage of the study. The frequency of the reviews will be determined as needed. The IMC will be external to the study team and will be composed of at least one medical doctor and/or clinical science representative, with representatives from clinical safety, biostatistics, as well as statistical programming and analysis, who are not directly involved in the study. A separate IMC charter will outline the committee's composition, meeting timelines, and members' roles and responsibilities. The committee members will review all potential cases of serious adverse events, Grade 3 and 4 adverse events, adverse events of special interest, and deaths as specified in the IMC charter. The IMC will be apprised of all relevant efficacy and safety data from this study and other related clinical trials. Ad hoc meetings may be called as necessary in addition to scheduled meetings to provide recommendations on management of any new safety issues. The Sponsor will be the final decision maker regarding protocol procedures and modifications.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of study is planned to occur approximately 24 months after last patient in (LPI).

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Venetoclax Dose Selection in the Phase Ib Dose-Escalation Phase of the Study

Venetoclax has been investigated and shown to be well tolerated in multiple trials of hematopoietic malignancies at doses ranging from 200 mg to 1200 mg, both as a monotherapy and in combination with other agents including dexamethasone, rituximab, obinutuzumab, bortezomib, and chemotherapy. Venetoclax is approved in the U.S. and E.U. for the treatment of adult patients with CLL (or SLL in the U.S.), with or without 17p deletion, who have received at least one prior therapy. The recommended dose of venetoclax monotherapy in this setting is 400 mg QD in a ramp-up schedule (Venclexta® U.S. Package Insert) and this dosing is maintained during administration with rituximab. Venetoclax is also approved in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML, with 400 mg QD dosing when in

combination with azacitidine or decitabine and 600 mg QD dosing when in combination with LDAC in the U.S.

A Phase I dose-escalation trial investigating combinations of various doses of venetoclax (including 200 mg, 400 mg, 600 mg, and 800 mg) with tamoxifen assessed the safety and tolerability of venetoclax in combination with that ER modulator in patients with ER+, Bcl-2+ MBC (Lok et al. 2019). Venetoclax at the dose of 800 mg PO QD in combination with tamoxifen was well tolerated. The nature and frequencies of adverse events were consistent with the known safety profiles of venetoclax and tamoxifen, and no Grade 5 adverse events or DLTs occurred during the DLT observation period, based on the preliminary evidence of clinically relevant activity of venetoclax during the dose-escalation phase. Venetoclax dosing is further informed by the ongoing randomized Phase II VERONICA study (WO40181) evaluating venetoclax at 800 mg QD plus fulvestrant in patients with HR-positive MBC.

Based on the experience in hematologic malignancies as well as ER+ BC, and the expected limited overlapping toxicities and potential for drug–drug interactions (DDI) between venetoclax and trastuzumab emtansine (see Section 3.3.11), two dose levels have been selected for the dose-escalation phase of the study. This is based on population PK and saturation modeling to assess dose dependency of venetoclax exposure with the assumption that CLL/DLBCL modeling can adequately predict solid tumors. This modeling has shown limited value of studying a 600 mg dose of venetoclax as an intermediate step in a 400 mg to 800 mg dose escalation (internal Genentech data). Moreover, the toxicities are considered to be monitorable and manageable, and enabling a starting dose of 400 mg continuous QD and moving up to the second dose level of 800 mg continuous QD (refer to Section 3.1.1).

Patients with solid tumors may require a higher dose of venetoclax when compared with the 400 mg QD dose in hematologic malignancies such as CLL. This is reflected in the lower 50% effective concentration values of venetoclax for circulating lymphocyte counts (0.00863 μg/mL) compared with tumor size (0.146 μg/mL; Freise et al. 2017). Possible explanations for this observation include reduced blood flow and subsequent less efficient delivery of systemic venetoclax within a tumor, and altered signaling interactions between lymphoma cells and the cells of the tumor microenvironment. Therefore, a second dose level of 800 mg continuous QD is being evaluated, allowing for increased exposure of venetoclax in the tumor compartment.

3.3.2 Rationale for Venetoclax Dose Selection in the Phase II Randomized Portion of the Study

The dose-escalation phase will provide further information on the venetoclax dose that is considered safe and tolerable to be combined with trastuzumab emtansine. The venetoclax RP2D and MTD for the combination with trastuzumab emtansine, which will be the same for both the expansion and randomized phases, will be determined based on the dose-escalation phase of the study (see Section 3.1.1). The RP2D may be lower

than the MTD, dependent on the evaluation of the cumulative and aggregated data from the dose-escalation phase of the study. An IMC will conduct periodic reviews of safety data for all patients treated in the randomized Phase II stage of the study in order to confirm the safety and tolerability of the combination therapy at the RP2D (see Section 3.1.4).

3.3.3 Rationale for Trastuzumab Emtansine Dose and Schedule

The globally approved and standard-of-care regimen of trastuzumab emtansine is 3.6 mg/kg Q3W, as confirmed in Study TDM4370g/BO21977 (Verma et al. 2012), the pivotal Phase III trial comparing trastuzumab emtansine to lapatinib plus capecitabine in patients with HER2+ MBC who were previously treated with trastuzumab and a taxane.

3.3.4 Rationale for Dose-Finding Rules

The rules for dose escalation are designed to ensure patient safety while providing an opportunity to identify the optimal venetoclax dose and schedule in combination with trastuzumab emtansine to maximize the benefit–risk profile of the combination. Key elements of dose escalation based on a standard 3+3 design are described in Section 3.1 and depicted in Figure 2.

Rules based on the nature and timing of observed safety events have been implemented.

3.3.5 Rationale for Dosing Schedule

Given the anticipated limited overlapping toxicities between venetoclax and trastuzumab emtansine (Section 5), continuous dosing of venetoclax on a 21-day cycle based on the trastuzumab emtansine infusion schedule is being evaluated initially. NC 7- or 14-day schedules may be evaluated based on the severity and timing of occurrence of adverse events experienced.

3.3.6 Rationale for Patient Population

Clinical benefit with trastuzumab emtansine has been demonstrated in a randomized study to improve PFS and OS compared to lapatinib plus capecitabine, for patients with HER2-positive MBC who have received prior trastuzumab or taxane (Verma et al. 2012). Trastuzumab emtansine is the standard of care in this population; however, the PFS of approximately 8.6 months and OS of approximately 30 months for this patient population represent a continued unmet medical need. Despite advances in care for patients with HER2-positive MBC, it remains an incurable disease. Nearly all patients with HER2-positive MBC will eventually suffer disease progression and succumb to their disease. Thus, there is still a pressing need for more efficacious therapies with acceptable safety profiles in patients with HER2-positive disease.

3.3.7 Rationale for Control Group

This control arm treatment is recognized as the recommended standard of care for HER2-positive MBC based on the results from Study TDM4370g/BO21977 (see

Section 1.2) (Verma et al. 2012). Trastuzumab emtansine has become widely accepted as the standard of care in patients who have been previously exposed to trastuzumab alone or trastuzumab and a taxane, which is the patient population being studied in the current trial (Cardoso et al. 2018; NCCN 2019). The control arm data will be used to ascertain the individual contribution of venetoclax to efficacy with trastuzumab emtansine.

3.3.8 Rationale for Randomization and Blinding

Randomization will minimize differences between treatment groups at the outset of the trial and blinding will help prevent differential treatment of the groups later in the trial or the differential assessment of outcomes. Both randomization and blinding will mitigate bias and will aid to minimize the likelihood of differential treatment or assessments of outcomes.

3.3.9 Rationale for Objective Response Rate and Progression-Free Survival as Co-Primary Endpoints for the Randomized Phase II Stage

Investigator-assessed ORR by RECIST v1.1 and PFS are the co-primary endpoints for this study.

ORR (as defined in Section 2.1.1) is an increasingly important endpoint for accelerated development of highly active anticancer therapies. Investigator-assessed ORR by RECIST v1.1 has been shown to be a meaningful trial endpoint correlating well with PFS and OS endpoints (Oxnard et al. 2016). In this patient population, ORR has been used as an early signal of clinical benefit (Verma et al. 2012, Tamura et al. 2019). Therefore, for this study ORR will be used alongside PFS as a measure of the individual contribution of venetoclax to efficacy with trastuzumab emtansine. The clinical significance of the ORR will be assessed by the magnitude and duration of response.

PFS is the standard and accepted endpoint reflecting clinical benefit in HER2-positive MBC. PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends upon the magnitude of the effect and the benefit-risk of the new treatment compared with available therapies (FDA 2007; EMA 2017).

To ensure the validity of investigator-assessed PFS as the primary endpoint, a number of measures have been implemented: a substantial target magnitude of benefit and study assessments that will allow a robust evaluation of benefit–risk. This includes conventional criteria using RECIST v1.1 to define radiographic disease progression with fixed assessment intervals that are identical in both treatment arms, a robust definition of PFS as well as prospectively defined methods to assess, quantify, and analyze PFS, including sensitivity analyses.

3.3.10 Rationale for Pharmacokinetic Assessments

This is the first study for which venetoclax will be given in combination with trastuzumab emtansine to patients with MBC. Accordingly, PK plasma or serum samples will be taken to characterize the pharmacokinetics of venetoclax and trastuzumab emtansine when given in combination (see Section 4.5.7 for details).

3.3.11 Rationale for Assessments of Drug–Drug Interactions between Study Treatments

The potential for venetoclax to affect trastuzumab emtansine pharmacokinetics is considered to be low. The antibody component of trastuzumab emtansine is a therapeutic protein and therefore is not expected to interact with CYP450 or transporter pathways. The potential for DDIs between venetoclax and DM1, the small molecule component of trastuzumab emtansine, are also expected to be low based on knowledge of the metabolic and transporter pathways for each molecule. Although venetoclax (a P-glycoprotein [P-gp] inhibitor) could potentially affect the pharmacokinetics of DM1 (a P-gp substrate) through a transporter-mediated interaction, the potential for a clinically meaningful effect is considered to be low, given that the DM1 catabolite of IV administered T-DM1 is less likely to be impacted by P-gp inhibition by venetoclax in the gut. Additionally, trastuzumab emtansine will be dosed in the linear PK range for this study, and co-administration of other anticancer agents with trastuzumab emtansine has not impacted trastuzumab emtansine pharmacokinetics (see the Trastuzumab Emtansine Investigator's Brochure). These results suggest that target-mediated clearance does not significantly contribute to the overall systemic clearance of trastuzumab emtansine, suggesting a low potential for venetoclax to impact trastuzumab emtansine PK.

The risk of a clinically significant PK drug interaction for trastuzumab emtansine to alter venetoclax pharmacokinetics is expected to be low on the basis of their metabolic pathways. Venetoclax is primarily metabolized by CYP3A in vitro and is a reversible inhibitor of CYP2C8 and CYP2C9 in vitro. Trastuzumab emtansine is a biologic administered intravenously and is not expected to modulate CYP3A activity and affect venetoclax metabolism.

Based on the evidence provided above, limited blood samples will be collected to characterize the DDI interactions between venetoclax and trastuzumab emtansine when given in combination (see Section 4.5.7 for details).

3.3.12 Rationale for Biomarker Assessments

BC is a heterogeneous disease, and HER2 and Bcl-2 expression have been shown to vary among patients (unpublished data). All patients may not be equally likely to benefit from treatment with venetoclax and trastuzumab emtansine. Predictive biomarker samples (tissue and blood) collected prior to dosing will be assessed in an effort to identify those patients who are most likely to respond to venetoclax and trastuzumab

emtansine. PD biomarkers will be assessed to demonstrate evidence of biologic activity of venetoclax and trastuzumab emtansine in patients, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

Currently, there are limited data about the correlation of response to Bcl-2 inhibition in BC and Bcl-2 expression levels. Bcl-2 levels are elevated in ER-positive subgroups relative to the other molecular subgroups that comprise BC. Furthermore, nonclinical data have demonstrated increased antitumor activity in high Bcl-2 expressing BC cell lines (see Section 1.5). Therefore, predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with Bcl-2-driven pathogenesis who are most likely to respond to venetoclax. The study aims to prospectively explore if Bcl-2 expression might have predictive or prognostic value or may be associated with disease progression in the studied population.

Fresh tissue acquisition in some patients with MBC may not be feasible; consequently, assessment of more easily accessible biomarkers in circulation is of high interest. In addition to identification of disease-specific, potentially prognostic, or predictive biomarkers in predose, baseline blood specimens, on-treatment collection of blood to evaluate circulating tumor DNA (ctDNA) may enable identification of biomarkers informing the relationship with established clinical response assessments, the monitoring of disease progression, and the identification of markers of resistance.

Tumor tissue samples will be analyzed through use of IHC to assess protein expression, and/or RNA sequencing to assess gene expression levels. Both tissue and blood samples will be analyzed by next-generation sequencing (NGS) to identify somatic alterations that are predictive of response to study drug, are associated with progression, are associated with acquired resistance to study drug, or can increase the knowledge and understanding of disease biology.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.13 Rationale for Stratification and Enrichment by B-Cell Lymphoma-2 (Bcl-2) Status

Bcl-2 levels are elevated in ER-positive tumors; however, there are scant clinical data demonstrating a pathogenic role for Bcl-2 in HER2-positive BC. Venetoclax specifically inhibits Bcl-2 activity and there is potential that Bcl-2 target-expression levels may

correlate with activity. The role of Bcl-2 in pathogenesis is confounded by the prognostic profile associated with the ER-positive subtype. To distinguish the potential for predictive value of Bcl-2 expression levels with targeted Bcl-2 inhibition, patients will be 1) randomized into venetoclax plus trastuzumab emtansine versus trastuzumab emtansine plus placebo arms to distinguish prognostic effects; and 2) stratified into Bcl-2 high and Bcl-2 low populations (as defined in Section 4.1.1.1).

In nonclinical analyses, elevated Bcl-2 expression levels in NHL cell lines correlate with venetoclax activity using this high versus low cutoff. Stratification will ensure that the relative populations of Bcl-2 high and low are well balanced between both arms and therefore enable evaluation of the correlation between Bcl-2 expression and venetoclax activity in BC. In addition, specifying a minimum number of Bcl-2 high tumor patients will enable evaluation of Bcl-2 status as a potential predictive biomarker. Responses will be evaluated by comparing the two stratified subgroups.

Since a cutoff for Bcl-2 levels in BC has not been established, retrospective analyses may also be performed to evaluate alternative cutoffs.

3.3.14 Rationale for Stratification by Visceral Metastases

The site(s) and degree of metastatic dissemination are among the principal prognostic factors for patients with MBC. Patients with visceral metastases to the liver and/or lung in HER2-positive MBC have been shown to have poor prognosis (Verma et al. 2012; Perez et al. 2017; Emens et al. 2019b). In the KATE2 study (Emens et al. 2019b), patients treated with trastuzumab emtansine plus placebo harboring visceral disease as compared to patients with no evidence of visceral disease performed worse (median PFS 4.3 months vs. NE). Visceral disease was defined as the presence of disease in the lung, liver, adrenal gland, central nervous system, pleural cavity or peritoneal cavity. All locations that included tumors in the breast, bone, bone marrow, lymph nodes, skin and soft tissue were classified as non-visceral disease. Moreover, the proportion of patients with visceral involvement is expected to be higher than those with non-visceral disease (70.8% vs. 29.2%, respectively) in KATE2, further justifying use of visceral disease as a stratification factor.

