EProst # 20151055

IND# (IND EXEMPT)

A Phase I/II Study to Evaluate the Safety and Efficacy of Vinorelbine with Trastuzumab Emtansine in Pre-Treated HER2-Positive Metastatic Breast Cancer

SPONSOR-INVESTIGATOR:	Reshma Mahtani, DO Assistant Professor of Medicine Division of Hematology/ Oncology University of Miami-Sylvester Comprehensive Cancer Center (SCCC)
INVESTIGATIONAL AGENT(S):	Vinorelbine – Commercial supply Trastuzumab emtansine (Kadcyla®) – Genentech, Inc.
OTHER AGENT(S):	(N/A)
IND STATUS:	IND or IDE #: (IND exempt) **IND Sponsor:** (IND exempt)
PROTOCOL VERSION AND DATE:	3.0 dated 28Nov2017

CONTACT INFORMATION

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FUNDING SOURCE	Genentech, Inc.

[redacted]

PROTOCOL REVISION HISTORY

Version #	Summary of Changes	Version Date
3.0	**Safety and Dosing changes per DSMC notification:** The document was updated throughout to make administrative changes to improve the clarity and consistency of protocol. Section 3.0 (Endpoints) updated to provide clarification on who is evaluable for DLT. Section 7.1 (Dose Escalation/Dose De-Escalation) updated to improve clarity and consistency Section 7.3.1 updated to add grade 5 to SAEs and include only possible, probable, or definite findings to be considered DLT. Updated DLT language to include non-hematologic grade 3+ AEs that limit the patient's ability to complete treatment or are problematic in the eyes of the investigator will be considered DLT. Updated the time to evaluate DLTs to 21-42 days rather than 42. Section 8.0 (Treatment Plan) updated to add ±5 minutes to the administration of subsequent infusions. Added that study procedures can be held due to AE, SAE, or at the discretion of the investigator if it is necessary. Section 12.0 (Schedule of Clinical and Laboratory Evaluations) updated to add that once patient meets all eligibility criteria, the date of first dose is considered the enrollment date. Clarified that screening evaluations should be done within 28-days prior to enrollment unless otherwise specified. Section 18.0 (Investigator Responsibilities) updated to remove language regarding IND annual reports since this is an IND exempt study. Removed language regarding 1572. Appendix A (Expedited Adverse Event (AE) Reporting) Requirements updated to remove FDA Expediting Reporting section as this is an IND exempt study. Removed language regarding MedWatch 3500A form.	28NOV2017

2.0	**Version numbering and Pharmacy changes**: The starting dose of vinorelbine is 22.5 mg/m2 given as a direct intravenous pb over 8 minutes ± (plus or minus)_2 minutes on day 1 and day 8 of every 3-week (i.e. 21-day) cycle.	14NOV2016
1.3	**Administrative/editorial changes for consistency:** Removed all references to FDG-PET scans from section 13.1.3 as these are not required procedures in this study. Corrected drug name in title of Figures 1 and 3 for consistency with protocol text.	09MAR2016
1.2	**Administrative/editorial changes to eliminate duplication:** (Inclusion criteria section 5.1.15 removed extra entry for alkaline phosphase ≤ 5 X ULN)	09MAR2016
1.1	**Administrative/editorial changes for consistency and to minimize confusion** (e.g. verbiage regarding imaging)	09MAR2016
1.0	**Version numbering and Sponsor's Safety edits:** Version numbering reverted to 1.0 to reflect protocol development office's format to provide only whole numbered versions to the IRB for approval. Genentech safety edits and request for reports were added to p. 93 and to Section 18.6 (p.87)	09MAR2016

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ABBREVIATIONS & DEFINITIONS

Term	Abbreviation	Definition
Dose-Limiting Toxicity	DLT	Describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment. (DLTs are defined before beginning the trial and are protocol-specific.)
Maximum Tolerated Dose	MTD	The highest dose of a drug or treatment that does not cause unacceptable side effects. The MTD is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found.
Overall Survival	OS	The length of time from the date of the start of treatment for a disease, that patients diagnosed with the disease are still alive.
Progression-Free Survival	PFS	The length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse.
Recommended Phase 2 Dose	RP2D	The highest dose level below the maximally administered dose (highest dose administered) at which ≤1 out of 6 patients treated, may have experienced a DLT.
Time to Progression	TTP	The length of time from the date of diagnosis or the start of treatment for a disease until the disease starts to get worse or spread to other parts of the body.

Reference: National Cancer Institute (NCI) Dictionary of Cancer Terms
http://www.cancer.gov/dictionary

PROTOCOL SYNOPSIS

<table>
<tr><td>Protocol Title</td><td>A Phase I/II Study to Evaluate the Safety and Efficacy of Vinorelbine with Trastuzumab Emtansine in Pre-Treated HER2-Positive Metastatic Breast Cancer</td></tr>
<tr><td>Targeted Patient Population</td><td>Patients with HER2-positive metastatic, locally advanced, or unresectable breast cancer.</td></tr>
<tr><td>Study Design</td><td>Phase I/II open label, non-randomized, single-arm study to establish the recommended phase II dose (RP2D) of vinorelbine with a fixed dose of trastuzumab emtansine. A standard 3+3 design will be utilized in phase I to test the combination of trastuzumab emtansine and vinorelbine. (Please see Section 7.0 for further details, including the definition of a DLT for this trial.)</td></tr>
<tr><td>Treatment Schema</td><td>
<table>
<tr><td>Cycle(s) every 21 days</td><td colspan="6">Treatment</td><td rowspan="4">Imaging every 6 weeks (±7 days) until Cycle 6</td><td colspan="6">Treatment</td><td rowspan="4">Imaging every 6 weeks (±7 days) until Cycle 6</td><td colspan="6">Treatment</td><td rowspan="4">(After Cycle 6) Imaging every 12 weeks (±7 days)</td><td colspan="3">5, 6, 7, etc until progression</td></tr>
<tr><td colspan="3">1</td><td colspan="3">2</td><td colspan="3">3</td><td colspan="3">4</td><td colspan="3">5</td><td colspan="3">6</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Week(s)</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td><td>1</td><td>2</td><td>3</td></tr>
<tr><td>Day(s)</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td><td>1</td><td>8</td><td>15</td></tr>
<tr><td>Trastuzumab emtansine IV day 1</td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td><td>X</td><td></td><td></td></tr>
<tr><td>Vinorelbine direct IV push days 1 and 8</td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td>X</td><td>X</td><td></td></tr>
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<tr><td>Duration of Treatment</td><td>Patients may remain on treatment with the trastuzumab emtansine/ vinorelbine combination until documented disease progression or other criteria for discontinuation is met (Section 11.0).</td></tr>
<tr><td>Follow-up Required Post-Treatment</td><td>Patients (regardless of reason for treatment discontinuation) will then be followed for survival every 12 weeks (±2 weeks) for at least 3 years, until death, lost to follow-up, withdrawal of consent*, or study termination by the Principal Investigator. A telephone call to the patient and/or the patient's family may be made to evaluate the patient's status on Post-study anticancer therapy status and Survival status. *Note: Some patients may withdraw their consent from study treatment but still agree to participate in survival follow-up. For these patients survival follow-up shall occur every 12 weeks (±7 days) until death, lost to follow-up or withdrawal from study. See also section 12.4 for details.</td></tr>
<tr><td>Objectives</td><td>Phase I Primary Objectives:
To identify the maximum tolerated dose (MTD) of vinorelbine combined with a fixed dose of trastuzumab emtansine to be recommended for the phase II portion of the study (RP2D).
To identify dose limiting toxicities (DLT).
Phase II Primary Objective</td></tr>
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	• To evaluate the efficacy, as determined by PFS, of the RP2D of vinorelbine combined with a fixed dose of trastuzumab emtansine in pre-treated HER2-positive MBC. Phase II Secondary Objectives: • To determine the overall response rate (ORR), clinical benefit rate (CBR), and overall survival (OS) of the RP2D of vinorelbine combined with a fixed dose of trastuzumab emtansine
Expected Number of Patients	50
Expected Number of Centers	1 – Sylvester Comprehensive Cancer Center (SCCC) Main Campus (inclusive of constituent Satellite Sites: Deerfield Beach and Plantation)
Expected Duration of the Protocol	Expected total study duration is 4.5 to 5 years.
Inclusion Criteria	1. Histologically or cytologically documented breast cancer. 2. Metastatic or unresectable locally advanced/recurrent breast cancer. 3. HER2-positive disease documented as: IHC 3+ positive, and/or FISH ≥ 2.0, and/or gene copy number greater than 6, on previously collected tumor or metastatic site. IHC testing, FISH assay(s), and gene copy number may all have been performed; however, a positive result from *only one* of the above is required for eligibility. 4. Documented disease progression on the last regimen by radiographic measurement (progression demonstrated by tumor markers only is unacceptable). 5. Documented disease progression (by investigator assessment) after at least one regimen of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting. 6. For patients with hormone receptor-positive disease: disease progression or recurrence in any setting on prior hormonal therapy, given with or without HER2 directed therapy. 7. Measurable or bone only disease. 8. Prior treatment with a taxane, in the neoadjuvant, adjuvant, locally advanced or metastatic setting. 9. A minimum of 6 weeks of prior trastuzumab for the treatment of metastatic or unresectable locally advanced/recurrent disease is required. 10. Prior use of Pertuzumab in any setting is permitted (but not required).