3.3.15 Rationale for Stratification by HER2 Expression Status

HER2 overexpression is an important prognostic and predictive biomarker in MBC (Pauletti et al. 2000). Specifically, in the recent KATE2 study (Emens et al. 2019b) evaluating trastuzumab emtansine in combination with atezolizumab or atezolizumab and placebo, higher HER2 expression (IHC 3+) and lower HER2 expression (IHC 2+/ISH+) demonstrated different prognosis for trastuzumab emtansine outcome (median PFS: 8 months. vs 3.2 months, respectively). The majority of patients were IHC 3+ (74%) as compared to IHC 2+ (19%). Given the association with variable prognosis as well as differences in prevalence, HER2 expression status by IHC has been selected as a

stratification factor in the current study. Patients will be stratified based on HER2 IHC 3+ status and responses will be evaluated by comparing these two stratified subgroups.

3.3.16 Rationale for Patient-Reported Outcome Assessments

As MBC is not curable with currently approved and available therapies, the main goals of treatment are to prolong survival and maintain or improve quality of life (Cardoso et al. 2018). Examining and measuring patients' symptoms and their impact of functioning and quality of life is important, particularly to inform how delays in radiographic progression and PFS might be associated with delays in clinical progression of symptoms and their interference with functioning, including maintenance of low disease burden. In addition, patients' reporting of their experience with treatment burden will complement the evaluation of treatment tolerability.

Symptoms, their impact on functioning and quality of life, and treatment burden will be assessed using validated patient reported outcome (PRO) measures. The EORTC QLQ-C30 will be administered to patients to assess symptoms and their impacts on functioning and quality of life (see Section 4.5.9 and Appendix 6), while the EORTC IL46 will be administered to assess treatment burden.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 226–284 patients with previously treated, HER2-positive LABC or MBC will be enrolled on this study.

4.1.1 Inclusion Criteria (All Study Phases)

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed invasive MBC or LABC that is incurable, unresectable, and previously treated with multimodality therapy:
  - Prior treatment for BC in the adjuvant, unresectable locally advanced, or metastatic settings, which must include a taxane, trastuzumab (alone or in combination with another agent), *and pertuzumab*
    - *For patients who have not received pertuzumab in early breast cancer setting, prior treatment with pertuzumab in the metastatic setting is required prior to enrollment*
  - Progression must have occurred during or after most recent treatment for LABC/MBC or within 6 months after completing adjuvant therapy
- Measurable disease that is evaluable per RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

- Willing to provide tumor biopsy sample at the time of screening

  A tumor biopsy sample (either archival or fresh) must be collected from all patients from either the primary tumor or a metastatic site (preferred and within 6 months of enrollment, if clinically feasible) for determination of HER2 status by central laboratory testing for patient eligibility purposes, for Bcl-2 expression, and for research on biomarkers.

  The tumor specimen must contain adequate evaluable tumor cells ($\geq$20% tumor cells) to enable Bcl-2, HER2, and other relevant biomarker analysis. Samples can be a tissue block (preferred) or at least 20 unstained freshly cut serial slides. If fewer than 20 slides are available, the Sponsor should be consulted. If a tumor sample is not available, a fresh biopsy must be collected.

  The specimen must be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration samples are not acceptable.
- Local histological or cytological confirmation of ER and/or progesterone receptor status as defined by using IHC per American Society of Clinical Oncology/College of American Pathologists criteria (Hammond et al. 2010)
- Percentage of ER and/or progesterone receptor positivity, if available
- Willing to provide blood samples at the time of screening, on-study, and at progression for exploratory research on biomarkers
- HER2-positive BC as defined by an IHC score of 3+ or gene amplified by ISH as defined by a ratio of $\geq$2.0 for the number of HER2 gene copies to the number of chromosome 17 copies

  For the expansion phase and randomized Phase II stage: Centrally confirmed HER2-positive status prospectively tested by a Sponsor-designated central laboratory prior to enrollment.

  For the dose-escalation phase: Enrollment can be based upon prospective central testing or local IHC or ISH results; however, for local IHC or ISH results, the same tissue sample must be sent for central HER2 confirmation and the testing platform documented in the eCRF.

  Both IHC and ISH assays can be performed; however, unless reflex testing is necessary, only one positive result is required for eligibility.

  If multiple tumor specimens are submitted, the HER2 IHC score and or ISH amplification ratio will first be assessed on the most recently obtained specimen for the purpose of determining eligibility. For patients with bilateral BC, HER2 positivity must be demonstrated in both locations for archival tissue or in a metastatic biopsy.

  Centrally confirmed HER2 results (either IHC or ISH) from a current or previous Sponsor study can be used to determine eligibility for this study. Approval must be obtained from the Medical Monitor prior to randomization.

- Adequate hematologic and end-organ function, as evidenced by the following local laboratory results obtained within 7 days prior to the first study treatment (Cycle 1, Day 1):
  - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte-colony stimulating factor support within 7 days prior to Cycle 1, Day 1)
  - Platelet count $\geq 100{,}000$/μL (without transfusion within 7 days prior to Cycle 1, Day 1)
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.
  - Albumin ≥ 25 g/L (2.5 g/dL)
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exceptions:

    Patients with previously documented Gilbert syndrome who may have bilirubin $< 5 \times$ ULN

    Patients with documented liver metastases may have bilirubin $\leq 2.5 \times$ ULN
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases may have ALP $\leq 5 \times$ ULN
  - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of either 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$

  - INR or aPTT $\leq 1.5 \times$ ULN

    For patients requiring anticoagulation therapy with warfarin or other coumarins, a stable INR between 2 and 3 is required. If anti-coagulation is required for a prosthetic heart valve, then INR should be between 2.5 and 3.5.
- Screening left ventricular ejection fraction (LVEF) $\geq 50\%$ on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan

  LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility.
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

The HBV DNA test will be performed only for patients who have a negative HBsAg test and a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 30 days after the last dose of

venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever is later to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.1.1 *Inclusion Criteria for Dose-Escalation Phase Only*

In addition to the general inclusion criteria, patients in the dose-escalation phase of the study must also meet the following criteria for study entry:

- *Prior exposure to trastuzumab emtansine in any setting (advanced/metastatic or early breast cancer) is required*

4.1.1.2 Inclusion Criteria for Expansion Phase Only

In addition to the general inclusion criteria, patients in the expansion phase of the study must also meet the following criteria for study entry:

- Trastuzumab emtansine experienced cohort:
  - Disease progression during or after trastuzumab emtansine *treatment* in the advanced/metastatic setting or disease recurrence in the neoadjuvant/adjuvant setting
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high.

    Bcl-2 high is defined as ≥ 50% of tumor cells stained with an intensity of IHC 2+ or 3+, and Bcl-2 low is defined as IHC 0 or 1+ or < 50% of tumor cells stained with an intensity of IHC 2+ or 3+.

- Trastuzumab deruxtecan (DS-8201a) experienced cohort:
  - Disease progression during or after trastuzumab deruxtecan in the advanced/ metastatic setting
  - Prior trastuzumab emtansine in any setting is allowed
  - At least 50% patients in the expansion cohort (e.g., 10 out of 20) must have tumor that is Bcl-2 high (as defined above).

4.1.1.3 Inclusion Criteria for Randomized Phase II Stage

In addition to the general inclusion criteria, patients in the randomized Phase II stage of the study must also meet the following criteria for study entry:

- Bcl-2 expression status by IHC either from fresh tissue or the most recent archival tissue (see criteria in Section 4.1.1) by a central laboratory using the Ventana Bcl-2 IHC assay prior to randomization.

  At least 50% of patients in the randomized Phase II (e.g., 110 out of 220 patients) must be Bcl-2 high (as defined in Section 4.1.1.1).

4.1.2 Exclusion Criteria

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

- Receipt of any anticancer drug/biologic or investigational treatment 21 days prior to Cycle 1, Day 1 except hormone therapy, which can be given up to 7 days prior to Cycle 1, Day 1
- Radiation therapy within 2 weeks prior to Cycle 1, Day 1

  The patient must have recovered from any resulting acute toxicity (to Grade <1) prior to randomization.
- History of exposure to the following cumulative doses of anthracyclines as specified below:
  - Doxorubicin >500 mg/m^2
  - Liposomal doxorubicin >500 mg/m^2
  - Epirubucin >720 mg/m^2
  - Mitoxantrone >120 mg/m^2
  - Idarubicin >90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 doxorubicin.
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence
- Cardiopulmonary dysfunction as defined by:
  - Uncontrolled hypertension (systolic >150 mm Hg and/or diastolic >100 mm Hg with or without medication)
  - Inadequate LVEF at baseline, <50% by either ECHO or MUGA
  - History of symptomatic congestive heart failure (CHF)-Grade ≥ 3 per NCI CTCAE version 5.0 or Class $\geq$ II New York Heart Association
  - History of a decrease in LVEF to <40% or symptomatic CHF with prior trastuzumab treatment

  - Myocardial infarction or unstable angina within 6 months of randomization
  - Concurrent dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Evidence of transmural infarction on ECG
  - Significant symptoms (Grade $\geq$2) relating to LVEF, cardiac arrhythmia, or cardiac ischemia
  - High-risk uncontrolled arrhythmias (i.e., supraventricular tachycardia with a heart rate $>$100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 (Mobitz 2) or third-degree AV-block])
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease; wound healing disorders; ulcers; bone fractures)
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, autoimmune hepatic disorders, sclerosis cholangitis, or active infection with HBV or HCV)
- Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Known HIV infection or human T-cell leukemia virus 1 infection
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $>$ 2 weeks prior to randomization
- Known central nervous system (CNS) disease, except for patients treated and currently with asymptomatic CNS metastases, provided that all of the following criteria are met:
  - Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)
  - No ongoing requirement for corticosteroids as therapy for CNS disease
  - No stereotactic radiation within 14 days prior to randomization
  - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

    Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may be eligible

without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed regardless of drainage frequency.
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium or calcium $>$ 12 mg/dL or corrected serum calcium greater than the ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue use of denosumab and replace it with a bisphosphonate instead while on study.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Current Grade $\geq$ 3 peripheral neuropathy (according to the NCI CTCAE v 5.0)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies, excipients of any drugs formulated in polysorbate 80 or 20 or fusion proteins
- Prior allogeneic stem cell or solid organ transplantation
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 30 days after the last dose of venetoclax or 7 months after the last dose of trastuzumab emtansine after the final dose of study treatment, whichever is later

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Strong or moderate CYP3A inhibitors (see Appendix 14 for examples)
  - Strong or moderate CYP3A inducers (see Appendix 14 for examples)

  Additional restrictions for on-study use of CYP3A inhibitors/inducers are outlined in Section 4.4.2.
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade-containing Seville oranges), or starfruit (carambola) within 3 days before anticipated first dose of study drug until the last dose of study drug (see Section 4.4.2)
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment

- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History of active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) requiring specific medication in the 12 months prior to randomization, or active and uncontrolled bowel inflammation (e.g., diverticulitis) at time of randomization
- Inability or unwillingness to swallow a large number of tablets
- Known hypersensitivity to venetoclax or trastuzumab emtansine or to any of their excipients
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Other medical or psychiatric conditions that, in the opinion of the investigator, may interfere with the patient's participation in the study
- Blood transfusions if performed within 2 weeks prior to screening

4.1.2.1 Exclusion Criteria for Randomized Phase II Stage

In addition to the general exclusion criteria, patients in the randomized Phase II stage of this study who meet the following criteria will be excluded:

- Prior treatment with trastuzumab emtansine in any setting (neoadjuvant/adjuvant or advanced/metastatic setting)
- Prior treatment with venetoclax in any setting
- Prior treatment with anti-HER2 antibody drug conjugates (e.g. trastuzumab deruxtecan [DS-8201a]), margetuximab, pyrotinib, or tucatinib

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING (APPLICABLE TO RANDOMIZED PHASE II STAGE ONLY)

4.2.1 Treatment Assignment

The Phase II randomized portion of this study is randomized and double-blind. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS.

Patients in the randomized Phase II stage will be randomly assigned to one of two treatment arms: venetoclax in combination with trastuzumab emtansine or trastuzumab emtansine plus placebo. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm with respect to pre-specified stratification factors. Randomization will be stratified according to the following criteria:

- Bcl-2 status (Bcl-2 high vs. Bcl-2 low; as defined in Section 4.1.1.1)
- Visceral disease (Yes vs. No; as defined below)

- HER2 status IHC 3+ (Yes vs. No; as defined in Section 4.1.1)

Visceral disease will be defined as the presence of disease in the lung, liver, adrenal gland, central nervous system, pleural cavity, or peritoneal cavity. All locations that include tumors in the breast, bone, bone marrow, lymph nodes, skin, and soft tissue will be classified as non-visceral disease. Patients with tumors in multiple locations that cover both visceral and non-visceral disease (e.g., a patient with a tumor in the liver and bone lesions) will be designated as having visceral disease for the purposes of the analysis.

Patients who are randomized into this study will not be allowed to be re-randomized to receive a second course of study treatment. Once a patient has been randomized into the study, the IxRS will be used to assign the kit numbers for study drugs to be dispensed at each treatment visit. It is important that the study drugs dispensed for each visit are the correct kit number, as assigned by the IxRS. This will ensure that drug use by dates and automatic study drug resupply to sites are managed appropriately via the IxRS.

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

While PK and immunogenicity samples will be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct of the study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for venetoclax PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The

investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above) will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are venetoclax, trastuzumab emtansine, and placebo.

Rescue medications and pre-medications are considered non-investigational medicinal products (NIMPs). In this study, diphenhydramine is considered a NIMP.

4.3.1.1 Venetoclax and Placebo

Venetoclax (GDC-0199/ABT-0199) is manufactured by AbbVie, Inc. and will be supplied by the Sponsor as oral film-coated tablets of 100-mg strength. Venetoclax tablets will be packaged in high-density polyethylene (PE) plastic bottles to accommodate the study design. Venetoclax tablets must be stored at 15°C–25°C (59°F–77°F).

For information on the formulation and handling of venetoclax, see the pharmacy manual and the Venetoclax Investigator's Brochure.

The formulation of placebo is equivalent to venetoclax but without the active agent. The handling of placebo is described in the pharmacy manual.

If unblinding occurs, the treatment assignment placebo will no longer be administered to patients randomized to Arm A (trastuzumab emtansine and placebo).

4.3.1.2 Trastuzumab Emtansine

Trastuzumab emtansine will serve as the comparator/active control and will not be blinded. Trastuzumab emtansine will be provided as a lyophilized formulation in a single-use 20 mL glass vial. Each 20 mL vial contains enough product to deliver approximately 160 mg of trastuzumab emtansine. Trastuzumab emtansine vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until use. Do not freeze vials. Trastuzumab emtansine vials should not be used beyond the expiration date provided by the manufacturer.

For information on the packaging, reconstitution, and handling of trastuzumab emtansine, refer to the pharmacy manual and the Trastuzumab Emtansine Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens for the dose-escalation phase, dose-expansion phase, and randomized Phase II stage are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

If trastuzumab emtansine is held, then venetoclax/placebo should continue, provided the dosing selected in the dose-escalation phase of this study is continuous. In the case of NC dosing of venetoclax/placebo, when trastuzumab emtansine is held, then venetoclax placebo should be held as well and restart concomitantly to preserve treatment synchronization. If trastuzumab emtansine is permanently discontinued for toxicity, then venetoclax/placebo can continue, provided that the patient is deriving clinical benefit from venetoclax/placebo, in the opinion of the investigator. Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Venetoclax and Placebo

At the start of each cycle, patients will be supplied with sufficient venetoclax and placebo tablets for that cycle. A drug diary will be provided to the patient to record oral administration of doses, including the date and time of dosing. Patients will be instructed to return empty bottles or unused tablets.

The investigator is responsible for monitoring patient compliance by monitoring the patient diary and counting unused tablets. Patient compliance with the assigned daily dose of study medication will be assessed by standard pill counts. Previously distributed bottles will be returned to the clinic and tablets counted. Any discrepancy will be resolved with the patient at each clinic visit and documented in the patient record.

Each dose of venetoclax or placebo will be taken orally once daily with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or patient's first meal of the day. Patients should self-administer venetoclax at approximately the same time each morning. On days that PK sampling is required, the patient's first meal of the day and all study treatment doses should occur in the clinic to ensure accurate timing of the PK sampling. On those days, the time of each dose of venetoclax will be recorded to the nearest minute.

A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax. The following is an example of a breakfast that contains approximately 520 Kcal and has 30% of the total caloric content of the meal from fat that is, approximately 17 grams of fat: one box cereal (30–40 g), skim milk (240 mL), one boiled egg, one slice of toast (15 g) with 1 tablespoon of margarine (14 g). The toast and margarine may be replaced with one medium croissant or two large pancakes. If there is a substantial period of time between the patient's regular time of breakfast and their venetoclax dosing in the clinic on PK sampling days, patients may have a low-fat snack in the morning. Patients must be instructed not to take their study treatment with the snack and to take their study treatments in the clinic after a meal.

Venetoclax tablets should be swallowed whole and never be chewed, cut, or crushed. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another venetoclax dose should be taken, and the second dose should be noted in the drug diary. If tablets are not intact or if vomiting occurs more than 15 minutes after taking venetoclax, no replacement dose is to be taken. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose with food as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose. Otherwise, the dose should not be taken.

4.3.2.2 Trastuzumab Emtansine

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion Q3W. The initial dose of trastuzumab emtansine will be administered on the basis of the patient's baseline weight. Weight will be measured at each visit and dose must be re-adjusted for weight changes ≥10% compared to the previous visit or baseline, whichever is most recent. The investigator may choose to recalculate the dose at every cycle using actual weight at that time, according to their local practice. Administration may be delayed to assess or treat adverse events. Dose reduction will be allowed, following the dose reduction levels provided in *Table 5*. Once a dose has been reduced for adverse event(s), it must not be re-escalated. If trastuzumab emtansine is discontinued because of toxicity, it should not be re-administered. Guidelines for dosage discontinuation for patients who experience adverse events are provided in Section 5.1.3.

If the timing of a protocol-mandated procedure, such as administration 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.

Refer to Table 1 for guidelines on administration of first and subsequent infusions of trastuzumab emtansine.

Table 1 Administration of First and Subsequent Infusions of Trastuzumab Emtansine

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs as indicated in Appendix 1 and Appendix 2. • Administer the initial dose as a 90-minute IV infusion. • Patients should be observed during the infusion and for at least 90 minutes following the initial dose for fever, chills, or other infusion-related reactions. • The infusion rate should be slowed or interrupted if the patient develops infusion-related symptoms. • The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.	• Record patient's vital signs as indicated in Appendix 1 and Appendix 2. • If prior infusions were well tolerated, subsequent doses may be administered as 30-minute infusions. • Patient should be observed during the infusions and for at least 30 minutes after infusion.

4.3.2.3 Sequence of Study Drug Administration

The oral dose of venetoclax should be administered first, followed by infusion of trastuzumab emtansine.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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.

4.3.3.1 Continued Access to Venetoclax and Trastuzumab Emtansine

The Sponsor will offer continued access to Roche IMPs venetoclax and trastuzumab emtansine free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs venetoclax and trastuzumab emtansine after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMPs venetoclax and trastuzumab emtansine after completing the study if any of the following conditions are met:

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

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1)
- Hormone-replacement therapy

- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) to non-target sites is allowed as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  Study drug treatment may be continued during palliative radiotherapy.
- Pain medications administered per standard clinical practice
- Inactive influenza vaccinations during influenza season
- Bisphosphonates for prevention of skeletal related events

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

The use of anti-emetics and anti-diarrhea prophylaxis is permitted and should be administered per protocol guidelines (see Table 9 and Section 5.1.3 for more details). The use of anti-emetics must be documented in the eCRF. Use of prophylactic anti-microbial agents, TLS prophylaxis and/or treatment, and/or growth factors is also recommended according to standard institutional practice and should be documented in the eCRF.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion associated- events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Prohibited Food

Use of the following foods is prohibited for at least 3 days prior to initiation of treatment, throughout venetoclax administration, and for 28 days after the last dose of study treatment:

- Constituents of these foods have been shown to inhibit CYP3A4, the major enzyme responsible for the metabolism of venetoclax. Consumption of these foods could lead to increased venetoclax exposure:
  - Grapefruit
  - Grapefruit products
  - Seville oranges (including marmalade containing Seville oranges)
  - Star fruit (carambola)

4.4.3 Prohibited and Cautionary Therapy

Use of the following concomitant therapies are prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 21 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment, depending on the agent , and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details).
- The administration of live, attenuated influenza vaccine (e.g., FluMist®) is prohibited during treatment and within 28 days following the last dose of venetoclax.

Some additional therapies are prohibited only for specific study phases, or are allowed with caution, restrictions, and/or dose adjustments. These are described in Table 7 and are to be implemented after relevant exclusion criteria for these medications are met (see Section 4.1.1).

Venetoclax is a substrate of CYP3A and therefore venetoclax exposure can be impacted by concomitant strong and moderate of CYP3A inducers and inhibitors. DM1, the cytotoxic component of trastuzumab emtansine, is metabolized mainly by CYP3A4 and to a lesser extent by CYP3A5. Relevant restrictions and dosing recommendations for concurrent CYP3A inhibitors/inducers are described in Table 2. *Examples of CYP3A4 inhibitors/inducers and P-gp substrates/inhibitors* are listed in Appendix 14.

After discontinuation of a moderate or strong CYP3A inhibitor that led to a venetoclax dose reduction as per the following guidelines, the investigator should wait for 3 days before increasing the venetoclax dose back to the original maintenance/target dose.

Table 2 Therapies Prohibited for Specific Study Phases, or Allowed with Caution, Restrictions, and/or Dose Adjustments

Therapy	Phase Ib: Dose-Escalation		Phase Ib: Expansions and Phase II: Randomized
	DLT Window [a]	Post DLT Window [a] at Cohort-Designated Dose	Cohort-Designated Dose
Strong CYP3A inhibitors	Prohibited	Avoid and consider alternative medications. Consult with the medical monitor if considering use. If usage is approved by the medical monitor, reduce venetoclax dose by at least 4-fold (see Table 3) and follow applicable local prescribing information. Consider delaying T-DM1 treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If T-DM1 treatment cannot be delayed, patients should be closely monitored for adverse reactions.	
Moderate CYP3A inhibitors	Prohibited	Avoid and consider alternative medications. Consult with the medical monitor if considering use. If usage is approved by the medical monitor, reduce venetoclax dose by 2-fold (see Table 3).	
Strong CYP3A inducer	Prohibited		
Moderate CYP3A inducer	Prohibited		Exclude through completion of the first cycle of venetoclax. After the first cycle, avoid and consider alternative medications with less induction. If used, contact the Medical Monitor for guidance.
P-gp inhibitors	If P-gp inhibitor must be used, monitor closely for toxicities and follow the applicable local prescribing information		
P-gp substrates	Concomitant use of narrow therapeutic index P-gp substrates should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.		
Warfarin and coumarin derivatives (e.g., phenprocoumon)	Use with caution with close monitoring of the international normalized ratio (INR).		
Excessive alcohol intake	Should be avoided (occasional to moderate use is permitted).		

DLT = dose-limiting toxicity; P-gp = P-glycoprotein.
Note: See Appendix 14 for examples of CYP3A4 inhibitors/inducers and P-gp substrates/inhibitors.
[a] DLT window applicable to dose-escalation stage only.

Table 3 Venetoclax Dose Reductions for Strong and Moderate CYP3A Inhibitors

Venetoclax Assigned Dose (mg)	Venetoclax Reduced Dose (mg)	
	Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors
100	Consult with Medical Monitor.	Consult with Medical Monitor.
200	Consult with Medical Monitor.	100
400	100 (70 for posaconazole in U.S. and countries with USPI-based approval)	200
600		300
800	200	400

U.S. = United States; USPI = United States Prescribing Information.

Appendix 14 contains examples of CYP3A4 inhibitors/inducers and P-gp substrates/inhibitors. Additional examples of these classes of medications are provided at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The above lists are not necessarily comprehensive; the investigator should also consult the prescribing information for any concomitant medication when determining the drug-drug interaction potential.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed. A decision may be made to allow the use of prohibited medications on a case by case basis, following discussion with the Medical Monitor and assessment of the benefit-risk ratio.

Patients who require the use of any therapies when they are prohibited (unless an allowance is made after consultation with the medical monitor) will be discontinued from study treatment and followed for safety outcomes and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anticancer therapy, whichever comes first.

4.4.3.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.2) may be used during the study at the discretion of the investigator.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. 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.

4.5.1 Informed Consent Forms and Screening Log

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

Prior to signing the main Informed Consent Form for the study, patients may consent to the collection of tumor tissue (archival or newly obtained via biopsy) for determination of Bcl-2 expression by signing a Prescreening Informed Consent Form.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, and foods that have been shown to inhibit CYP3A4 [Section 4.4.2]) used by the patient within 28 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Breast cancer history includes prior cancer therapies and procedures.

Demographic data will include age, sex, and self-reported race/ethnicity. Local HER2 testing information will also be collected, if available.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Tumor and Response Evaluations

All sites of measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in Appendix 1 and Appendix 2; a time window of ±7 days is allowed for all timepoints regardless of drug delays or interruptions. Tumor assessments will continue until disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Initial screening assessments must include CT scans (with oral or IV contrast unless contraindicated) or MRI scans of the chest, abdomen, and pelvis. A bone scan or positron emission tomography (PET) scan should also be performed to evaluate for bone metastases. MRI scans of the chest, abdomen, and pelvis or non-contrast CT scan may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast) or MRI scan with contrast (if CT contrast is contraindicated) of the head must be done at screening to evaluate CNS metastasis in all patients. If CT with contrast is performed and the presence of brain metastases is considered equivocal, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline. Patients with active or untreated symptomatic CNS metastases are not eligible for the study (see Section 4.1.1). Patients with untreated asymptomatic CNS metastasis at screening may be eligible. For untreated patients, brain MRI scan with contrast at screening is required, and needs to meet all eligibility criteria as specified in Section 4.1.

If a CT scan for tumor assessment is performed as part of a PET/CT, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Further investigations such as bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease according to RECIST v1.1 may be used.

Evaluation of tumor response conforming to RECIST v1.1 (Appendix 11) will be performed every 6 weeks (±7 days) following randomization until the primary PFS analysis, with additional scans performed as clinically indicated. The same radiographic procedures used to assess measurable disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT and/or MRI scans). Following the primary PFS analysis, tumor assessments will be conducted as per standard of care and recorded in the eCRF until disease progression.

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of the following assessments every 6 weeks until the primary PFS analysis:

1. CT and/or MRI of the chest/abdomen/pelvis, as well as other known sites of disease, including brain
2. If a patient has only bone as a site of involvement at screening, which is determined to be measurable disease as per RECIST v1.1, then a bone scan or PET scan is mandated at every tumor assessment, or a bone scan or PET scan is to be performed as clinically indicated (e.g., suspicion of disease progression)
3. In cases where patients demonstrate control of their systemic disease but who newly develop isolated brain metastases and are eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments
4. Any other imaging studies felt to be clinically indicated by the treating physician

Response will be assessed by the investigator using RECIST v1.1 (Appendix 11) at each tumor assessment. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if PD is suspected. If the initial screening bone scan or PET scan indicates bone metastases and this is the only site of involvement and is determined to be measurable disease per RECIST v1.1, then a bone scan or PET scan needs to be performed every 6 weeks. If the screening scan shows evidence of either non-measurable bone metastases or no bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion. If the brain is not identified as a site of involvement at screening, then brain CT or MRI only needs to be repeated beyond screening, if clinically indicated. In cases where a patient demonstrates control of their systemic disease but who newly develops isolated brain metastases and is eligible to remain on study treatment, brain MRI or CT are performed along with regularly scheduled tumor assessments (Section 3.1).

If study drug treatment is discontinued prior to disease progression according to RECIST v1.1, tumor response assessment should continue to be performed as per the schedule specified in Appendix 1 and Appendix 2.

4.5.6 Left Ventricular Ejection Fraction Assessment

LVEF will be assessed by ECHO or MUGA. LVEF will be monitored at baseline and every fourth cycle thereafter. Additional LVEF measurements may be performed if LVEF declines are clinically suspected at the discretion of the investigator.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Chemistry panel (serum): glucose, BUN or urea, sodium, magnesium, chloride, bicarbonate, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin

  TLS laboratory assessments include serum creatinine, uric acid, potassium, calcium, phosphorous, and LDH.
- Coagulation: aPTT and INR
- HIV serology
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood)
- Thyroid function test (thyroid-stimulating hormone [TSH], free T3, and free T4)

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis.

- Blood samples for exploratory research on biomarkers and biomarker assay development

  Blood samples will be processed to obtain plasma, and serum for the determination of baseline level changes in surrogate PD biomarkers.

- C-reactive protein
- Blood samples for auto-antibody testing

  For patients who show evidence of immune-mediated toxicity, additional samples may be collected and will be analyzed centrally:

  - Anti-nuclear antibody
  - Anti–double-stranded DNA
  - Circulating anti-neutrophil cytoplasmic antibody
  - Perinuclear anti-neutrophil cytoplasmic antibody

- Plasma samples for venetoclax PK analysis
- Serum samples for trastuzumab emtansine PK analysis
- Serum samples for total trastuzumab analysis
- Serum samples for trastuzumab emtansine immunogenicity analysis

  Note: Alternative PK and ADA assessments may be explored if there is substantial difficulty in obtaining the timepoints listed in Appendix 3. Depending on the results from interim PK and ADA analyses, the frequency of PK and ADA sampling may be reduced or halted later in the study.

- Archival or newly collected tumor tissue sample obtained at baseline for determination of protein expression of Bcl-2 and HER2 by central laboratory testing for patient eligibility purposes and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut. If only 10–19 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of $\geq$ 20% viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Exploratory biomarker research may include, but will not be limited to, analysis of tissue and ctDNA (i.e., mutation profiles associated with disease) and genes or gene signatures associated with apoptosis (i.e., BCL-2 family). Research may involve extraction of DNA, ctDNA, or RNA; analysis of somatic mutations; and use of NGS of a comprehensive panel of genes. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11.3), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum and plasma samples collected for PK or immunogenicity analysis may be needed for additional pharmacokinetics (e.g., PK biomarkers or relevant analytes/catabolites/metabolites) and immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, or earlier depending on local regulations.
- Tumor tissue and blood samples collected for biomarker research and biomarker assay development will be destroyed no later than no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the

samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings may be stored at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study

drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.9 Patient-Reported Outcome Assessments

PRO instruments will be completed during the randomized Phase II stage of the study to assess the treatment benefit and/or more fully characterize the safety profile of venetoclax in combination with trastuzumab emtansine compared to trastuzumab emtansine plus placebo. In addition, PRO instruments will enable the capture of each patient's direct experience with venetoclax in combination with trastuzumab emtansine compared to trastuzumab emtansine alone.