	11. Prior use of Lapatinib in any setting is permitted (but not required). 12. Age ≥ 18 years 13. Life expectancy ≥3 months 14. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See Appendix C for details. 15. Patients must have normal organ and marrow function as defined below: • absolute neutrophil count (ANC) >1,500 cells/mm3 • platelets >100,000 cells/mm3 • hemoglobin > 9.0 g/dL (Patients are permitted to receive transfused red blood cells to achieve this level.) • total bilirubin ≤1.5 X institutional upper limit of normal (ULN) [**Note**: For patients with previously documented Gilbert's syndrome, total bilirubin ≤ 3 mg/dL.] • AST(SGOT) ≤2.5 X ULN • ALT(SGPT) ≤2.5 X ULN • alkaline phosphatase (alk phos) ≤2.5 X ULN • serum creatinine < 1.5 X ULN 16. International normalized ratio (INR) < 1.5 X ULN 17. Left ventricular ejection fraction (LVEF) ≥ 50% by either echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) within screening window. 18. (This trial is open to males and females.) Negative results of serum pregnancy test for premenopausal women of reproductive capacity and for women < 12 months after menopause. For men and women of childbearing potential, agreement by the patient and/or partner to use two effective, *non-hormonal* forms of barrier contraception at the same time, throughout treatment on study. Women should agree to continued use for at least 90 days after the end of treatment. Men should agree to continued use for at least 7 months after the end of treatment. Examples of barrier contraception include: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide. 19. Ability to understand and willingness to sign a written informed consent and HIPAA document.
Exclusion Criteria	1. Chemotherapy ≤21 days prior to first dose of study treatment 2. If last dose of trastuzumab was: • 6mg/kg then ≤21 days prior to first dose of study treatment

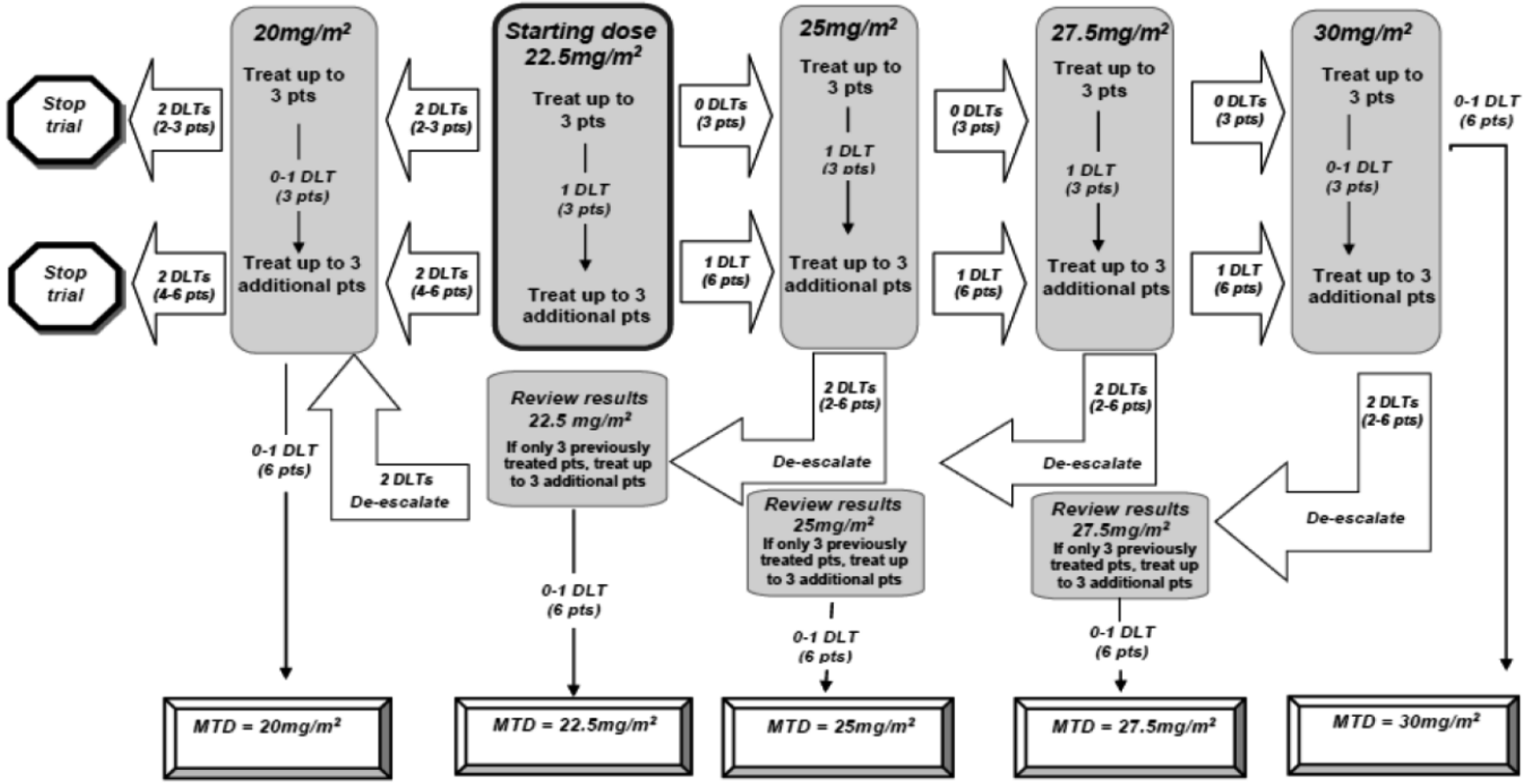
	• 4mg/kg then ≤14 days prior to first dose of study treatment • 2mg/kg then ≤7 days prior to first dose of study treatment 3. Lapatinib ≤14 days prior to first dose of study treatment 4. Pertuzumab ≤21 days prior to first dose of study treatment 5. Hormone therapy ≤7 days prior to first dose of study treatment 6. Investigational therapy or any other such experimental therapy ≤28 days prior to first dose of study treatment 7. Prior treatment with trastuzumab emtansine, (on or off a study protocol) 8. Prior use of vinorelbine (in any setting). 9. Previous radiotherapy for the treatment of unresectable, locally advanced, recurrent or metastatic breast cancer is <u>not</u> allowed if: • The last fraction of radiotherapy has been administered within 14 days prior to study enrollment • More than 25% of marrow-bearing bone has been irradiated 10. Brain metastases that are untreated or symptomatic, or require any radiation, surgery, or continued steroid therapy to control symptoms from brain metastases within 14 days of study enrollment. 11. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins. 12. History of exposure to the following cumulative doses of anthracyclines: • Doxorubicin ≥550mg/m^2 • Liposomal doxorubicin >500 mg/m^2 • Epirubicin >900 mg/m^2 • Mitoxantrone > 120 mg/m^2 • If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of ≥550 mg/m^2 doxorubicin. 13. Current peripheral neuropathy of Grade ≥3 per the NCI CTCAE, v4.0 14. The patient has not recovered from any other acute toxicity (to Grade ≤1 as per NCI CTCAE v4.03) prior to study enrollment. 15. History of other malignancy within the last 3 years, except for appropriately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome. 16. Cardiopulmonary Function Criteria: • Current unstable ventricular arrhythmia requiring treatment • History of symptomatic congestive heart failure (CHF) as per New York Heart Association [NYHA] Classes II–IV; see Appendix D for details. • History of myocardial infarction or unstable angina within 6 months of study enrollment • History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment • Severe dyspnea at rest due to complications of advanced malignancy or requiring current continuous oxygen therapy

	17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease) • Major surgical procedure or significant traumatic injury within 28 days -before enrollment or anticipation of the need for major surgery during the course of study treatment • Current pregnancy or lactation • Current known uncontrolled active infection with HIV, hepatitis B, and/or hepatitis C virus 18. Any uncontrolled, intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia. 19. Any other serious medical or psychiatric illness/condition likely in the judgment of the Investigator(s) to interfere or limit compliance with study requirements/treatment.