PRO data will be collected through use of the following instruments: the EORTC QLQ-C30 *questionnaire* and the EORTC IL46 *item*.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments, translated into the local language as appropriate, will be self-administered via paper questionnaires. Instructions for completing the questionnaires will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor or entered into the study database by site personnel as appropriate. The data will be available for access by appropriate study personnel.

The EORTC QLQ-C30 and IL46 assessments will occur as outlined in the schedule of activities (Appendix 2).

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to receiving any information on disease status, prior to the performance of non-PRO assessments that could bias patients' answers, and prior to the administration of study treatment, unless otherwise specified.

During clinic visits, PROs should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 10 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.

- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- If completed on paper, site staff should review and ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

The questionnaires (EORTC QLQ-C30 and EORTC IL46 *item*) will be completed during the randomized Phase II stage only: at Cycle 1, Day 1 (baseline) prior to administration of study drug; then at every study treatment cycle prior to administration of study drug (i.e., on Cycle 2, Day 1; Cycle 3, Day 1; and Cycle 4, Day 1, etc.) and at the study treatment discontinuation visit (see Appendix 2).

Patients who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will complete the EORTC QLQ-C30 at each tumor assessment visit until radiographic disease progression per RECIST v1.1, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first.

Patients whose native language is not available with the questionnaires are exempted from completing all PRO assessments.

The Sponsor will not derive adverse event reports from PRO data.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

EORTC QLQ-C30

The EORTC QLQ-C30 (see Appendix 6) is a validated and reliable self-report measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales. The EORTC QLQ-C30 module takes approximately 15 minutes to complete.

EORTC IL46

The EORTC IL46 is a validated single-item question assess*ing the* overall *burden or* impact of study drug side effects (see Appendix 6)*, i.e.,* patient experience *of tolerability*.

4.5.10 Optional Tumor Biopsies

Consenting patients will undergo an optional tumor biopsy (if deemed clinically feasible by the investigator) at Cycle 1, Day 1 and/or Cycle 2, Day 1 (see Appendix 1 and Appendix 2) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Where fresh biopsy is possible, samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are acceptable. Biopsies collected via fine-needle aspirations are not acceptable.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.7 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to venetoclax, trastuzumab emtansine, disease, or drug safety:

- Blood samples collected at baseline
- Additional archival tumor tissue samples (e.g., from an earlier biopsy) collected at screening
- Tumor tissue samples from biopsies performed at the investigator's discretion during the study
- Leftover blood, serum, plasma, peripheral blood mononuclear cell (PBMC), and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides).

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC approved- Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

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

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.11.5 Consent to Participate in the Research Biosample Repository

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

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical

Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.11.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anticancer therapy not required per protocol
- Radiographic disease progression according to RECIST v1.1

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

Patients who discontinue treatment prematurely during the DLT-evaluation period during the dose-escalation phase will be replaced. Patients who discontinue study treatment prematurely during the randomized portion of the study will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit 28 days (+14 days) after the last dose of study drug (see Appendix 1 and Appendix 2 for additional details). After treatment discontinuation due to disease progression, information on survival follow-up and new anticancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are discontinued from study treatment for reasons including disease progression and have started follow-on treatment/s will be followed for survival approximately every 6 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Patients who are discontinued from study treatments for reasons other than disease progression and have not started follow-on treatment/s will be followed for disease status every 8 weeks (± 5 days) from the date of randomization until Week 24 (± 5 days) and every 12 weeks (± 5 days), thereafter, until disease progression, loss to follow-up, withdrawal of consent, death or study termination by the Sponsor, whichever occurs first (see Appendix 1 and Appendix 2 for additional details).

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Venetoclax has been granted approval in the U.S. (Venclexta® U.S. Prescribing Information) and by the European Medicines Agency (Venclyxto® E.U. SmPC) for the treatment of patients with CLL, with or without 17p deletion, who have received at least one prior therapy. Venetoclax has also received accelerated approval in the U.S. in combination with azacitidine, decitabine, or LDAC to treat adults with newly diagnosed AML.

Venetoclax, however, is not approved for the treatment of BC, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with venetoclax in completed and ongoing studies. The anticipated important safety risks for venetoclax are outlined below. Please refer to the most recent version of Venetoclax Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Venetoclax

Clinical experience gained thus far with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the current Venetoclax Investigator's Brochure for more information.

On the basis of clinical data to date, the following known and potential risks with venetoclax are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.3.

5.1.1.1 Tumor Lysis Syndrome

Available data suggest that in patients with cancers other than CLL, with the exception of those with mantle cell lymphoma, the risk of TLS is low. Due to different biology between HER2-positive BC and hematological malignancies, the risk of TLS is considered to be very low in patients with HER2-positive BC. Therefore, TLS prophylaxis is not recommended by any of the international guidelines for patients with HER2-positive BC, even in those patients who have developed visceral crisis and are receiving chemotherapy.

TLS is rarely observed in solid tumors such as breast cancer (Aslam et al. 2019; Cairo et al. 2009). In addition, as the target population in this trial would have received treatment for their HER2+ BC prior to enrollment, these patients would be considered to have low risk of developing TLS. Nevertheless, patients should be advised to remain well hydrated for the first week of study drug administration. Although not mandatory, at the discretion of the investigator, a prophylactic oral agent (e.g., allopurinol 300 mg QD) may be initiated in patients who are deemed to be at risk of TLS in order to reduce the uric acid level. In the dose-escalation phase, TLS laboratory values obtained before the dose of venetoclax will be used to determine whether a patient developed a change related to TLS. Laboratory results from 24 hours post-dose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 7.

Patients with TLS should be treated as per institutional practice and local guidelines, including correction of electrolyte abnormalities and monitoring of renal function and fluid balance. *In general, patients with baseline elevation of uric acid, dehydration, oliguria, renal dysfunction, and/or hypotension are considered to be more prone to TLS. Additionally, patients with bulky disease with extensive metastases to the liver, lungs, or bone marrow may be at an increased risk of developing TLS.* Recommendations for initial management of electrolyte imbalances and prevention of TLS are provided in Appendix 7. In some cases, dialysis may be indicated. Guidelines for defining TLS are provided in Appendix 8.

To evaluate any possible risk of TLS with venetoclax in patients with HER2-positive BC, patients enrolled in the dose-escalation phase of the study will each have a sample

collected for a serum chemistry panel 24 hours after the first dose of study drug. The Sponsor will review the chemistry panel results and establish a management plan for TLS if an increased risk is identified, if needed.

5.1.1.2 Neutropenia

Neutropenia is an important identified risk for venetoclax. Clinical data from oncology studies suggest that neutropenia adverse events are observed among patients who receive venetoclax as a single agent or in combination with other therapeutic agents, with higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in Table 6. Granulocyte colony stimulating factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infection.

5.1.1.3 Serious Infections

Serious infection is an important identified risk for venetoclax. Infections have been reported in oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated patients with hematologic malignancies and are similar across all indications. Infections are closely monitored in venetoclax program across all indications. Patients should be advised to report fever or symptoms suggestive of serious infection and should be assessed for further management as per standard medical practice. In the oncology studies, recommendations are included in the protocol regarding the need for anti-infective prophylaxis per standard of care (e.g., NCCN guidelines for oncology subjects).

5.1.1.4 Other Hematological Effects

Anemia has been reported across oncology studies investigating venetoclax, with a higher frequency in some studies in which venetoclax is combined with other reference therapies; however, most of the events were non-serious and confounded by disease factors and prior therapies.

Thrombocytopenia adverse events have been reported in oncology studies investigating venetoclax, with a higher frequency in those studies in which venetoclax was combined with other chemotherapeutic agents. However, most of the events were non-serious and assessment of these events is confounded by the patients' underlying hematologic malignancy disease state, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several patients.

Lymphopenia has been observed in nonclinical studies and in the Phase I clinical study conducted in heavily pretreated patients with CLL and NHL. While opportunistic infections have been reported in the clinical program, data are confounded by the

patients' underlying disease and prior therapies. Patients in this study who develop lymphopenia are potentially at risk for atypical infections. As such, prophylaxis against varicella zoster virus and *Pneumocystis jiroveci* pneumonia should be considered and implemented (if applicable) as per local institutional practice, although some guidance is provided in Appendix 8.

5.1.1.5 Effects on Reproductive System and Pregnancy

This study is open to enrollment of both male and female patients. The effect of Bcl-2 inhibition on pregnancy has not been fully characterized. In animal studies, venetoclax resulted in increased post-implantation loss, and decreased fetal body weights were observed in the mouse embryo-fetal development study at the highest dosage administered. Venetoclax was not teratogenic. Six human pregnancies have been reported in the clinical program with venetoclax so far, including two pregnancies reported in a partner; in four out of six cases, a live infant with no neonatal complication, congenital anomalies, or birth defects was delivered. One out of six cases ended in therapeutic abortion in a patient with CLL who experienced progressive disease. One out of six cases was reported in a partner of a patient who had not received any study drug and for which the projected due date is pending.

In nonclinical studies, both venetoclax and trastuzumab emtansine have shown a potential to cause reproductive and embryo-fetal developmental toxicities as single agents. Therefore, there is the potential for this combination to cause overlapping or additional reproductive and embryo-fetal toxicities compared with the individual molecules. Consequently, both venetoclax and trastuzumab emtansine should not be administered to pregnant women, and both drugs must be discontinued if a patient becomes pregnant. Additionally, patients are advised to remain abstinent (i.e., refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 28 days after the last dose of study drug. Please refer to Section 4.1.1 for further details on study eligibility and contraceptive requirements for patients.

5.1.1.6 Treatment-Emergent Malignancies (Second Primary Malignancies)

Second primary malignancies are important potential risk for venetoclax. Events of second primary malignancies have been reported across the venetoclax hematologic oncology program. However, no causal association with the venetoclax administration has been confirmed, and no pattern has been observed. The overall observed incidence rate of malignancy in the venetoclax clinical trial programs were comparable to that reported in the general population. Second primary malignancies will be closely monitored in this study.

5.1.1.7 Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to

5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal as described in Section 4.3.2.1.

5.1.1.8 Concomitant Use with Other Medications

Specific recommendations are provided for co-administration of venetoclax with other medications, including inhibitors and inducers of CYP3A (see Section 4.4).

Live, attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live, attenuated vaccines during or following venetoclax therapy have not been studied. Patients should be advised that vaccinations may be less effective.

Due to possible CYP3A mediated metabolic interaction, certain food items (e.g., grapefruit and Seville oranges) should not be consumed during treatment with venetoclax. Further details of excluded food items are provided in Section 4.4.

5.1.2 Risks Associated with Trastuzumab Emtansine

5.1.2.1 Pulmonary Toxicity

Cases of ILD, including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving trastuzumab emtansine. Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at risk of pulmonary events.

Patients who have experienced a pulmonary event should be carefully evaluated before commencing trastuzumab emtansine treatment.

Guidelines for management of trastuzumab emtansine in patients who develop ILD or pneumonitis are provided in Appendix 10.

5.1.2.2 Hepatotoxicity

The following events have been reported with administration of trastuzumab emtansine:

- Serious hepatobiliary disorders

  Serious hepatobiliary disorders, including NRH of the liver and hepatobiliary disorders with a fatal outcome due to drug-induced liver injury, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases may have been confounded by concomitant medications with known hepatotoxic potential.

- Increased serum transaminases

  Asymptomatic increases in serum transaminase concentration (transaminitis) have been observed. Grade 1 and 2 events have been observed frequently; Grade 3 and 4 events have been observed less commonly. The incidence of increased AST was substantially higher than that for increased ALT. Increases

in AST and ALT were commonly observed by Day 8 of each cycle and generally improved or returned to baseline by Day 21. A cumulative effect of trastuzumab emtansine, that is, an increase in the proportion of patients with Grade 1 or 2 elevations in transaminases with successive cycles has been observed; however, there was no increase in the proportion of patients with Grade 3 abnormalities over time.

- NRH

  NRH is a form of noncirrhotic portal hypertension that can be caused by chronic use of medications. NRH typically presents with the insidious or unexpected onset of signs or symptoms of portal hypertension (weakness, ascites, splenomegaly, esophageal varices) in a patient with little evidence of chronic liver disease.

  Cases of NRH have been identified from liver biopsies in patients treated with trastuzumab emtansine who presented with signs and symptoms of portal hypertension. 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. Biopsy-confirmed NRH leading to fatal hepatic failure has been reported (refer to Appendix 13).

  NRH should be considered in all patients with clinical symptoms of portal hypertension, even with normal transaminases, and no other manifestations of cirrhosis; in patients with a cirrhosis-like pattern seen on a CT scan of the liver; and/or in patients with liver failure following long-term treatment with trastuzumab emtansine.

Patients must meet specified hepatic laboratory test requirements to be included in this study (Section 4.1.1).

Hepatic laboratory parameters will be monitored as described in the schedule of assessments (Appendix 1 and Appendix 2).

Guidelines for management of trastuzumab emtansine in patients who develop increased serum transaminases, increased serum bilirubin, or NRH are provided in (Appendix 10).

5.1.2.3 Left Ventricular Dysfunction

Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. To date, significant cardiac events, including LVEF of $<$40%, have been observed (infrequently) in clinical trials of trastuzumab emtansine; therefore, symptomatic CHF is a potential risk.

Patients must meet specified LVEF requirements to be included in this study (Section 4.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO) or MUGA scans as described in Section 4.5 and the schedule of assessments (Appendix 1 and Appendix 2).

Guidelines for patient monitoring and management of trastuzumab emtansine in patients who develop left ventricular dysfunction are provided in (Appendix 10).

5.1.2.4 Infusion-Related Reactions and Hypersensitivity Reactions

Infusion-related reactions (IRRs) and hypersensitivity reactions have been reported with administration of trastuzumab emtansine. Despite the different pathophysiology of IRRs (reactions involving cytokine release) and hypersensitivity (allergic) reactions, the clinical manifestations are the same. In general, IRRs are expected to be more frequent and severe with the first infusion and to decrease in number and severity over time. The severity of true hypersensitivity reactions would be expected to increase with subsequent infusions.

IRRs, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of 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.

Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine. Patients with a history of intolerance to trastuzumab will be excluded from this study (Section 4.1).

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 should be closely monitored for IRRs during and after each infusion of trastuzumab emtansine, as described in Section 4.3.2.1.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in (Appendix 10).

5.1.2.5 Hematologic Toxicity

Thrombocytopenia has been reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (platelet count $\geq$50,000/μL), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (platelet count $\geq$75,000/μL) by the next scheduled dose (i.e., within 3 weeks). In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

Patients with thrombocytopenia ($\leq$100,000/mm^3) and patients on anticoagulant treatment should be monitored closely during treatment with trastuzumab emtansine. It is recommended that platelet counts are monitored prior to each trastuzumab emtansine dose. Trastuzumab emtansine has not been studied in patients with platelet

counts ≤ 100,000/mm^3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (< 50,000/mm^3), do not administer trastuzumab emtansine until platelet counts recover to Grade 1 (≥ 75,000/mm^3).

Declines in other hematopoietic lineages, for example, leukopenia, neutropenia, and anemia, were less frequent than that observed for platelets.

Patients must meet specified hematologic laboratory test requirements to be included in this study (Section 4.1).