PROTOCOL SCHEMA

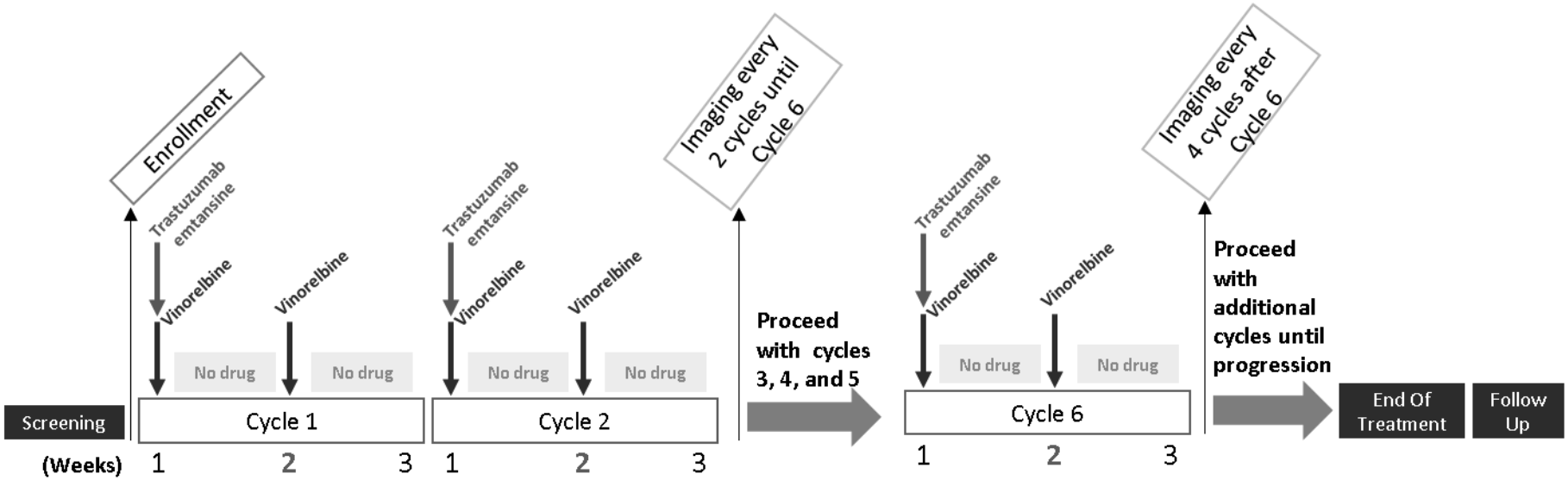
Figure 1: Phase I

Schema for Escalating/De-Escalating Vinorelbine from a Starting Dose of 22.5 mg/m^2 with a fixed dose (3.6 mg/kg flat dose) of Trastuzumab emtansine



Note: The maximum tolerated dose will be the highest tested dose at which no more than 1 patient among 6 experiences DLT. If unacceptable toxicity (DLT in 2 out of 2-6 patients) occurs at a reduced dose of 22.5 mg/m^2, the trial will stop without finding a recommended dose.

Figure 2: Phase II



1.0 **BACKGROUND**

1.1 **Breast Cancer**

Breast cancer is the most common type of non-cutaneous malignancy and the second leading cause of cancer death among women. In the United States, more than 230,000 new breast cancer cases and approximately 40,000 deaths are estimated in 2014.[1] Although patients with metastatic breast cancer (MBC) are living longer, treatment goals remain largely palliative, and efficacy gains must be balanced against quality of life concerns.

Cytotoxic agents are somewhat indiscriminant, and are therefore associated with significant side effects. In that regard, clinical research has focused on identifying better tolerated therapies that target specific signaling receptors, such as the human epidermal growth factor receptor (HER2). Overexpression or amplification of HER2 is observed in approximately 20% of human breast cancers. There is a large body of evidence to support a direct role for HER2 overexpression in the aggressive growth and poor clinical outcomes associated with these tumors.[2] The development of trastuzumab in the 1990s provided patients with HER2-overexpressing tumors a markedly better outcome than was possible with chemotherapy alone. Increases in response rate, response duration, and progression-free survival (PFS) were associated with a 5-month survival advantage when given in the first-line metastatic setting as demonstrated in the pivotal Phase III trial that led to its approval by the Food and Drug Administration (FDA).[3]

For patients with HER2-positive MBC, there are many therapeutic options. Until the recent approval of pertuzumab as an additive to docetaxel and trastuzumab based on the CLEOPATRA study,[4] the doublet of trastuzumab with a taxane was the most commonly used and FDA approved first-line treatment option of choice based on the survival advantage demonstrated in two large pivotal trials (H0648g (3) and M77001).[5]

In spite of improved treatment regimens, virtually all patients with HER2-positive MBC develop progressive disease (PD) and require additional therapies for palliation. These patients' tumors continue to express high levels of HER2 after progression on trastuzumab and a taxane,[6] and HER2-directed therapy is often given with chemotherapy in subsequent lines of treatment. Evidence of improved time to progression (TTP) with lapatinib, an inhibitor of HER1 and HER2 receptor tyrosine kinases, has provided support for the practice of continued suppression of HER2 signaling as an effective treatment strategy. In a Phase III trial involving patients with advanced HER2-positive breast cancer who were previously treated with an anthracycline, a taxane, and trastuzumab, the addition of lapatinib to capecitabine resulted in an increased response rate (24% vs. 14%) and TTP (6.2 months vs. 4.3 months).[7] In another trial of patients who had experienced progression on prior trastuzumab-containing regimens, the combination of trastuzumab and lapatinib improved PFS compared with the administration of lapatinib alone (median PFS 12.0 weeks vs. 8.1 weeks).[8]

1.2 **Trastuzumab emtansine (T-DM1)**

Despite the availability of other HER2 targeted therapies such as lapatinib, as well as several other cytotoxic drugs, most patients with HER2+ breast cancer will ultimately develop progression of disease and the approval of other options for these patients is eagerly awaited. T-DM1 is a novel antibody-drug conjugate (ADC) and was approved in 2012 for the treatment of HER2+ metastatic breast cancer patients whose disease had progressed on trastuzumab and a taxane.

ADCs represent a new therapeutic approach in that these agents utilize the linkage of a cytotoxic agent to highly specific monoclonal antibodies. This mechanism thereby targets unique and/or overexpressed cell surface tumor antigens and focuses the delivery of such agents to tumor cells, potentially creating a more favorable therapeutic window than could be achieved by their administration as free drugs.

T-DM1 is specifically designed for the treatment of HER2-positive cancer. It is composed of the following components: trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an anti-microtubule agent derived from maytansine; and succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate (SMCC), a thioether linker molecule used to conjugate DM1 to trastuzumab.[9,10]

T-DM1 binds to HER2 with an affinity similar to that of unconjugated trastuzumab.[11] It is hypothesized that after binding to HER2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization; it binds to tubulin competitively with vinca alkaloids.[9] T-DM1 also has been shown in preclinical studies to retain the activities of unconjugated trastuzumab including inhibition of HER2 shedding, inhibition of PI3K/AKT signaling pathways, and antibody dependent cellular cytotoxicity.[11]

Completed and ongoing Phase I, II and III studies of T-DM1 have demonstrated its clinical activity when given as a single agent to patients with HER2-positive MBC who have progressed on a trastuzumab-containing chemotherapy regimen. Data from clinical trials of T-DM1 that are relevant to the design of the current trial are summarized below. Please refer to the T-DM1 Investigator's Brochure (IB) for further information on all completed and ongoing studies.

1.3 **Trastuzumab emtansine (T-DM1): Clinical experience**

The following phase II and phase III studies have demonstrated clinical benefit of T-DM1 in women with metastatic breast cancer: TDM4450g, TDM5248g, and TDM 4370g/BO21977.

1.3.1 Study TDM4450g (Single-Agent T-DM1 in Previously Untreated Metastatic Breast Cancer Patients)

TDM4450 was a randomized, multicenter, Phase II study of the efficacy and safety of T-DM1 versus trastuzumab plus docetaxel in patients with metastatic

HER2-positive breast cancer who have not received prior chemotherapy for metastatic disease.[12] This study completed enrollment in December 2009 (n = 137). The primary objectives were to assess the efficacy of T-DM1 compared with the combination of trastuzumab and docetaxel, as measured by PFS based on investigator tumor assessments, and to characterize the safety of T-DM1 compared with the combination of trastuzumab and docetaxel in this population. Secondary endpoints included ORR, survival, and duration of response, clinical benefit rate, and quality of life.

Seventy patients were randomized to the control arm and 67 patients to the T-DM1 arm. The median duration of follow-up was approximately 14 months for the efficacy analysis and approximately 23 months for the updated safety analysis.

The median duration of treatment was 8.1months for trastuzumab, 5.5 months for docetaxel, and 10.4 months for T-DM1. In the primary efficacy analysis, T-DM1 provided an improvement in PFS. The median PFS was 14.2 months in the T-DM1 arm versus 9.2 months in the trastuzumab plus docetaxel arm. The hazard ratio (HR) for PFS was 0.594 (95% CI: 0.364, 0.968; p = 0.0353). The ORR in the T-DM1 arm was 64.2% (95% CI: 51.8%, 74.8%) compared with 58.0% (95% CI: 45.5%, 69.2%) in the control arm (based on 69 evaluable patients). The clinical benefit rate was 74.6% (95% CI: 63.2%, 84.2%) in the T-DM1 arm versus 81.2% (95% CI: 70.7%, 89.1%) in the trastuzumab plus docetaxel arm (based on 69 evaluable patients).

Based on safety data analyzed at the data cutoff date, single-agent T-DM1 appears to have a favorable overall safety profile compared with trastuzumab and docetaxel in first-line MBC. The incidence of Grade ≥ 3 AEs in the control arm (90.3%; n = 66) was nearly twice that of T-DM1 (46.4%; n =69). The rates of SAEs for both arms were similar (control arm 25.8% vs. T-DM1 20.3%). One patient in the T-DM1 group died as a result of an AE (sudden death). This patient was randomized to receive trastuzumab plus docetaxel but mistakenly received a single dose of 6 mg/kg T-DM1 instead of 6 mg/kg trastuzumab. (Data on File, Genentech) One patient in the trastuzumab plus docetaxel group died due to cardiopulmonary failure. With respect to cardiotoxicity, based on local assessments of LVEF, T-DM1 was not associated with an increase in cardiotoxicity compared with trastuzumab plus docetaxel.

1.3.2 Study TDM4258g (Single-Agent T-DM1 in Previously Treated Metastatic Breast Cancer Patients)

Study TDM4258g was a single arm phase II study that evaluated the safety and efficacy of T-DM1 administered at a dose of 3.6 mg/kg (intravenous [IV]) q3w in HER2-positive MBC patients who had progressed on previous HER2-directed therapy and conventional chemotherapy.[10]

The primary objectives for this study were to assess ORR by independent radiologic review associated with T-DM1 3.6 mg/kg IV q3w, and to characterize the safety and tolerability of T-DM1 at this dose. The study was activated on July 20, 2007, and enrollment was completed (n = 112) on July 31, 2008. The final analysis of ORR was performed with a data cutoff date of June 25, 2009, 11 months after the last patient was enrolled. The reported ORR in all patients was 25.9% (95% CI, 18.4%, 34.4%) by Independent Review Committee (IRC) and was 37.5% (95% confidence interval [CI], 28.6%, 46.6%) by investigator assessment. The clinical benefit rate (defined as complete response [CR], partial response [PR], or stable disease [SD] for > 6 months) was 39.3% by independent review and 46.3% by investigator assessment. The median PFS was 4.6 months by both the IRC and the investigators. In the subset of patients whose archival primary tumors were retrospectively confirmed to be HER2-positive (74 of 95 patients with submitted tumor samples), the ORR was 33.8% by independent review and 47.3% based on investigator assessment.

The most common adverse events (AEs; occurring in ≥ 20% of patients) were fatigue (65.2%), nausea (50.9%), headache (40.2%), epistaxis (35.7%), pyrexia (34.8%), constipation (30.4%), cough (27.7%), hypokalemia (26.8%), diarrhea (25.9%), vomiting (24.1%), arthralgia (22.3%), pain in extremity (22.3%), anemia (20.5%), and dyspnea (20.5%) (10). Most of these AEs were Grade 1−2. The three most common Grade 3−4 AEs observed in this trial were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). There was one reported Grade 5 event in a patient who died of respiratory failure attributed by the investigator to underlying disease. (Data on File, Genentech) No grade ≥ 3 left ventricular systolic dysfunction events (symptomatic congestive heart failure [CHF] and/or left ventricular ejection fraction [LVEF] of < 40%) were observed.

1.3.3 TDM 4370g/BO21977 (EMILIA)

TDM4370g/BO21977 was a randomized, Phase III study of T-DM1 versus lapatinib + capecitabine for the treatment of patients with HER2-positive unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.[13] Patients received T-DM1 (3.6 mg/kg IV on Day 1 of a 21-day cycle) or lapatinib (1250 mg orally once per day) plus capecitabine (1000 mg/m^2 orally twice daily on Days 1−14 of a 21-day cycle) until PD or unmanageable toxicity. Eligible patients must have had confirmed HER2-positive MBC (immunohistochemistry [IHC] 3+ and/or fluorescence in situ hybridization [FISH] positive) and must have received prior therapy with trastuzumab and a taxane. Primary endpoints were PFS by independent review, overall survival (OS), and safety.

From February 2009 through October 2011, a total of 991 patients were enrolled; 496 were assigned to lapatinib + capecitabine, and 495 were assigned to T-

DM1.[13] Median duration of follow-up for the first and second interim analysis was approximately 13 months and 19 months, respectively. Baseline patient demographics, prior therapy, and disease characteristics were balanced. The study met the primary endpoint with an improvement in PFS by independent review with a HR = 0.65, (95% CI, 18.4%, 34.4%), p<0.001. The median PFS was 9.6 months in the T-DM1 arm and 6.4 months in the lapatinib + capecitabine arm. A strong trend in OS was observed in favor of the T-DM1 arm (HR = 0.62, [95% CI 0.48-0.81], p = 0.0005). At the first interim analysis, median OS was not reached in the T-DM1 arm and was 23.3 months in the lapatinib + capecitabine; the interim efficacy stopping boundary for OS was not crossed. However, at the second interim analysis, OS data crossed the prespecified boundary that showed patients receiving T-DM1(median OS = 30.9 months) survived significantly longer than the control group (median OS=25.1 months), with a HR=0.68, 95% CI, 0.55-0.85, p<0.001). The ORR was 43.6% for the T-DM1 arm versus 30.8% for the lapatinib + capecitabine arm, with a median duration of objective response (DOR) of 12.6 months versus 6.5 months, respectively.

T-DM1 was well tolerated, with no unexpected safety signals. The most common Grade ≥ 3 AEs in the T-DM1 arm were thrombocytopenia (12.9% vs. 0.2%), increased AST (4.3% vs. 0.8%), and increased ALT (2.9% vs. 1.4%); the most common Grade ≥ 3 AEs in the lapatinib + capecitabine arm were diarrhea (20.7% vs. 1.6%) palmar plantar erythrodysesthesia (16.4% vs. 0), and vomiting (4.5% vs. 0.8%) (Verma et al 2012). The incidence of Grade 3/4 AEs in the T-DM1 arm was 40.8% versus 57.0% in the lapatinib + capecitabine arm.

1.4 **Trastuzumab emtansine (T-DM1): Clinical Safety**

In clinical trials, T-DM1 has been evaluated as single-agent in 884 patients with HER2-positive metastatic breast cancer. The most common (frequency ≥ 25%) adverse drug reactions (ADRs) seen in 884 patients treated with T-DM1 were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.