Hematologic laboratory parameters will be monitored as described in Section 4.5 and the schedule of assessments (Appendix 1 and Appendix 2). Patients on anticoagulant or antiplatelet treatment should be monitored closely.

Guidelines for management of trastuzumab emtansine in patients who develop hematologic toxicity are provided in (Table 6).

5.1.2.6 Hemorrhage

Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported with trastuzumab emtansine. Some of these bleeding events resulted in fatal outcomes. In some of the observed cases, the patients were also receiving anti-coagulation therapy, antiplatelet therapy, or had thrombocytopenia; in others, there were no known additional risk factors. Caution should be used with these agents, and additional monitoring should be considered when concomitant use with trastuzumab emtansine is medically necessary.

5.1.2.7 Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine.

Patients with Grade ≥3 peripheral neuropathy will be excluded from this study (Section 4.1).

Patients will be clinically monitored on an ongoing basis for signs or symptoms of peripheral neuropathy as described in Section 4.5 and the schedule of assessments (Appendix 1 and Appendix 2).

Guidelines for management of trastuzumab emtansine in patients who develop peripheral neuropathy are provided in (Appendix 10).

5.1.2.8 Extravasation

In trastuzumab emtansine clinical studies, 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. These reactions have been observed more frequently within 24 hours of infusion.

The infusion site will be closely monitored for possible subcutaneous infiltration during drug administration, as described in Table 1). Specific treatment for trastuzumab emtansine extravasation is unknown at this time. Patients should be managed symptomatically per local institutional guidelines.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.
The severity of adverse events will be graded according to the NCI CTCAE v5.0.

- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.

If, in the opinion of the investigator, a toxicity is considered to be attributable solely to one component of the study treatment (i.e., trastuzumab emtansine, venetoclax or placebo, then the dose of that component should be delayed or modified in accordance with the guidelines below. If trastuzumab emtansine is held, then venetoclax/placebo should continue provided the dosing selected in the dose-escalation phase of this study is continuous. In the case of NC dosing of venetoclax/placebo, when trastuzumab emtansine is held, then venetoclax placebo should be held as well and restart concomitantly to preserve treatment synchronization. If trastuzumab emtansine is permanently discontinued for toxicity, then venetoclax/placebo can continue provided that the patient is deriving clinical benefit from venetoclax/placebo, in the opinion of the investigator. Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Venetoclax Dose Modifications

Although patients with adverse events are to be managed according to the particular clinical circumstances based on the investigator’s medical judgement, dose reduction of venetoclax by one and, if needed, two dose levels will be allowed depending on the type and severity of the toxicity encountered (refer to Table 6 and Appendix 9). The dose reduction of venetoclax will occur per Table 4 below. Patients requiring clarification regarding management of adverse events and dosing and all patients who received starting dose of 800 mg requiring more than three dose reductions should be discussed with the Medical Monitor. All dose modifications/adjustments must be clearly documented in the patient's source notes and eCRF. Once a dose has been reduced for a given patient, all subsequent cycles should be administered at the reduced dose level, unless further dose reduction is allowed. Dose re-escalation is not allowed.

Table 4 Dose Modification Scheme for Venetoclax/Placebo

Dose Reduction Schedule	Dose Level (mg)	Dose Level (mg)
Starting dose	800 mg	400 mg
First dose reduction	600 mg	200 mg
Second dose reduction	400 mg	100 mg
Third dose reduction	200 mg	Not Applicable
Requirement for further dose reduction	Discuss with Medical Monitor	Not Applicable

Trastuzumab Emtansine Dose Modifications

The dose of trastuzumab emtansine can be reduced by two dose levels for management of drug-related toxicities (i.e., from 3.6 mg/kg to 3.0 mg/kg and then from 3.0 mg/kg to 2.4 mg/kg). If further dose reduction is indicated after two dose reductions, the patient must discontinue trastuzumab emtansine. No dose re-escalation of trastuzumab emtansine is permitted in the study.

If significant trastuzumab emtansine-related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days after the last dose was 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, an adverse event of alopecia—even if considered related to trastuzumab emtansine—would most likely not be considered significant. Fatigue may or may not be considered either related to trastuzumab emtansine or significant. In general, when the significant 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 is not $>$42 days from the last dose received. In exceptional situations, patients may resume treatment after more than 42 days delay with the approval of the Medical Monitor or his delegate.

Patients should be re-evaluated weekly during the delay, whenever possible. If dosing resumes, the patient may receive trastuzumab emtansine either at the same dose level as before or at one lower dose level, at the discretion of the investigator. Subsequent cycles should remain Q3W, and patients should be assessed for toxicity as described in Section 5.1.3. If a patient requires a dose reduction, dosing will be reduced by one dose level as per Table 5.

Table 5 Dose Modification Scheme for Trastuzumab Emtansine

Dose Reduction Schedule	Dose Level (mg/kg, Q3W)
Starting dose	3.6
First dose reduction	3.0
Second dose reduction	2.4
Requirement for further dose reduction	Discontinue treatment

Q3W = every 3 weeks.

Note: The dose of trastuzumab emtansine, once reduced, may not be re-escalated. A maximum of two dose reductions is allowed; patients with any further requirement for dose reduction will discontinue treatment with trastuzumab emtansine.

No dose re-escalation is permitted. A patient treated with 2.4 mg/kg of trastuzumab emtansine who develops an adverse event requiring a dose reduction must discontinue study treatment and will be followed for safety, disease progression, and survival (Appendix 1 and Appendix 2).

Patients who experience a Grade 3 or 4 hematologic events, other than thrombocytopenia, 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 trastuzumab emtansine. Patients who discontinue trastuzumab emtansine can continue venetoclax/placebo provided that, in the opinion of the investigator, the patient is deriving clinical benefit from venetoclax/placebo. Patients who discontinue both study drugs will be followed for safety, disease progression, and survival (Appendix 1 and Appendix 2).

5.1.3.2 Treatment Interruption

Patients who interrupt venetoclax secondary to treatment-related adverse events for longer than 28 days from the last dose should discontinue venetoclax. However, patients who are deriving benefit from the treatment should continue trastuzumab emtansine treatment.

If significant trastuzumab emtansine–related toxicities have not recovered to Grade 1 or baseline, the next scheduled dose may be delayed for >42 days after the last dose was received. Patients who discontinue trastuzumab emtansine can continue venetoclax/placebo provided that, in the opinion of the investigator, the patient is deriving clinical benefit from venetoclax/placebo and they are to continue evaluation per protocol.

5.1.3.3 Management Guidelines

Guidelines for management of adverse events associated with study treatment are provided in Appendix 9 (venetoclax) and in Appendix 10 (trastuzumab emtansine).

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 9, Appendix 10, and Table 6 below and prescribing information, as outlined below:

Table 6 below provides guidelines for the management of patients who experience the following potential overlapping toxicities for venetoclax and trastuzumab emtansine: hematologic, gastrointestinal, and hepatic events. It is recommended that study treatments be withheld or discontinued per the guidelines below. For these potential overlapping toxicities, refer to guidelines in Table 6.

Appendix 9 provides guidelines for the management of patients who experience venetoclax-specific non-hematologic toxicity that is not specifically described in Table 6. It is recommended that venetoclax be withheld or discontinued per the guidelines in Appendix 9.

Appendix 10 provides guidelines for the management of patients who experience trastuzumab emtansine-associated adverse events such as left ventricular dysfunction, pulmonary toxicity, infusion-related reactions, hypersensitivity, and NRH reactions. It is recommended that trastuzumab emtansine be withheld or discontinued per the guidelines in Appendix 10.

For cases in which management guidelines are not covered in Table 6, Appendix 9, and Appendix 10, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Venetoclax and Trastuzumab Emtansine

NCT CTCAE Category	Dose delay or dose modification

Grade ≥3 febrile neutropenia	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	• Administer treatment including G-CSF or growth factors for neutropenia as indicated and per institutional guidelines.
	  ○ When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo and trastuzumab emtansine.
	• For subsequent episodes of Grade ≥3 febrile neutropenia:
	  ○ Withhold venetoclax/placebo and trastuzumab emtansine.
	  When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo at one dose level reduction (refer to Table 4) and trastuzumab emtansine at previous dose.

Grades 3 and 4 neutropenia	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo and trastuzumab emtansine.
	• For subsequent episodes of Grade 4 neutropenia:
	  ○ Withhold venetoclax/placebo and trastuzumab emtansine.
	  ○ Consider secondary prophylaxis with G-CSF as indicated or per institutional guidelines.
	  When counts recover to ANC $\geq 1 \times 10^9$/L (Grade ≤2), resume venetoclax/placebo at one dose level reduction (refer to Table 4) and trastuzumab emtansine at previous dose.

Grade 3 thrombocytopenia (25,000 to < 50,000/mm^3)	• Withhold venetoclax/placebo. • Withhold trastuzumab emtansine. ○ When platelet count recovers to ≤ Grade 1 (≥ 75,000/mm^3), resume venetoclax/placebo and trastuzumab emtansine at the previous dose level.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Venetoclax and Trastuzumab Emtansine (cont.)

NCT CTCAE Category	Dose delay or dose modification

Grade 3 thrombocytopenia (platelets 50,000 to 25,000/μL) with clinically significant bleeding; or
 	
Grade 4 thrombocytopenia (platelets < 25,000/μL)
	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ Platelets may be transfused if Grade 4 thrombocytopenia is associated with symptomatic bleeding or in the case of platelet count < 10,000/μL, or per institutional guidelines.
	  ○ When platelet level rises to > 75,000/μL, resume venetoclax/placebo at previous dose. The dose of trastuzumab emtansine should be reduced by one dose level (refer to Table 5).
	• For a subsequent episode of Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia:
	  ○ Withhold both venetoclax/placebo and trastuzumab emtansine.
	  ○ Platelets may be transfused if Grade 4 thrombocytopenia is associated with symptomatic bleeding or in the case of platelet count < 10,000/μL, or per institutional guidelines
	  ○ When platelet level rises to > 75, 000/μL, resume venetoclax/placebo at one dose level reduction (refer to Table 4). The dose of trastuzumab emtansine should be reduced by one dose level (refer to Table 5).
	• For recurrent Grade 4 thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, consult the Medical Monitor regarding continuation on study treatment.

Non-hematologic toxicity	

Grade 1–2 Diarrhea	• Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, antacids), infection by *C. difficile*, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber.
	• Dietary modifications:
	  ○ Stop all lactose-containing products and eat small meals.
	  ○ The BRAT (banana, rice, apples, toast) diet may be helpful.
	  ○ Encourage adequate hydration.
	• Loperamide treatment:
	  ○ Suggested dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool, up to a maximum of 16 mg/day.
	  ○ Recommend to continue loperamide treatment until diarrhea-free for 24 hours.
	  ○ If Grade ≤ 2 diarrhea persists after 48 hours total treatment with loperamide, consider second-line agents (diphenoxylate and atropine or tincture of opium).
	No change in study drug dosing will be implemented for Grade ≤2 diarrhea; patients should receive maximal supportive care as described above.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Venetoclax and Trastuzumab Emtansine (cont.)

NCT CTCAE Category	Dose delay or dose modification

Grade ≥ 3 Diarrhea	• Withhold venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ When diarrhea has improved to Grade ≤ 1, restart venetoclax/placebo and trastuzumab emtansine at the previous dose level.
	• If Grade ≥ 3 diarrhea recurs:
	  ○ Withhold venetoclax/placebo.
	  ○ Withhold trastuzumab emtansine.
	  When diarrhea has improved to Grade ≤ 1, resume venetoclax/placebo at one dose level reduction (refer to Table 4). Resume trastuzumab emtansine at the previous dose level.

Grade ≥ 3 increased transaminase (AST/ALT) (> 5 to ≤ 20× ULN)	• Withhold venetoclax/placebo. • Withhold trastuzumab emtansine. ○ When AST/ALT recovers to Grade ≤2, resume trastuzumab emtansine reduced by one dose level (refer to Table 5). Resume venetoclax/placebo at previous dose.
Grade 4 increased transaminase (AST/ALT) (> 20× ULN)	• Discontinue both trastuzumab emtansine and venetoclax/placebo. ○ Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.
TBILI increase > 1.5 × ULN to ≤ 3 × ULN (Grade 2)	• Withhold both venetoclax/placebo. • Withhold trastuzumab emtansine. When TBILI recovers to ≤ 1.5 × ULN, resume venetoclax/placebo and trastuzumab emtansine at the previous dose level.

TBILI increase > 3 × ULN to ≤ 10 × ULN (Grade 3)	• Withhold both venetoclax/placebo.
	• Withhold trastuzumab emtansine.
	  ○ When TBILI recovers to ≤ 1.5 × ULN, resume venetoclax at the previous dose level and trastuzumab emtansine with one dose level reduction (refer Table 5).
	  ○ Discontinue trastuzumab emtansine if the event has not resolved to ≤ 1.5 × ULN within 42 days after the last dose received.

TBILI increase > 10 × ULN (Grade 4)	• Discontinue venetoclax/placebo and trastuzumab emtansine.

TBILI = total bilirubin; ULN = upper limit of normal.

Recommendations for the initial management of electrolyte imbalances and prevention of TLS are provided in Appendix 7. Additional guidelines are provided in the subsections below.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.10 and Section 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- TLS
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with symptomatic bleeding
- Grade ≥3 diarrhea
- Pneumonitis

- Grade ≥3 infusion-related reaction or hypersensitivity reaction
- Grade 4 febrile neutropenia

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of the 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 adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.2.3 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug or initiation of another anticancer therapy (whichever occurs first).

Serious adverse events and adverse events of special interest will continue to be reported (independent of causality) until 90 days after the last dose of study drug or until initiation of new systemic anticancer therapy, whichever occurs first.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that occur after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug), if the event is believed to be related to prior treatment with study drug, regardless if the patient has initiated another anticancer therapy treatment (Section 5.2.3).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of HER2-positive MBC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An IMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Metastatic Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on both clinical and laboratory findings (physical exam, biopsy, breast imaging, radiologic evidence, etc.). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying MBC

An event that leads to hospitalization under the following circumstances is not considered to be serious adverse event, but should be reported as adverse events instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

- Hospitalization for a minor condition for which the patient suffers an adverse event, but does not meet the definition of an overnight admission (e.g., tooth extraction)

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose}
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For trastuzumab emtansine, venetoclax or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with trastuzumab emtansine, venetoclax or matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], M.D., Ph.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), 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, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug after the final dose of study drug or until initiation of another anticancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 30 days after the final dose of venetoclax or 7 months after the last dose of trastuzumab emtansine, whichever

occurs last. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In 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 trastuzumab emtansine. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. 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.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Trastuzumab emtansine	Trastuzumab Emtansine Investigator's Brochure
Venetoclax	Venetoclax Investigator's Brochure

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

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

An IMC will monitor efficacy and safety data 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 analysis populations are defined as follows:

- The ITT population for the Phase II portion of the study is defined as all randomized patients, whether or not they were assigned to the arm where the study drug was administered.
- The ITT population for the non-randomized cohorts is defined as all enrolled patients who received any drug.
- The Bcl-2 high population consists of patients within the ITT population with $\geq$ 50% of tumor cells stained with an intensity of IHC 2+ or 3+.
- The safety-evaluable population is defined as patients who received any amount of any component of the investigational or non-investigational study treatments.

The ITT population is the primary analysis population for efficacy for the study, and efficacy analyses will be analyzed according to the intended treatment. Efficacy analyses will also be performed in the Bcl-2 high population. Safety analyses will be performed in the safety population according to treatment received.