Adverse events were identified in patients with HER2-positive metastatic breast cancer treated in a randomized trial, TDM 4370g/BO21977 (EMILIA). Patients were randomized to receive T-DM1 or lapatinib plus capecitabine. The median duration of study treatment was 7.6 months for patients in the T-DM1 -treated group and 5.5 months and 5.3 months for patients treated with lapatinib and capecitabine, respectively. Two hundred and eleven (43.1%) patients experienced ≥ Grade 3 adverse events in the T-DM1 -treated group compared with 289 (59.2%) patients in the lapatinib plus capecitabine-treated group. Dose adjustments for T-DM1 were permitted. Thirty-two patients (6.5%) discontinued T-DM1 due to an adverse event, compared with 41 patients (8.4%) who discontinued lapatinib, and 51 patients (10.5%) who

discontinued capecitabine due to an adverse event. The most common adverse events leading to T-DM1 withdrawal were thrombocytopenia and increased transaminases. Eighty patients (16.3%) treated with T-DM1 had adverse events leading to dose reductions. The most frequent adverse events leading to dose reduction of T-DM1 (in ≥ (1% of patients) included thrombocytopenia, increased transaminases, and peripheral neuropathy. Adverse events that led to dose delays occurred in 116 (23.7%) of T-DM1 treated patients. The most frequent adverse events leading to a dose delay of T-DM1 (in ≥ 1% of patients) were neutropenia, thrombocytopenia, leukopenia, fatigue, increased transaminases and pyrexia.

The most common ADRs seen with T-DM1 were nausea, fatigue, musculoskeletal pain, thrombocytopenia, increased transaminases, headache, and constipation (frequency > 25%). The most common NCI–CTCAE (version 3) ≥ Grade 3 ADRs were thrombocytopenia, increased transaminases, anemia, hypokalemia, peripheral neuropathy and fatigue (frequency >2%).

1.5 **Background on Vinorelbine**

Vinorelbine belongs to the group of vinca alkaloids, which block cell division with G2/M in the cell cycle by inhibiting the assembly of microtubuli, which are necessary for cell division. Vinorelbine monotherapy is most frequently administrated as 30 mg/m^2 weekly and results in response rates of 40-60% as first line treatment with MBC.[14-18] In combination with other cytostatic agents, vinorelbine has shown high response rates of 62-65%, with time to progression similar to other combination chemotherapy regimens.[19, 20] A prospective randomized Phase III study compared a cyclophosphamide, anthracycline, fluoropyrimidine regimen to vinorelbine 25 mg/m^2 in combination with doxorubicin 50 mg/m^2 for first line treatment of metastasizing breast cancer and found comparable efficacy.[21] Vinorelbine is regarded as less toxic than taxanes and anthracyclines, and displays less neurotoxicity compared with other vinca alkaloids, which can be a problem with prolonged treatment. The results of a Phase III study comparing vinorelbine plus trastuzumab with docetaxel plus trastuzumab, as first line therapy for HER2-positive breast cancer showed that the vinorelbine and trastuzumab combination resulted in fewer adverse effects than the docetaxel and trastuzumab combination. Efficacy of the two combinations was similar.[22] The results of a Phase I study showed that the maximum tolerated dose of vinorelbine is 35 mg/m^2 weekly, if vinorelbine is administrated as monotherapy.[23] Granulocytopenia was a limiting toxicity in this study. Results from another Phase I study showed that the maximum tolerated dose is 40 mg/m^2 when vinorelbine is administrated on Day 1 and Day 8 every 3 weeks. The dose for the subsequent Phase II study was determined to be 35 mg/m^2.[24]

1.6 **Rationale for Study Design**

Although as previously stated, a taxane, trastuzumab and pertuzumab should be considered a standard first line therapy based on the CLEOPATRA data, upon

progression many other cytotoxic agents are also routinely used in combination with trastuzumab. Vinorelbine, as a single agent, has historically demonstrated efficacy and good tolerability in several early studies in the metastatic setting.[15,25,26] It seemed natural to explore the combination of this agent with trastuzumab, and two early studies,[27,28] were mounted to demonstrate its efficacy and appealing safety profile, while the preclinical data of their synergy emerged.[29] In fact, as demonstrated in the subsequent randomized phase II trial,[27,30] both vinorelbine/trastuzumab and taxane/trastuzumab treatments were active as first-line therapy for HER2-positive, metastatic breast cancer and had comparable rates of efficacy and tolerability. The obvious advantages of vinorelbine over the traditional taxane-based regimens include lack of alopecia, lower rates of grade 3/4 neuropathy and steroid-free administration. While the approval of pertuzumab is a welcome addition to the docetaxel-based doublet with trastuzumab, this regimen still causes alopecia and requires steroids as premedication. Therefore vinorelbine-based combinations are an attractive option to explore.

With the approval of T-DM1, further studies are warranted to evaluate the efficacy and tolerability of this agent in earlier lines of therapy and in combination with other agents. First line data in combination with Pertuzumab, another HER2 targeted therapy, will be reported when results are available from the MARIANNE study. However, in order to improve upon the already impressive efficacy data, there is a rationale to combine this agent with other cytotoxics as well as HER2 directed therapies. It is generally accepted that combination therapies tend to improve response rates at the cost of toxicity. For example, Rorbert *et al*. reported a randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer.[31] The addition of carboplatin to paclitaxel and trastuzumab improved ORR as well as PFS. Given the fact that T-DM1 is an inherent doublet, the addition of another cytotoxic such as vinorelbine could potentially improve upon the impressive efficacy data that have already been reported with this agent, with probably a modest increase in toxicity. In addition, the rationale of combining two agents that target microtubules has been established in the neoadjuvant setting utilizing docetaxel, vinorelbine and trastuzumab [28] as well in a phase II study in the metastatic setting with the same agents, reported by Livingstone *et al*. in 2011.[32] Furthermore, given that one of the toxicities reported with T-DM1 is thrombocytopenia, while vinorelbine is generally a platelet-sparing agent, the combination could potentially be highly efficacious without overlapping toxicity profiles. Finally, there are pre-clinical data that suggest the combination of these two agents may be synergistic in animal models. Therefore, the current study proposes to evaluate the safety and efficacy of the combination of trastuzumab emtansine (T-DM1) and vinorelbine in HER2+ metastatic breast cancer patients.

2.0 **OBJECTIVES**

2.1 **Primary Objectives**

Phase I

- To identify the maximum tolerated dose (MTD) of vinorelbine combined with a fixed dose of trastuzumab emtansine to be recommended for the phase II portion of the study (RP2D).
- To identify dose limiting toxicities (DLT).

Phase II

- To evaluate the efficacy, as determined by PFS, of the RP2D of vinorelbine combined with a fixed dose of trastuzumab emtansine in pre-treated HER2-positive MBC.

2.2 **Secondary Objectives**

Phase II

- To determine the overall response rate (ORR), clinical benefit rate (CBR), and overall survival (OS) of the RP2D of vinorelbine combined with a fixed dose of trastuzumab emtansine.

3.0 **ENDPOINTS**

3.1 **Primary endpoints: Phase I**

- Adverse events including dose-limiting toxicities (DLTs) and serious adverse events (SAEs). AEs will be assessed and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.
- The Maximum Tolerated Dose (MTD) of vinorelbine and trastuzumab emtansine combination therapy.

3.1.1 Evaluable Population:

- Evaluable for Safety: Eligible patients who receive at least one dose of vinorelbine or trastuzumab emtansine, including those who experience a DLT as defined in Section 7.3.

3.2 **Primary endpoints: Phase II**

- Progression-Free Survival (PFS): Patients will be evaluated during treatment and by follow-up assessments post-treatment at: 30-days (+5 days). PFS is defined as the time from date from first treatment received on study until documented disease progression or death (by any cause, in the absence of progression). In progression-

free patients, PFS will be censored at the last evaluable tumor assessment (RECIST v1.1).

3.2.1 Evaluable Population:

- Evaluable for Progression-Free Survival (PFS): Eligible patients who receive at least one dose of vinorelbine/trastuzumab emtansine combination therapy.

3.3 **Secondary endpoints**

- Clinical Response including objective response rate (ORR) and clinical benefit rate (CBR): per RECIST v1.1 to RP2D of vinorelbine and trastuzumab emtansine combination therapy. ORR will be calculated as the percentage of patients with best overall response of partial or complete response on therapy (PR or CR). CBR will be calculated as the percentage of patients with PR, CR and SD for >/= 6 months.
- Overall Survival (OS): Patients will be evaluated during treatment and by follow-up assessments post-treatment at: 30-days (+5 days). Follow-up for OS will occur every 12 weeks (±2 weeks) until death or withdrawal of consent from the study. OS is defined as the elapsed time from date from first treatment received on study to death or date of censoring. Patients alive or those lost to follow-up will be censored at the last date of contact (or last date known to be alive).