Analyses will be performed separately for the dose-escalation phase, expansion phase, and randomized Phase II stage of the study.

The primary efficacy analysis will be performed in the ITT population of the randomized Phase II stage, which will be based on the co-primary endpoints of ORR and PFS. A key secondary efficacy analysis will be efficacy analyses in the Bcl-2 high population of the randomized Phase II stage. Descriptive efficacy analyses will also be performed on the non-randomized cohorts.

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Dose-Escalation Phase

The sample size for the dose-escalation phase is based on the dose-escalation rules described in the protocol. The planned enrollment for the dose-escalation phase is approximately 6–24 patients enrolled across 2–4 dose-escalation treatment groups.

6.1.2 Expansion Phase

Approximately 20 patients each may be enrolled in the expansion phase (trastuzumab emtansine-experienced cohort and trastuzumab deruxtecan-experienced cohort).

With 20 patients per cohort and an observed ORR of 60%, the exact 90% Clopper-Pearson confidence interval for the ORR would be 39%–78%, which would rule out an ORR of 35% or less.

Table 8 provides exact 90% confidence intervals for a range of observed proportions of ORR based on a sample size of 20 patients.

Table 8 Potential 90% Confidence Interval Estimated for the True ORR

Observed ORR	Exact 90% Confidence Interval for the True ORR
40%	(22%, 61%)
50%	(30%, 70%)
55%	(35%, 74%)
60%	(39%, 78%)
65%	(44%, 82%)
70%	(49%, 86%)

ORR = objective response rate.

For a given adverse event with a true rate of 10%, 5%, or 1%, the probability of observing at least one such event in a cohort of 20 patients is 87.8%, 64.2%, and 18.2%, respectively. Table 9 describes exact 90% confidence intervals for a range of observed proportions of adverse events based on a sample size of 20 patients.

Table 9 Potential 90% Confidence Interval Estimates for Adverse Event Rates

Observed Event Rate	Exact 90% Confidence Interval for the True ORR
1%	(0%, 16%)
5%	(0%, 22%)
10%	(2%, 28%)
20%	(7%, 40%)
30%	(14%, 51%)

ORR = objective response rate.

6.1.3 Randomized Phase II Stage

After the RP2D has been determined for venetoclax when given in combination with a fixed dose of trastuzumab emtansine, a total of 220 patients will be enrolled in the randomized Phase II stage of the study. The purpose of the randomized Phase II stage is estimation and hypothesis generation regarding the effect of venetoclax in combination with trastuzumab emtansine on ORR and duration of PFS relative to trastuzumab emtansine plus placebo. The point and interval estimates of the true underlying HR will be obtained.

For the co-primary endpoints of ORR and PFS in the primary efficacy analysis population, the trial will have:

- 85% power ($\alpha = 0.05$) to detect a 20% improvement in ORR (i.e., ORR Δ) (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm). In the meantime, a 20% improvement in ORR will have a 95% CI of (7%, 33%).
- 90% power ($\alpha = 0.05$) to detect a PFS HR of 0.6 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 161 total PFS events have occurred. In the meantime, a PFS HR of 0.6 will have a 95% CI of (0.44, 0.82). The assumptions of the sample size calculation are that the median PFS in the control arm is 6.8 months and that enrollment would occur non-uniformly over 24 months. Enrollment is anticipated to be lower during the second half of the enrolment period because it will be restricted to the Bcl-2 high population.

Within the Bcl-2 high population the study will have:

- 85% power ($\alpha = 0.05$) to detect a PFS HR of 0.5 venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm, when approximately 75 total PFS events have occurred. In the meantime, a PFS HR of 0.5 will have a 95% CI of (0.32, 0.79).

The study will not, however, have adequate power to detect all potentially clinically meaningful differences in ORR and PFS. For example, within the entire ITT population:

- With 110 patients in each arm, there is only 60% power ($\alpha = 0.05$) to detect a 15% improvement in ORR (assuming a 44% ORR in the trastuzumab emtansine plus placebo arm), and
- With approximately 161 total PFS events, only 62% power ($\alpha = 0.05$) to detect an HR of 0.70, in venetoclax plus trastuzumab emtansine arm relative to the trastuzumab emtansine plus placebo arm.

Thus, a statistically negative outcome in any of the co-primary endpoints does not necessarily rule out a clinically meaningful outcome. The below tables show the power and CIs for several possible true underlying improvements in ORR and PFS in favor of the venetoclax plus trastuzumab emtansine arm.

Due to the smaller sample size of the Bcl-2 high population the power to detect a HR of 0.60 in the Bcl-2 population is 60% compared to 90% for the entire ITT population. The study has adequate power (85%) to detect a HR of 0.5 in the Bcl-2 high population.

Table 10 Operating Characteristics for Proposed Study Design for Possible True Underlying ORR Δ Values

	True Underlying ORR $\underline{\Delta}$		
	15%	20%	25%
Power to detect ORR Δ [a]	60%	85%	96%
95% confidence interval for true ORR Δ [b]	(2%, 28%)	(7%, 33%)	(12%, 38%)

ORR = objective response rate.

Note: trastuzumab emtansine plus placebo arm is assumed to have an ORR of 44%. Results are based on 110 patients in each arm.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the ORR $\underline{\Delta}$ in each column.

Table 11 Operating Characteristics for Proposed Study Design for Possible True Underlying PFS Hazard Ratio Values

	True Underlying Hazard Ratio			
	0.60	0.65	0.70	0.75
Power of log-rank test [a]	90%	78%	62%	44%
95% confidence interval for true hazard ratio [b]	(0.44, 0.82)	(0.48, 0.89)	(0.51, 0.95)	(0.55, 1.00)

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, median PFS in the trastuzumab emtansine plus placebo arm is 6.8 months, 161 total PFS events.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

Table 12 Operating Characteristics in the Bcl-2 High Group for Proposed Study Design for Possible True Underlying PFS Hazard Ratio Values

	True Underlying Hazard Ratio			
	0.50	0.55	0.60	0.65
Power of log-rank test [a]	85%	73%	60%	46%
95% confidence interval for true hazard ratio [b]	(0.32, 0.79)	(0.35, 0.86)	(0.38, 0.94)	(0.41, 1.00)

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, median PFS in the trastuzumab emtansine plus placebo arm is 6.8 months, 75 total PFS events.

[a] Two-sided $\alpha = 0.05$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized by treatment arm and for all randomized patients within each phase of the study. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, lines of prior therapy, rapid disease progression to first-line therapy, Bcl-2 status, ER status, site of disease, and presence of visceral/liver metastases) will be summarized using means,

standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES (RANDOMIZED PHASE II STAGE ONLY)

The primary efficacy analysis population will consist of all randomized patients, with patients grouped according to their assigned treatment (the ITT population).

The primary efficacy analysis will occur when 161 patients have experienced a PFS event. It is anticipated that this will occur six months after the last patient enters treatment.

6.4.1 Co-Primary Efficacy Endpoints

6.4.1.1 Objective Response Rate

The co-primary endpoint ORR is defined as the proportion of patients with CR or PR as assessed by the investigator on two consecutive assessments at least 28 days apart using the criteria in RECIST v1.1. Patients with no disease assessments for any reason will be classified as non-responders. An estimate of ORR with 95% CI will be calculated for each treatment arm using the normal approximation to the binomial distribution. An estimate and 95% CI for the difference in ORR between the two treatment groups will be presented based on the normal approximation to the binomial distribution.

6.4.1.2 Progression-Free Survival

The co-primary efficacy endpoint PFS is defined as the time from randomization to the first occurrence of disease progression (as defined by the investigator according to RECIST v1.1) or death from any cause, whichever comes first. Data for patients without the occurrence of disease progression or death as of the clinical data cut-off date will be censored at the time of last tumor assessment (or the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. Kaplan-Meier curves of time to PFS for each treatment group will be provided. The Cox proportional hazards model stratified by the randomization stratification factors (Bcl-2 status [high, low], visceral disease [yes, no], and HER2 status IHC 3+ [yes, no] will be used to provide an estimate of the hazard ratio of venetoclax plus trastuzumab emtansine to placebo plus trastuzumab emtansine with associated 95% CI and p-value. The unstratified hazard ratio estimate and 95% CI will also be presented.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Duration of Objective Response

DOR is defined as the time from the first documented objective response (CR or PR) to the time of first documented disease progression (as determined by the investigator using RECIST v1.1) or death from any cause, whichever occurs first. Data for patients

without the occurrence of disease progression or death as of the clinical data cut-off will be censored at the time of the last tumor assessment.

DOR will be estimated using the Kaplan-Meier methodology. Only patients achieving a CR or PR will be included in the assessment of DOR. No formal hypothesis testing will be performed due to the non-randomized population.

6.4.2.2 Overall Survival

OS is defined as time from randomization to death from any cause. Data for patients who are alive at the time of the analysis data cut-off will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day.

OS will be analyzed using the same methodology as PFS (see Section 6.4.1).

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Clinical Benefit Rate

CBR is defined as CR or PR (as defined in Section 6.4.1) or achieving SD lasting ≥6 months from randomization as assessed by the investigator using RECIST v1.1. Patients with no disease assessments for any reason will be classified as non-responders.

CBR will be analyzed using the same methodology as ORR (see Section 6.4.1).

6.4.3.2 Patient-Reported Outcomes Data

Summary statistics and the mean change from baseline of linear-transformed scores will be reported for all of the items and subscales of the EORTC QLQ-C30 and EORTC IL46 (an item for trouble with side effects) questionnaires at each timepoint, at the end of treatment, at the time of progression, and at the time of clinical progression (if different from time to progression). In addition, mean scores for global health status, physical functioning, and selected symptom scales will be presented. The scores will be derived according to the EORTC scoring manual guidelines.

Completion and compliance rates will be summarized at each timepoint by treatment arm. The analysis populations for PRO changes will be all randomized patients with a non-missing baseline assessment and at least one non-missing post-baseline assessment.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

Safety will be assessed separately for each study phase through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Individual pharmacokinetic concentration data will be tabulated and summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, and maximum) after appropriate grouping. Pharmacokinetic parameters may also be calculated as data allow (e.g., C_{max}, AUC, clearance, volume of distribution, half-life, etc.) and tabulated and/or summarized after appropriate grouping. Population PK analyses of concentration data (with or without the PK data from other studies) may be conducted as appropriate. Potential PK DDIs may be assessed by comparison with relevant historical data for venetoclax and/or trastuzumab emtansine. Potential correlations between exposure and response (e.g., PD, efficacy, ECG, and safety endpoints) may also be explored, if warranted.

The results of population PK analyses and exploratory exposure-response analyses may be reported separately from the clinical study report. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of venetoclax and/or trastuzumab emtansine.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients for trastuzumab emtansine at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if: 1) they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response) or 2) they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies to better understand disease pathobiology and guide the development of new therapeutic approaches. Exploratory biomarker analyses may be performed in an effort to understand the association of these biomarkers with study treatment response. Results will be presented in a separate report.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses (Randomized Phase II Stage Only)

Periodic analyses of cumulative safety data and one interim analysis is planned for this study. Given the hypothesis-generating nature of this study, the Sponsor considers the interim efficacy analysis as exploratory.

The planned interim efficacy analysis of cumulative safety, ORR, and PFS will occur when approximately 56 PFS events have occurred. This is expected to occur after the enrollment of the first 110 patients who have been followed up for at least 6 months.

If the interim analysis coincides within approximately 1 month of a planned safety review, the safety review may be combined with the efficacy interim analyses. Outcomes from these reviews that may affect study conduct will be communicated in a timely manner to the investigators, and IRBs/ECs will be notified.

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 through use of eCRFs. 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 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.

PRO data (EORTC QLQ-C30 and IL46) will be captured via paper questionnaires, with data entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes,

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or 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 applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

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 (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

In the U.S., this trial will be sponsored and managed by Genentech. F. Hoffmann-La Roche Ltd will sponsor this trial outside of the U.S. with management responsibilities being shared by Genentech and Roche. Genentech and Roche have authorized Roche

Registrations, a company formed under the laws of England, to act as their legally authorized representative for the purposes of Article 19 of Directive 2001/20/EC relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use. Reference to “Sponsor” in this protocol will mean Genentech for the United States and F. Hoffmann−La Roche Ltd for all countries outside of the United States.

Approximately 145 sites globally will participate in this study to enroll approximately 284 patients. Data will be recorded via an EDC system from Medidata Solutions (New York, NY, with use of eCRFs; see Section 7.2). Central laboratories will be used for the analyses of and/or management of PK, PD, genotyping, and tissue samples. An IxRS will be used for patient registration, patient number, and dose assignment.

An IMC will review data on a regular basis at predefined timepoints during the study. The IMC will review results from the analyses of unblinded safety data and make recommendations to the Sponsor regarding continuation and/or modification of the study. The final decision on the IMC recommendation will be made by the Sponsor. The details of the composition, roles, and responsibilities of the IMC will be documented in detail in the IMC charter and submitted to Health Authorities as applicable.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.7 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 Activities: Dose Escalation

Assessment or Procedure	Screening Period	Treatment Period (Cycle 1)				Treatment Period (Cycle 2 through Study Treatment Discontinuation) [a]	Study Treatment Completion/Early Discontinuation [b]	3 Month Follow-Up (±14 Days) [c]
	Days −28 to −1	Day 1	Day 2	Day 8	Day 15	Day 1 *(and Day 8 for NC Ven PK only)* (± 3 Days)	≤30 Days after Last Dose of Study Treatment	
Informed consent [d]	x							
Demographics [e]	x							
General medical history [f]	x							
Central HER2 and Bcl-2 testing [g]	x							
Complete physical examination [h]	x							
Limited symptom-directed physical examination [i]		x	x	x	x	x	x	
ECOG performance status	x	x				x	x	
Weight and BSA [j]	x					x		
Vital signs [k]	x	x	x	x	x	x		
Hematology [l]	7 days prior to C1D1	x		x	x	x	x	
Serum chemistry [m]	7 days prior to C1D1	x	x	x	x	x	x	
TLS laboratory assessments [n]	within 3 days of C1D1 or prior to C1D1 dose	x	x					
Thyroid function test (TSH/free T3/free T4)	x	x				Every 4th cycle *(e.g. C4, C8, C12, C16, etc)*	x	
C-reactive protein	x							
INR or aPTT	x	x				As clinically indicated		
HIV, HCV, and HBV serology [o]	x	x						
Urinalysis [p]	x					As clinically indicated		
Pregnancy test [q]	x					x	x	x
Tumor response assessment [r]	x	x				x		

Appendix 1: Schedule of Activities: Dose Escalation (cont.)