3.3.1 Evaluable Population:

- Evaluable for Clinical Response (ORR and CBR): Eligible patients who receive at least two cycles of vinorelbine/trastuzumab emtansine combination therapy at the RP2D, have measurable disease at baseline, and have at least one post-baseline disease response assessment.
- Evaluable for Overall Survival (OS): Patients who receive at least one dose of vinorelbine/trastuzumab emtansine combination therapy.

4.0 SUBJECT RECRUITMENT & SCREENING

Men and women of all races and ethnic groups are eligible for this trial. Subjects will be recruited at Sylvester Comprehensive Cancer Center (SCCC) main campus and Satellite Sites (i.e. Deerfield Beach and Plantation). Informed consent forms (ICF) will be translated and available in both English and Spanish.

5.0 PATIENT SELECTION

5.1 Inclusion Criteria

1. Histologically or cytologically documented breast cancer.
2. Metastatic or unresectable locally advanced/recurrent breast cancer.
3. HER2-positive disease documented as: IHC 3+ positive, and/or FISH ≥ 2.0, and/or gene copy number greater than 6, on previously collected tumor or metastatic site. IHC testing, FISH assay(s), and gene copy number may all have been performed; however, a positive result from *only one* of the above is required for eligibility.
4. Documented disease progression on the last regimen by radiographic measurement (progression demonstrated by tumor markers only is unacceptable).
5. Documented disease progression (by investigator assessment) after at least one regimen of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting.
6. For patients with hormone receptor-positive disease: disease progression or recurrence in any setting on prior hormonal therapy, given with or without HER2 directed therapy.
7. Measurable or bone only disease.
8. Prior treatment with a taxane, in the neoadjuvant, adjuvant, locally advanced or metastatic setting.
9. A minimum of 6 weeks of prior trastuzumab for the treatment of metastatic or unresectable locally advanced/recurrent disease is required.
10. Prior use of Pertuzumab in any setting is permitted (but not required).
11. Prior use of Lapatinib in any setting is permitted (but not required).
12. Age ≥ 18 years
13. Life expectancy ≥3 months
14. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See Appendix C for details.
15. Patients must have normal organ and marrow function as defined below:
    - absolute neutrophil count (ANC) >1,500 cells/mm3
    - platelets >100,000 cells/mm3
    - hemoglobin > 9.0 g/dL (Patients are permitted to receive transfused red blood cells to achieve this level.)
    - total bilirubin ≤1.5 X institutional upper limit of normal (ULN) [**Note**: For patients with previously documented Gilbert's syndrome, total bilirubin ≤ 3 mg/dL.]
    - AST(SGOT) ≤2.5 X ULN
    - ALT(SGPT) ≤2.5 X ULN
    - alkaline phosphatase (alk phos) ≤2.5 X ULN
    - serum creatinine < 1.5 X ULN

16. International normalized ratio (INR) < 1.5 X ULN
17. Left ventricular ejection fraction (LVEF) ≥ 50% by either echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA).
18. (This trial is open to males and females.) Negative results of serum pregnancy test for premenopausal women of reproductive capacity and for women < 12 months after menopause. For men and women of childbearing potential, agreement by the patient and/or partner to use **two effective *non-hormonal* forms of barrier contraception at the same time**, throughout treatment on study. Women should agree to continued use for at least *90 days* after the end of treatment. Men should agree to continued use for at least *7 months* after the end of treatment. Examples of non-hormonal barrier contraception include: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide.
19. Ability to understand and willingness to sign a written informed consent and HIPAA document.

5.2 **Exclusion Criteria**

1. Chemotherapy ≤21 days prior to first dose of study treatment
2. If last dose of trastuzumab was:
    - 6mg/kg then ≤21 days prior to first dose of study treatment
    - 4mg/kg then ≤14 days prior to first dose of study treatment
    - 2mg/kg then ≤7 days prior to first dose of study treatment
3. Lapatinib ≤14 days prior to first dose of study treatment
4. Pertuzumab ≤21 days prior to first dose of study treatment
5. Hormone therapy ≤7 days prior to first dose of study treatment
6. Investigational therapy or any other such experimental therapy ≤28 days prior to first dose of study treatment
7. Prior treatment with trastuzumab emtansine, (on or off a study protocol)
8. Prior use of vinorelbine (in any setting).
9. Previous radiotherapy for the treatment of unresectable, locally advanced, recurrent or metastatic breast cancer is <u>not</u> allowed if:
    - The last fraction of radiotherapy has been administered within 14 days prior to study enrollment
    - More than 25% of marrow-bearing bone has been irradiated
10. Brain metastases that are untreated or symptomatic, or require any radiation, surgery, or continued steroid therapy to control symptoms from brain metastases within 14 days of study enrollment.
11. History of intolerance (including Grade 3 or 4 infusion reaction) or hypersensitivity to trastuzumab or murine proteins.
12. History of exposure to the following cumulative doses of anthracyclines:
    - Doxorubicin ≥550mg/m^2
    - Liposomal doxorubicin >500 mg/m^2

- Epirubicin >900 mg/m^2
- Mitoxantrone > 120 mg/m^2
- If another anthracycline, or more than one anthracycline, has been used, the cumulative dose must not exceed the equivalent of ≥550 mg/m^2 doxorubicin.

13. Current peripheral neuropathy of Grade ≥3 per the NCI CTCAE, v4.0
14. The patient has not recovered from any other acute toxicity (to Grade ≤1 as per NCI CTCAE v4.03) prior to study enrollment.
15. History of other malignancy within the last 3 years, except for appropriately treated carcinoma *in situ* of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other cancers with a similar outcome.
16. Cardiopulmonary Function Criteria:
    - Current unstable ventricular arrhythmia requiring treatment
    - History of symptomatic congestive heart failure (CHF) as per New York Heart Association [NYHA] Classes II–IV; see Appendix D for details.
    - History of myocardial infarction or unstable angina within 6 months of study enrollment
    - History of a decrease in LVEF to < 40% or symptomatic CHF with previous trastuzumab treatment
    - Severe dyspnea at rest due to complications of advanced malignancy or requiring current continuous oxygen therapy
17. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease)
    - Major surgical procedure or significant traumatic injury within 28 days - before enrollment or anticipation of the need for major surgery during the course of study treatment
    - Current pregnancy or lactation
    - Current known uncontrolled active infection with HIV, hepatitis B, and/or hepatitis C virus
18. Any uncontrolled, intercurrent illness including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia.
19. Any other serious medical or psychiatric illness/condition likely in the judgment of the Investigator(s) to interfere or limit compliance with study requirements/treatment.

6.0 **Enrollment Procedures**

To enter a patient, the Investigator or Study Team will contact the Clinical Research Services' (CRS) Representative. All eligibility requirements must be reviewed prior to the patient entering the study. The following information must be provided to the CRS Representative:

1) Completed and signed protocol-specific eligibility checklist;
2) All pages of the original signed informed consent form (ICF) including HIPAA Form B;
3) Relevant source documents including but not limited to: subject medical history, concomitant medications and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

6.1 **Cancellation Guidelines**

If a patient does not receive protocol therapy, the patient may withdraw. Contact the CRS Representative, or e-mail the information including the reasons for withdrawal within 10-business days.

6.2 **Emergency Registration**

If an emergency registration takes place after business hours, the items listed above must be submitted by the next business day.

7.0 **STUDY DESIGN**

This is a Phase I/II, single arm, open-label clinical trial designed to establish the recommended phase II dose (RP2D) of vinorelbine with a fixed dose of trastuzumab emtansine. The study will also evaluate the safety and efficacy of the RP2D in patients with HER2-positive metastatic, locally advanced, or unresectable breast cancer. The study will be opened to accrual at the University of Miami Sylvester Comprehensive Cancer Center (SCCC) main campus and constituent satellite sites, Deerfield Beach and Plantation.

This phase I/II study will have a total of 50 enrolled patients, taking into account 10% drop-out in the phase II follow-up. The duration anticipated to enroll all study subjects in Phase I/II is 2 years. The estimated duration for the Investigators to complete this study (Phase I/II) is 4.5 to 5 years.

For the phase I portion, standard 3+3 dose escalation/de-escalation design will be applied. Approximately 15 to 21 patients will be needed to establish the recommended phase II dose (RP2D). For the phase II portion of the study, up to 35 patients will be treated at the RP2D (MTD) including 6 patients treated at RP2D in phase I. Patients may remain on treatment with the combination until disease progression or unmanageable toxicity.