Assessment or Procedure	Screening Period	Treatment Period (Cycle 1)				Treatment Period (Cycle 2 through Study Treatment Discontinuation) [a]	Study Treatment Completion/Early Discontinuation [b]	3 Month Follow-Up (±14 Days) [c]
	Days −28 to −1	Day 1	Day 2	Day 8	Day 15	Day 1 *(and Day 8 for NC Ven PK only)* (± 3 Days)	≤30 Days after Last Dose of Study Treatment	
Bone scan [s]	x	Perform as clinically indicated or as scheduled tumor assessment if only bone involvement at baseline						
CT or MRI of brain [t]	Mandatory at screening	Perform as clinically indicated or as scheduled tumor assessment [r]						
12-Lead electrocardiogram [u]	x	Perform as clinically indicated						
NYHA classification	x							
ECHO or MUGA scan [v]	x	Every Fourth Cycle Additional LVEF measurements may be performed at the discretion of the investigator if LVEF declines are clinically suspected.					If not performed within 6 weeks of this visit	
Venetoclax administration		x [w]						
Trastuzumab emtansine administration		x [x] (on Day 1 of each cycle)						
Serum and plasma samples for PK analysis *(See Appendix 3: Table 1 for Continuous Venetoclax Daily Dosing and Table 2 for Noncontinuous Venetoclax Dosing)*		x *(see Appendix 3)*		x *(see Appendix 3)*		*x* (see Appendix 3)		
Blood sample for biomarker analysis		x				C2D1, C3D1, every odd cycle D1 (see Appendix 4)	x	
Blood sample for auto-antibodies [y]	x							
Tissue sample for biomarker analysis [z]	x	x				x (see Appendix 4)	x	
Concomitant medications	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities: Dose Escalation (cont.)

Assessment or Procedure	Screening Period	Treatment Period (Cycle 1)				Treatment Period (Cycle 2 through Study Treatment Discontinuation) [a]	Study Treatment Completion/Early Discontinuation [b]	3 Month Follow-Up (±14 Days) [c]
	Days −28 to −1	Day 1	Day 2	Day 8	Day 15	Day 1 *(and Day 8 for NC Ven PK only)* (± 3 Days)	≤30 Days after Last Dose of Study Treatment	
Survival follow-up								x [b]
Initiation of anticancer treatments								x [b]

ADA = anti-drug antibody; Bcl-2 = B-cell lymphoma 2; BSA = body surface area; C = cycle; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NC = non-continuous; NYHA = New York Heart Association; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Notes: With the exception of Day 1 of Cycle 1, all assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used; such tests do not need to be repeated for screening.

[a] Visit dates for Cycle 2 and subsequent cycles must be calculated utilizing the previous visit date ±3 days.

[b] The treatment completion/discontinuation visit will optimally be scheduled for ≤30 days after last dose of study treatment.

[c] Patients will be followed for survival, serious adverse events, and adverse events of special interest considered as related to study drug (Section 5.4.2). Subsequent anticancer therapies (not all concomitant medications) need to be reported approximately every 3 months starting from the study drug completion visit until death, loss to follow-up, withdrawal of consent, or study discontinuation by the Sponsor. Survival follow-up information will be collected every 6 months via telephone calls, patient medical records, and/or clinic visits. Study staff may use a public information source (e.g., county records) to obtain information about survival status only where permitted.

[d] Written informed consent must be obtained before any study-specific screening assessments are performed.

[e] Demographics include age, sex, and self-reported race/ethnicity.

[f] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements, and foods that have been shown to inhibit CYP3A4 [Section 4.4.2]) used by the patient within 28 days prior initiation of study treatment. Breast cancer history includes prior cancer therapies and procedures.

[g] Refer to Appendix 4 for tissue requirements related to eligibility. HER2 and Bcl-2 status may be determined outside of the screening window of 28 days.

[h] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[j] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline and/or previous cycle.

[k] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Hematology includes CBC, with RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Hematologic evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[m] Serum chemistry includes glucose, BUN or urea, sodium, magnesium, chloride, bicarbonate, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[n] TLS laboratory assessments collected during dose escalation include serum creatinine, uric acid, potassium, calcium, phosphorous and LDH. If the screening assessments were done within 3 days prior to Cycle 1, Day 1, there is no need to repeat the TLS panel at Cycle 1, Day 1. Refer to Appendix 8 for further instructions.

[o] All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV serology includes HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA. HBV DNA must be collected on or before Cycle 1, Day 1, in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc. HCV serology includes HCV antibody and (if HCV antibody test is positive) HCV RNA.

[p] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

[q] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. During the treatment period, a urine pregnancy test in women of childbearing potential in all treatment arms must be performed within 3 days prior study drug administration of every 3rd cycle of protocol-mandated therapy. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For patients who discontinue therapy before end of planned therapy, a pregnancy test must be done at the completion/early termination visit (within 28 days after the last dose of HER2-targeted therapy), at 3 months, and additionally at 6 months after the discontinuation of study treatment.

[r] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. See Section 4.5.5 for details on imaging and tumor assessments. Tumor response will be evaluated using RECIST v1.1 (Appendix 11) *every 6 weeks (± 7 days)*. In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first. Results must be reviewed by the investigator before dosing at the next cycle. All tumor assessments should be documented in the eCRF before and after the primary PFS analysis. *Patients who discontinue from study treatments for reasons other than disease progression and have not started follow-on treatment(s) will be followed for disease status every 8 weeks (±5 days) from the date of randomization until Week 24 (±5 days) and then every 12 weeks (±5 days), thereafter, until disease progression, loss to follow-up, withdrawal of consent, death or study termination by the Sponsor (whichever occurs first).*

[s] A bone scan is to be performed within 28 days prior to Cycle 1, Day 1 (see Section 4.5.5 for further instructions).

[t] CT/MRI scan of the brain is mandatory at screening and should be performed 1) with scheduled tumor assessments when identified as a site of involvement at baseline, 2) as clinically indicated, or 3) if a patient demonstrates control of systemic disease but has a newly developed isolated brain metastases and is eligible to remain on study treatment, a brain MRI or CT will be performed along with regularly scheduled tumor assessments.

[u] A 12-lead ECG is required at screening. Subsequent ECGs may be performed as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[v] LVEF assessment by ECHO is preferred, but LVEF may also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

[w] Venetoclax will be administered on a once daily dosing schedule.

[x] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Cycle 1 Day 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[y] Auto-antibody testing includes anti-nuclear antibody, anti-double-stranded DNA, and circulating and perinuclear anti-neutrophil cytoplasmic antibody. The baseline sample will be obtained *any time during screening and prior to* treatment *(*Cycle 1, Day 1*)*, before the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally.

[z] At screening, the FFPE archival tumor block from the most recently collected, available tumor tissue or fresh core biopsy (3 cores) is mandated. If more than one FFPE block exists from different timepoints (e.g., initial diagnosis vs. metastatic disease tissue), the most recent block is mandatory to be sent. If the FFPE block from the earlier timepoint is available, then this would be requested to also be sent. In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided. At least 20 freshly serial cut, unstained slides will be acceptable in lieu of the FFPE block. Optional core biopsies will be obtained at Cycle 1, Day 1 and on Day 1 of any subsequent on treatment cycle (± 3 days) if patient consented. At the study drug discontinuation/early study completion visit, if reason for discontinuation is disease progression, a biopsy must be taken (if deemed clinically feasible) before next line of therapy begins, unless purely anti-hormonal therapy.

Appendix 2
Schedule of Activities: Expansion Cohorts/Randomized Phase II

Assessment or Procedure	Screening Period Days –28 to –1	Treatment Period (Cycle 1) Day 1 *(and Day 8 for NC Ven PK only)*	Treatment Period (Cycles 2 through Study Treatment Discontinuation) [a] Day 1 *(and Day 8 for NC Ven PK only)* (± 3 Days)	Study Treatment Completion/Early Discontinuation ≤ 30 Days after Last Dose of Study Treatment [b]	3 Month Follow-Up (±14 Days) [c]
Informed consent [e]	x				
Demographics [e]	x				
General Medical history [f]	x				
Central HER2 and Bcl-2 testing [g]	x				
Complete physical examination [h]	x				
Limited symptom-directed physical examination [i]		x	x	x	
ECOG performance status	x	x	x	x	
Weight and BSA [j]	x		x		
Vital signs [k]	x	x	x		
Hematology [l]	7 days prior to C1D1	x	x	x	
Serum chemistry [m]	7 days prior to C1D1	x	x	x	
TLS laboratory assessments [n]	within 3 days of C1D1 or prior to C1D1 dose	x			
Thyroid function test (TSH/free T3/free T4)	x	x	Every 4th cycle	x	
C-reactive protein	x				
INR or aPTT	x	x	As clinically indicated		
HIV, HCV, and HBV serology [o]	x	x			
Urinalysis [p]	x		As clinically indicated		

Appendix 2: Schedule of Activities: Expansion Cohorts/Randomized Phase II (cont.)

Assessment or Procedure	Screening Period Days –28 to –1	Treatment Period (Cycle 1) Day 1 *(and Day 8 for NC Ven PK only)*	Treatment Period (Cycles 2 through Study Treatment Discontinuation) [a] Day 1 *(and Day 8 for NC Ven PK only)* (± 3 Days)	Study Treatment Completion/Early Discontinuation ≤ 30 Days after Last Dose of Study Treatment [b]	3 Month Follow-Up (±14 Days) [c]
Pregnancy test [q]	x		x	x	x
Tumor and response assessment [r]	x	x	x		
Bone scan[t]	*x*	*Perform as clinically indicated or as scheduled tumor assessment if only bone involvement at baseline*			
CT or MRI of brain [s]	Mandatory at screening	Perform as clinically indicated or as scheduled tumor assessment [t]			
12-Lead electrocardiogram [u]	x	Perform as clinically indicated			
NYHA classification	x				
ECHO or MUGA scan [v]	x	x[w]		If not performed within 6 weeks of this visit	
Venetoclax/placebo administration		x [x]			
Trastuzumab emtansine administration		x [y] (on Day 1 of each cycle)			
Serum and plasma samples for PK/ADA analysis *(See Appendix 3: Table 1 for Continuous Venetoclax Daily Dosing and Table 2 for Noncontinuous Venetoclax Dosing)*		*x (see Appendix 3)*	*x (see Appendix 3)*	*x (see Appendix 3)*	
Blood sample for biomarker analysis		x	C2D1, C3D1, Every Odd Cycle D1 (See Appendix 4)	x	
Blood sample for auto-antibodies [z]	x				
Tissue sample for biomarker analysis [aa]	x	x	x (See Appendix 4)	x	
Concomitant medications	x	x	x	x	

Appendix 2: Schedule of Activities: Expansion Cohorts/Randomized Phase II (cont.)

Assessment or Procedure	Screening Period Days –28 to –1	Treatment Period (Cycle 1) Day 1 *(and Day 8 for NC Ven PK only)*	Treatment Period (Cycles 2 through Study Treatment Discontinuation) [a] Day 1 *(and Day 8 for NC Ven PK only)* (± 3 Days)	Study Treatment Completion/Early Discontinuation ≤30 Days after Last Dose of Study Treatment [b]	3 Month Follow-Up (±14 Days) [c]
Adverse events	x	x	x	x	x
Patient Reported Outcome Questionaires [bb]		*x*	*x*	*x*	
Survival follow-up					x [b]
Initiation of anticancer treatments					x [b]

ADA = anti-drug antibody; Bcl-2 = B-cell lymphoma 2; BSA = body surface area; C = cycle; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FFPE = formalin-fixed, paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NC = non-continuous; NYHA = New York Heart Association; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Notes: With the exception of Day 1 of Cycle 1, all assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. If the timing of a protocol-mandated procedure coincides with a holiday or weekend, it should be performed on the nearest following date. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to enrollment may be used; such tests do not need to be repeated for screening.

[a] Visit Dates for Cycle 2 and subsequent cycles must be calculated utilizing the previous visit date ±3 days.

[b] The treatment completion/discontinuation visit will optimally be scheduled for ≤30 days after last dose of study treatment*, with the exception of ADA sampling, which will optimally be scheduled for 120 days (±28 days) after treatment completion or discontinuation*.

[c] Patients will be followed for survival, serious adverse events, and adverse events of special interest considered as related to study drug (Section 5.4.2). Subsequent anticancer therapies (not all concomitant medications) need to be reported approximately every 3 months starting from the study drug completion visit until death, loss to follow-up, withdrawal of consent, or study discontinuation by the Sponsor. Survival follow-up information will be collected every 6 months via telephone calls, patient medical records, and/or clinic visits. Study staff may use a public information source (e.g., county records) to obtain information about survival status only where permitted.

[d] Written informed consent must be obtained before any study-specific screening assessments are performed.

[e] Demographics include age, sex, and self-reported race/ethnicity.

[f] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements, and foods that have been shown to inhibit CYP3A4 [Section 4.4.2]) used by the patient within 28 days prior to the Cycle 1, Day 1 visit. Breast cancer history includes prior cancer therapies and procedures.

[g] Refer to Appendix 4 or tissue requirements related to eligibility. HER2 and or Bcl-2 status are required and must be centrally confirmed prior to treatment.

[h] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[j] Weight is to be measured up to 3 days prior to Day 1 of each cycle and compared with baseline and/or previous cycle.

[k] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Hematology includes CBC, with RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Hematologic evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[m] Serum chemistry includes glucose, BUN or urea, sodium, magnesium, chloride, bicarbonate, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Screening laboratory tests are to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization, and their results may be used for randomization visit purposes. Results must be reviewed and documented prior to administration of the first dose of study treatment. Chemistry evaluations should be completed prior to dosing on Day 1 of each indicated cycle (or up to 3 days before).

[n] TLS assessment frequency during the dose-expansion and randomized phases will be determined based on a comprehensive review of data in the dose-escalation phase. TLS laboratory assessments include serum creatinine, uric acid, potassium, calcium, phosphorous and LDH. If the screening assessments were done within 3 days prior to Cycle 1 Day 1, there is no need to repeat the TLS panel at Cycle 1 Day 1. Refer to Appendix 8 for further instructions.

[o] All patients will be tested for HIV prior to the inclusion into the study; HIV-positive patients will be excluded from the study. HBV DNA must be collected on or before Cycle 1, Day 1, in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

[p] Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

[q] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. During the treatment period, a urine pregnancy test in women of childbearing potential in all treatment arms must be performed within 3 days prior study drug administration of every 3rd cycle of protocol-mandated therapy. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For patients who discontinue therapy before end of planned therapy, a pregnancy test must be done at the completion/early termination visit (within 28 days after the last dose of HER2-targeted therapy), at 3 months, and additionally at 6 months after the discontinuation of study treatment.

[r] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1, may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. See Section 4.5.5 for details on imaging and tumor assessments. Tumor response will be evaluated using RECIST v1.1 (Appendix 11) *every 6 weeks (± 7 days)*. In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first. Results must be reviewed by the investigator before dosing at the next cycle. All tumor assessments should be documented in the eCRF before and after the primary PFS analysis. *Patients who discontinue from study treatments for reasons other than disease progression and have not started follow-on treatment(s) will be followed for disease status every 8 weeks (±5 days) from the date of randomization until Week 24 (±5 days) and then every 12 weeks (±5 days), thereafter, until disease progression, loss to follow-up, withdrawal of consent, death or study termination by the Sponsor (whichever occurs first).*

[s] CT/MRI scan of the brain is mandatory at screening and should be performed 1) with scheduled tumor assessments when identified as a site of involvement at baseline, 2) as clinically indicated, or 3) if a patient demonstrates control of systemic disease but has a newly developed isolated brain metastases and is eligible to remain on study treatment, a brain MRI or CT will be performed along with regularly scheduled tumor assessments.

[t] A bone scan is to be performed within 28 days prior to Cycle 1, Day 1 (see Section 4.5.5 for further instructions).

[u] A 12-lead ECG is required at screening. Subsequent ECGs may be performed as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[v] LVEF assessment by ECHO is preferred, but LVEF may also be assessed by MUGA scan. The same method should be used throughout the study for each patient and preferably performed and evaluated by the same assessor.

[w] ECHO or MUGA assessments will be performed every fourth cycle. Additional LVEF or MUGA measurements may be performed at the discretion of the investigator if LVEF declines are clinically suspected.

[x] Venetoclax/placebo will be administered on a once daily dosing schedule.

[y] Trastuzumab emtansine will be administered second by IV infusion at a dose of 3.6 mg/kg on Cycle 1 Day 1, and on Day 1 of each 21-day cycle thereafter. Trastuzumab emtansine should be administered over approximately 90 minutes for the first dose and, in the absence of infusion-related adverse events, over approximately 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

[z] Auto-antibody testing includes anti-nuclear antibody, anti-double-stranded DNA, and circulating and perinuclear anti-neutrophil cytoplasmic antibody. The baseline sample will be obtained *any time during screening and prior to* treatment *(*Cycle 1, Day 1*)*, before the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected. All samples will be analyzed centrally.

[aa] At screening, the FFPE archival tumor block from the most recently collected, available tumor tissue or fresh core biopsy (3 cores) is mandated. If more than one FFPE block exists from different timepoints (e.g., initial diagnosis vs. metastatic disease tissue), the most recent block is mandatory to be sent. If the FFPE block from the earlier timepoint is available, then this would be requested to also be sent. In cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided. At least 20 freshly serial cut, unstained slides will be acceptable in lieu of the FFPE block. Optional core biopsies will be obtained at Cycle 1, Day 1 and on Day 1 of any subsequent on treatment cycle (±3 days) if patient consented. At the study drug discontinuation/early study completion visit, if reason for discontinuation is disease progression, a biopsy must be taken (if deemed clinically feasible) before next line of therapy begins, unless purely anti-hormonal therapy.

[bb] *The questionnaires (EORTC QLQ-C30 and EORTC IL46 item) are to be completed during the randomized Phase II stage only: at Cycle 1, Day 1 (baseline) prior to administration of study drug; then at every study treatment cycle prior to administration of study drug (i.e., on Cycle 2, Day 1; Cycle 3, Day 1; and Cycle 4, Day 1, etc.) and at the study treatment discontinuation visit.*

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Samples

Table 1 Continuous Daily Venetoclax Dosing

Study Visit	Venetoclax (Plasma PK Sample) [a]	Total Trastuzumab (Serum PK Sample) [b]	Trastuzumab Emtansine (Serum PK Sample) [c]	ADA to Trastuzumab Emtansine (Serum ADA Sample) [c]
Cycle 1, Day 1		Pre-infusion of trastuzumab emtansine (Within 24 hr prior to dosing)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 min after end of trastuzumab emtansine infusion	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
Cycle 2, Day 1	Predose (within 1 hr before dosing) 4 hr postdose (±20 min)		Pre-infusion of trastuzumab emtansine (within 24 hours prior to dosing)	
Cycle 4, Day 1	Predose (within 1 hr before dosing) 4 hr postdose (±20 min)		Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 minutes after end of trastuzumab emtansine infusion (±10 min)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
120 days (±28 days) after treatment completion or discontinuation				Anytime during visit

ADA = anti-therapeutic antibody; hr = hour; min = minute; PK = pharmacokinetic.

Notes: PK and ADA samples are to be collected, prepared, and shipped according to procedures outlined in the separate laboratory manual. Record exact date and time of venetoclax dosing on the day of and the day prior to the date of PK sampling. Patients should record venetoclax doses taken at home in a dosing diary. Record exact date and time of all PK and ADA sample collections. Sample collection times are relative to the administration of the study drug being measured.

[a] Venetoclax should be administered in the clinic on days that venetoclax PK sample is to be taken. Venetoclax PK will be collected for patients enrolled in all study phases.

[b] Total trastuzumab PK will be collected for patients enrolled in all study phases.

[c] Trastuzumab emtansine PK and ADA to trastuzumab emtansine samples will only be collected for patients enrolled in the randomized Phase II stage.

Table 2 Schedule of Pharmacokinetic and ADA Assessments for Non-Continuous 7/21 or 14/21 Venetoclax Dosing

Study Visit	Venetoclax (Plasma Sample) [a]	Total Trastuzumab (Serum Sample) [b]	Trastuzumab Emtansine (Serum Sample)[c]	ADA to Trastuzumab Emtansine (Serum Sample) [c]
Cycle 1, Day 1		Pre-infusion of trastuzumab emtansine (Within 24 hr prior to dosing)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 min after end of trastuzumab emtansine infusion	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
Cycle 1, Day 8 [d]	Predose (within 1 hr before dosing) 4 hr postdose (±20 minutes)			
Cycle 2, Day 1			Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)	
Cycle 4, Day 1			Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing) 30 minutes after end of trastuzumab emtansine infusion (±10 min)	Pre-infusion of trastuzumab emtansine (within 24 hr prior to dosing)
Cycle 4, Day 8 [d]	Predose (within 1 hour before dosing) 4 hours postdose (±20 min)			
120 days (±28 days) after treatment completion or discon.				Anytime during visit

ADA = anti-therapeutic antibody; discon = discontinuation; hr = hour; min = minute; PK = pharmacokinetic.

Notes: PK and ADA samples are to be collected, prepared, and shipped according to procedures outlined in the separate laboratory manual.

Record exact date and time of venetoclax dosing on the day of and the day prior to the date of PK sampling. Patients should record venetoclax doses taken at home in a dosing diary. Record exact date and time of all PK and ADA sample collections. Sample collection times are relative to the administration of the study drug being measured.

[a] Venetoclax should be administered in the clinic on days that venetoclax PK sample is to be taken. Venetoclax PK will be collected for patients enrolled in all study phases.

[b] Total trastuzumab PK will be collected for patients enrolled in all study phases.

[c] Trastuzumab emtansine PK and ADA to trastuzumab emtansine samples will only be collected for patients enrolled in the randomized Phase II stage.

[d] For a 7 out of 21 day venetoclax dosing schedule, where no dose is scheduled on Day 8 of each cycle, samples should be drawn on Day 7 of the cycle, with allowance to collect on Day 5 or 6 to avoid a weekend or holiday.

Appendix 4
Biomarker Assessments

Table 1 Blood Samples for Biomarker Analysis

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pre-infusion	Whole blood sample [a]
		Blood for plasma
Cycle 2, Day 1	Pre-infusion	Blood for plasma
Cycle 3, Day 1	Pre-infusion	Blood for plasma
Every Odd Cycle, Day 1	Pre-infusion	Blood for plasma
Study Treatment/Early Discontinuation Visit	At any time during visit	Blood for plasma

[a] Whole blood sample will be taken from all patients enrolled in the study.

Table 2 Tissue Sample for Biomarker Analysis

Visit	Timepoint	Requirement	Sample Type
Screening	Pre-infusion	Mandatory	○ FFPE archival tumor block or partial block most recently collected, available tumor tissue or Fresh core biopsy (3 cores) ○ If more than 1 FFPE blocks exists from different time points e.g. initial diagnosis vs. metastatic disease tissue, the most recent block or partial block is mandatory to be sent. If the FFPE block from the earlier timepoint is available then this would be requested to also be sent. ○ In the cases of bilateral breast cancer, an additional 8 unstained slides from the contralateral breast to where FFPE block have been provided ○ Upon discussion with the Medical Monitor (in case of site regulations that prevent sending a block), at least 20 freshly serial cut, unstained slides will be acceptable in lieu of FFPE block. ○ If fewer than unstained slides are available at baseline, discuss with the Medical Monitor to decide on eligibility.
Cycle 1 Day 1	Pre-infusion (within 28 days of C1D1)	Optional	Fresh Core Biopsy (3 cores) FFPE block or partial block preferred or freshly serial cut, at least 20 freshly serial cut slides
Any Subsequent on-treatment Cycle Day 1	Pre-infusion	Optional	Fresh Core Biopsy (3 cores) FFPE block or partial block preferred or freshly serial cut, at least 20 freshly serial cut slides
Study Treatment/ Early Discontinuation Visit	At time of Study treatment/early discontinuation visit (if the reason for discontinuation was PD) Must be taken before next line of therapy begins. In case new line therapy is purely anti-hormonal, biopsy could be taken after it is started.	Mandatory (if deemed clinically feasible)	Fresh Core Biopsy (3 cores) at site of progression if accessible or from any other lesion FFPE block preferred or freshly serial cut, at least 20 freshly serial cut slides

Appendix 5
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
- Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 6
Patient-Reported Outcomes Questionnaires

Figure 1 EORTC QLQ-30 (Version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

Figure 1 EORTC QLQ-30 (Version 3) (cont.)

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Figure 2 EORTC IL46

EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 7
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

FIRST DOSE OF VENETOCLAX

- Within the first 24 hours after the first dose, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150–200 mL/hr; not $<$ 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS) (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

In addition to the recommendations for patients receiving first dose of venetoclax:

- For potassium increase $\geq$ 0.5 mmol/L from baseline, or any value $>$ 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of $>$ 0.5 mg/dL AND $>$ 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

The Sponsor may explore a different TLS lab schedule in the randomized Phase II expansion portion of the study based on findings in dose-escalation phase.

Appendix 8
Guidelines for Defining Tumor Lysis Syndrome

All tumor lysis syndrome events should be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 criteria.

Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days after the start of therapy. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (±alkalinization) and a hypouricemic agent(s).

Table 1 Howard Definition of Laboratory Tumor Lysis Syndrome

Laboratory Assessment	Range
Uric acid	>476 μmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/L (<7.0 mg/dL) or ionized calcium <1.12 (0.3 mmol/L) [a]

Note: Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

[a] The corrected calcium level in mg/dL is the measured calcium in mg/dL + (0.8 × [4-albumin in g/dL]).

Table 2 Howard Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory TLS and one or more of the following criteria:
Creatinine [a]: An increase in serum creatinine level of 0.3 mg/dL (26.5 µmol/L); a single value >1.5 times the ULN of the age appropriate normal range if no baseline creatinine measurement is available; or the presence of oliguria, defined as average urine output of <0.5 mL/kg/hour for 6 hours
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia[b]

TLS=tumor lysis syndrome; ULN=upper limit of normal.

[a] Acute kidney injury is defined as an increase in the creatinine level of ≥0.3 mg/dL (26.5 umol/L) or a period of oliguria lasting ≥6 hours. By definition, if acute kidney injury is present, the patient has clinical TLS.

[b] Not directly attributable to a therapeutic agent.

REFERENCE

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New Engl J Med 2011;364:1844–54.

Appendix 9
Management of Venetoclax-Specific Adverse Events

Event	Action to Be Taken
Non-hematologic toxicity (Not specifically described in Table 6)	
Grade 3 or 4 non-hematologic events	• Delay venetoclax for a maximum of 28 days. First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose level reduction. • Certain treatment emergent non-hematologic adverse events (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases, if a patient is clinically stable, resumption of study drug may be possible after consultation with the Medical Monitor.
Grade 2 related non-hematologic toxicity	• Delay treatment with venetoclax until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. • After resolution, resume full dose of venetoclax.
Grade 1 non-hematologic toxicity	• No dose reduction or delay.

Appendix 10
Management of Trastuzumab Emtansine-Specific Adverse Events

Event	Action to Be Taken
Left ventricular dysfunction	
Symptomatic congestive heart failure	Discontinue trastuzumab emtansine.
Asymptomatic LVEF decrease	
LVEF $>45\%$	Continue trastuzumab emtansine at the same dose level.
LVEF 40% to $\leq 45\%$ and decrease from baseline of $\geq 10\%$ points	Withhold trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF decrease from baseline of $\geq 10\%$ points is confirmed, discontinue trastuzumab emtansine.
LVEF 40% to $\leq 45\%$ and decrease from baseline of $<10\%$ points	Continue trastuzumab emtansine at the same dose level. Repeat LVEF assessment within 3 weeks.
LVEF $<40\%$	Withhold trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF $<40\%$ is confirmed, discontinue trastuzumab emtansine.
Infusion-related reaction (caused by cytokine release) or hypersensitivity (allergic) reaction	
Grade 2 reaction	Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.
Grade 3 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine. Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may

Event	Action to Be Taken
	be given at the investigator's discretion.
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.
Neurotoxicity	
Grade ≥3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade ≤2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade ≤2 within 42 days after the last dose received.
Interstitial Lung Disease and Pneumonitis	
Grades 1–4	Discontinue trastuzumab emtansine treatment.
NRH	If there are signs of portal hypertension (e.g., ascites and/or varices) and/or a cirrhosis-like pattern is seen on a CT scan of the liver, the possibility of NRH should be considered. Discontinue trastuzumab emtansine treatment and have the patient evaluated by a hepatologist.

LVEF = left ventricular ejection fraction, LVSD = left ventricular systolic dysfunction; NRH = Nodular Regenerative Hyperplasia.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm 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.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and 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 measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation .

ASSESSMENT OF TUMOR BURDEN

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.

IDENTIFICATION 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 considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. 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").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring 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 node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) 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 measurement 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 "too small to measure" 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 "too small to measure" should also be ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. 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.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, 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 lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: 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 all 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.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1.

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.

REFERENCES

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.

Appendix 12
National Cancer Institute Common Terminology Criteria

In the present study, toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

A pdf of the NCI CTCAE v5.0 can be downloaded from the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Investigators who do not have access to Internet can contact the Data Center to receive a hard copy of this document by mail.

Appendix 13
Guidelines for Liver Biopsy

Because nodular regenerative hyperplasia (NRH) can be a very subtle diagnosis to make on liver biopsy, every attempt should be made to maximize the amount of tissue obtained.

The needle used should be at least 18 gauge, and percutaneous biopsies of length at least 1.5 cm are recommended, if clinically appropriate. In order to diagnose NRH, reticulin and trichrome stains are necessary.

Smaller biopsies obtained via a transjugular approach and smaller biopsy gun needle biopsies are discouraged. Small wedge biopsies should also be discouraged.

Appendix 14
Sample List of Excluded and Cautionary Medications

Examples of Strong and Moderate CYP3A Inhibitors and Inducers

CYP3A Inhibitors		CYP3A Inducers	
Strong	**Moderate**	**Strong**	**Moderate**
boceprevir	aprepitant	apalutamide	bosentan
clarithromycin	ciprofloxacin	carbamazepine	efavirenz
cobicistat	conivaptan	enzalutamide	etravirine
danoprevir	crizotinib	mitotane	phenobarbital
dasabuvir	cyclosporine	phenytoin	primidone
elvitegravir	diltiazem	rifampin	
idelalisib	dronedarone	St. John's Wort	
indinavir	erythromycin		
itraconazole	fluconazole		
ketoconazole	fluvoxamine		
lopinavir	imatinib		
nefazodone	tofisopam		
nelfinavir	verapamil		
ombitasvir			
paritaprevir			
posaconazole			
ritonavir			
saquinavir			
telaprevir			
telithromycin			
tipranavir			
troleandomycin			
voriconazole			

Refer to Section 4.4.3 for guidance related to prohibited and cautionary medications.

Examples of P-gp Substrates and Inhibitors

P-gp	
Substrates	**Inhibitors [a]**
dabigatran	amiodarone
digoxin	carvedilol
etexilate	clarithromycin
fexofenadine	dronedarone
	itraconazole
	lapatinib
	lopinavir
	propafenone
	quinidine
	ranolazine
	ritonavir
	saquinavir
	telaprevir
	tipranavir
	verapamil

P-gp=P-glycoprotein.

[a] These are anticancer agents; consult the Medical Monitor before use.

Refer to Section 4.4.3 for guidance related to prohibited and cautionary medications.