Tumor assessments will be conducted every 6 weeks (±7 days) to week 18. Thereafter, these assessments will be done every 12 weeks (±7 days). These will occur regardless of dose delays or dose interruptions, until Investigator-assessed progressive disease (PD), or death, whichever occurs first. More frequent tumor assessments may be performed as clinically indicated, at the discretion of the treating Investigator.

For the phase II portion of the study - patients who discontinue treatment for reasons other than PD will continue to have required tumor assessments completed until PD or the initiation of a new therapy. Once patients have progressed, they will be followed for survival approximately every 3 months for at least 3 years. Subsequent anti-cancer therapies will be documented until study completion.

Patients who are discontinued from study treatment will return for the Study Treatment Discontinuation Visit approximately 30 days (±7 days) after the last dose of study treatment. See also Protocol Schema.

7.1 **Dose Escalation/ Dose De-Escalation**

For the Phase I portion of the study, patients will be sequentially assigned to up to 5 dose levels according to standard 3+3 dose escalation/de-escalation design, as detailed below. In order to open the next higher cohort all patients within the previous cohort without DLT, must have received **a minimum of 2 cycles.**

Table 1: Dose Escalation Schedule

Dose Escalation Schedule		
Dose Level	**Dose***	
	Vinorelbine ***(mg/m^2)***	***Trastuzumab emtansine*** ***(mg/kg)***
Level -1	20	**3.6 (fixed dose)**
Level 1 (Starting)	**22.5**	
Level 2	25	
Level 3	27.5	
Level 4	30	

7.2 **Dose Escalation Rules**

There will be no dose modification(s) of vinorelbine nor trastuzumab emtansine permitted during the phase I portion of the study. Dose modifications of trastuzumab emtansine and vinorelbine will be permitted only on the phase II portion of the study in cases of hepatotoxicity, neutropenia, thrombocytopenia and neuropathy. Management guidelines and dose modifications are detailed later in the protocol in Section 10.0.

For the phase I portion of the study, if no dose-limiting toxicity (DLT) are reached at a dose level, the dose is escalated for the next cohort of patients. If only one of three patients at a particular dose level is noted to have a DLT, then up to three more patients

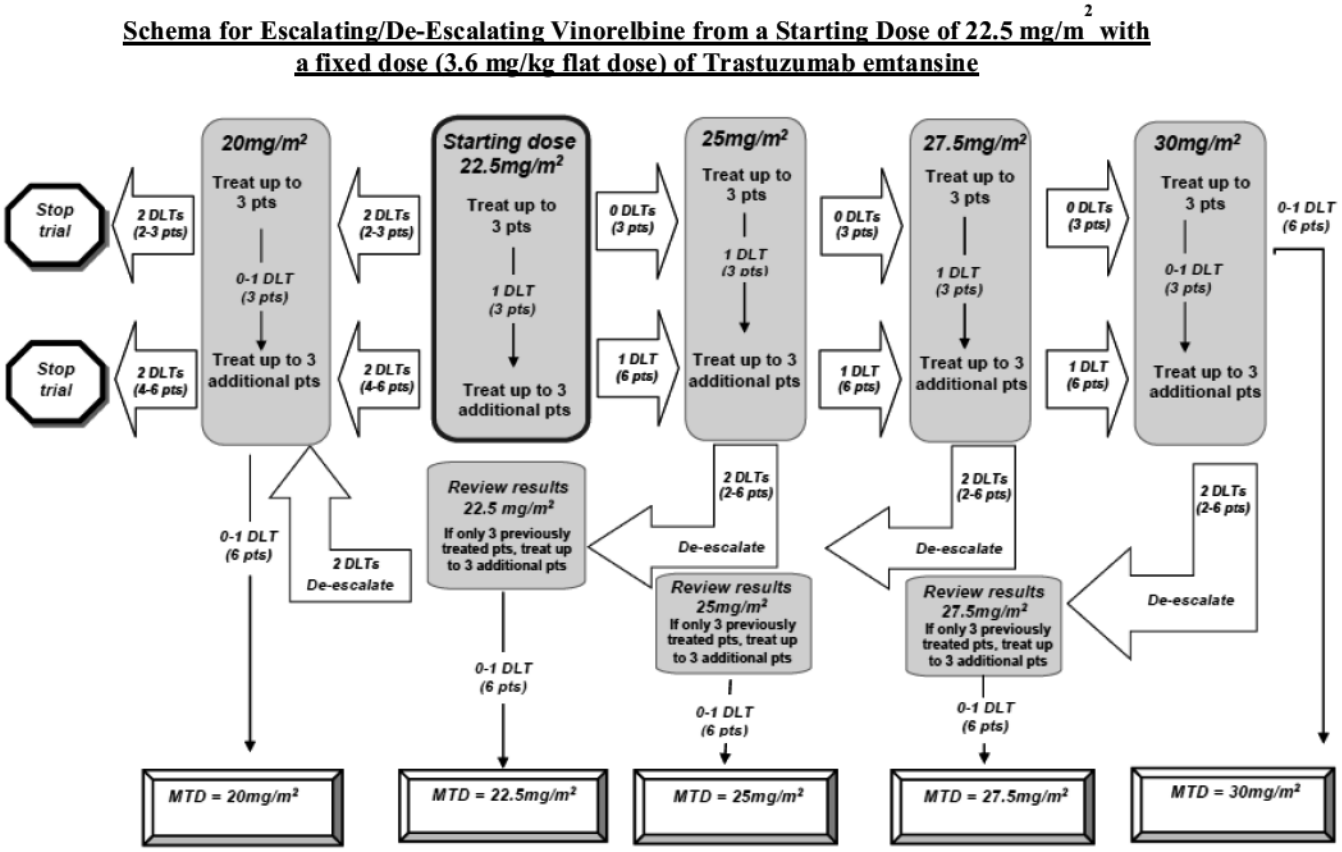
can be entered onto that dose level. If one of the additional group suffer DLT, then dose escalation is stopped (as 2 out of 6 patients would have then suffered a DLT), and the maximum tolerated dose (MTD) would be reached. In this case, three additional patients will be entered on the preceding dose level to ensure that the correct MTD was determined, and this preceding dose will be the dose to be taken into the phase II portion of the trial (see Table 2).

Dose escalation will proceed within each cohort according to the following scheme: (DLT is defined above.)

Table 2: Escalation Scheme

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next (higher) dose level.
1 out of 3	Enter at least 3 more patients at this (same) dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximum tolerated dose (MTD).
≥2 (from the original cohort of 3)	Dose escalation will be stopped. This dose level will be declared the maximally administered dose or MAD (highest dose administered). Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
NOTE: Enrollment of patients will be spaced at least 3 weeks (21 days) apart allowing for evaluation of DLT. Simultaneous enrollment is only permitted under the following circumstances: • If the first patient to receive a dose level does not experience DLT, patients 2 and 3 may be enrolled simultaneously at the same dose level.	

Figure 3: Schema for Phase I Dose Escalation/ De-escalation



Note: The maximum tolerated dose will be the highest tested dose at which no more than 1 patient among 6 experiences DLT. If unacceptable toxicity (DLT in 2 out of 2-6 patients) occurs at a reduced dose of 22.5 mg/m^2, the trial will stop without finding a recommended dose.

7.3 **Dose-Limiting Toxicity (DLT)**

7.3.1 Phase I Protocol-Specified DLT(s)

The occurrence of any of the following during the first 2 cycles (i.e. first 21-42 days) of study treatment will constitute a DLT (only treatment related possible, probable, or define attributions will be considered DLTs):

• Grade 3 or greater non-hematologic toxicities that limit the ability of the patient to tolerate treatment on schedule or are considered particularly problematic in the view of the investigator. If a patient's toxicity does not resolve to less than grade 1 within seven days, this qualifies as a DLT at the discretion of the investigator.

• Grade 3 neuropathy which does not resolve to grade 2 or less within 21 days of treatment.

• Grade 4 neutropenia which does not resolve to grade 2 or less within 14 days despite the use of growth factor support, when permitted per protocol.

• Grade 3 elevation of liver function tests (LFTs) that does not resolve to grade 2 or less within 14 days.

• Re-occurrence of grade 4 neutropenia or grade 3 elevation of LFTs despite two dose modifications or one dose modification and one protocol specified dose delay.

• Grade 3 left ventricular systolic dysfunction that does not resolve to grade 2 or less within 21 days of treatment.

• Grade 5 possible, probable, or definitely related to treatment.

8.0 **TREATMENT PLAN**

One cycle of trastuzumab emtansine/vinorelbine combination treatment is defined as 21-days (i.e. 3 weeks). For each day of treatment, trastuzumab emtansine should always be administered prior to vinorelbine.

8.1 **Trastuzumab emtansine**

For additional information on Trastuzumab emtansine including mechanism of action, drug metabolism, pharmacokinetics & toxicology, known side effects, composition, and storage recommendations, see [Section 9.1].

The recommended (starting) dose of trastuzumab emtansine is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle). *Do not administer* trastuzumab emtansine *at doses greater than 3.6 mg/kg. Do not substitute* trastuzumab emtansine *for or with trastuzumab.*

Closely monitor the infusion site for possible subcutaneous infiltration during drug administration. **Dosing will be according to the actual weight on day 1 of each cycle**.

There will be no dose modifications of trastuzumab emtansine permitted for the phase I portion of the study (fixed dose of 3.6mg/kg for all cohorts). See Section 7.0 and 10.0.

First infusion: Administer infusion over 90 minutes. 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.

Subsequent infusions: Administer over 30 minutes (± 5 minutes) if prior infusions were well tolerated.

8.2 **Vinorelbine**

For additional information on Vinorelbine including mechanism of action, drug metabolism, pharmacokinetics & toxicology, known side effects, composition, and storage recommendations, see [Section 9.2].

The starting dose of vinorelbine is 22.5 mg/m^2 given as a direct intravenous pb over 8 minutes ± (plus or minus) 2 minutes on day 1 and day 8 of every 3-week (i.e. 21-day) cycle. Premedicate with Zofran 8mg. Intravenous doses should be followed by at least 75-125 mL of saline or D5W to reduce the incidence of phlebitis and inflammation.

There will be no dose modifications of vinorelbine permitted during the phase I portion of the protocol. See Section 7.0 and 10.0.

8.3 **Treatment Schema**

Table 3: Treatment Schema

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Trastuzumab emtansine	*Patients should be observed during the infusion and for at least 90 minutes after the 1st dose for fever, chills, or other infusion-related reactions*	*** 3.6 mg/kg*	*IV over 90 minutes for the 1st dose; IV over 30 minutes for subsequent infusions if prior infusions were well tolerated*	*Day 1*	*21 days (3 weeks)*
Vinorelbine	*Premedicate with Zofran 8mg; Intravenous doses should be followed by at least 75-125 mL of saline or D_5W to reduce the incidence of phlebitis and inflammation.*	*** 22.5 mg/m^2*	*Direct IV push over 6-10 minutes*	*Days 1 and 8*	
***Doses as appropriate for **starting** dose level.*					

8.4 **Treatment Dispensation, Compliance and Accountability**

Trastuzumab emtansine and vinorelbine will be administered in the outpatient setting.

If a dose of trastuzumab emtansine or vinorelbine is held due to AE, SAE, or at the investigator's discretion, then he/she should resume treatment at the investigators discretion taking into account all of the dose escalation/modification/discontinuation guidelines provided in Section 7.0 and 10.0, respectively. The procedures can held due to AE, SAE, or at the discretion of the investigator if it is necessary.

8.5 **Supportive Care Guidelines**

8.5.1 Concurrent Medications/ Therapy

Concomitant therapy and premedication are defined as non-investigational medicinal products. **Concomitant therapy includes any prescription medication, over-the-counter preparation, or herbal therapy between the 14 days preceding study enrollment and the Study Treatment Discontinuation Visit.** After the study treatment discontinuation visit, only anti-cancer therapies will be collected as part of the survival follow-up period. Non-protocol anti-cancer therapies administered during the treatment period are not allowed as concomitant therapy.

Premedication is allowed according to standard practice guidelines. Concomitant **use of erythropoiesis-stimulating agents and/or colony-stimulating factors** is allowed per guidelines given in section 8.5.

Palliative radiotherapy may be permitted to treat pre-existing painful bone metastases. However, bone lesions that are radiated prior to start of protocol treatment cannot be used as the bone-only disease for entry onto study (i.e. patients must have other area of bone disease).

Palliative radiotherapy may be permitted to treat brain metastases (for patients who have disease control outside of the brain) but must be completed within 14 days of enrollment on protocol.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator. **Use of bisphosphonates or denosumab** is permitted for the control of bone pain, prevention and/or treatment of bone metastases, and treatment of osteoporosis. If bisphosphonates are required for the treatment of new-onset symptomatic malignancy-associated hypercalcemia, tumor assessments should be performed to assess for potential disease progression.

Patients on **LHRH agonists** may continue if deemed necessary by the investigator as a concomitant medication if used for non−breast cancer indications. This should be approved by the PI.

Patients who are on **anti-coagulant treatment** should be monitored closely during treatment with trastuzumab emtansine. Patients taking anticoagulants or starting anticoagulants while on study should have weekly platelet counts monitored for 2 cycles in order to assess whether a trastuzumab emtansine dose reduction may be necessary.

CYP3A Inhibitors: Exercise caution in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily. Concurrent administration of NAVELBINE with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of adverse reactions. See also Appendix E.

8.5.2 Prohibited Therapy

Use of certain therapies is prohibited during the study prior to discontinuation of study treatment (collectively, these will be referred to as non-protocol therapy). These therapies include anything intended for the treatment of breast cancer, other than trastuzumab emtansine and vinorelbine, whether approved by national health authorities or experimental. This includes cytotoxic chemotherapy, immunotherapy, hormonal therapy (other than megestrol acetate or LHRH agonists used for non−breast cancer indications), and biologic or targeted agents (other than granulocyte colony-stimulating factor and erythropoiesis-stimulating agents).

Radiotherapy for unequivocal disease progression is not permitted while on study treatment, with the exception of new brain metastases or isolated progression of previously treated brain lesions. Patients who have disease control outside of the brain, defined as continued PR or CR of any duration, or stable disease, but who have developed brain metastases that are treatable with radiation will be allowed to continue to receive study therapy until they either experience systemic progression of their disease and/or further progression in the brain that cannot be treated with additional radiation. Patients must not miss more than one cycle of study treatment for the treatment of their brain metastases and must have an ECOG performance status of 0 or 1 to continue on therapy. The Medical Monitor should be informed before a decision is made to resume study treatment after radiotherapy for brain metastases.

In clinical practice, physicians will typically continue HER2-directed therapy with or without chemotherapy in patients with HER2-positive breast cancer who receive local treatment for new brain metastases but otherwise maintain control of their systemic disease. A retrospective study in 86 patients demonstrated that

the median survival of patients with HER2-positive disease (n = 26) who continued treatment with trastuzumab after being diagnosed with brain metastases was significantly longer than for those patients (n = 60) who did not have HER2-positive disease (11.9 months vs. 3 months, p = 0.05) (Church et al. 2008). By allowing continued study treatment after isolated progression in the brain has been identified and treated, this study will explore the safety and efficacy of study treatment regimens in this setting.

8.6 **Duration of Treatment**

Patients may remain on treatment with the vinorelbine/ trastuzumab emtamsine combination until documented disease progression or other criteria for discontinuation is met (Section 11.0).

8.7 **Duration of Follow-Up**

All patients will be followed at 30-days (+5 days) after the last dose of vinorelbine/ trastuzumab emtansine combination therapy.

Patients (regardless of reason for treatment discontinuation) will then be followed for survival until death, lost to follow-up, withdrawal of consent*, or study termination by the Principal Investigator. See Section 12.4 for details.

*Note: Some patients may withdraw their consent from study *treatment* but still agree to participate in survival follow-up. For these patients survival follow-up shall occur until death, lost to follow-up or withdrawal from study. See also section 12.4 for details.

9.0 **AGENTS (DRUG FORMULATION AND PROCUREMENT)**

9.1 **Trastuzumab emtansine**

[Refer to the current version of the Investigator's Brochure for more information.]

9.1.1 Other name(s)

KADCYLA®, T-DM1, TRASTUZUMAB-MCC-DM1, PRO132365, RO5304020, trastuzumab emtansine

9.1.2 Mechanism of Action

Trastuzumab emtansine (Kadcyla®also known as T-DM1, trastuzumab emtansine) is a novel antibody-drug conjugate (ADC) that is specifically designed for the treatment of human epidermal growth factor receptor 2 (HER2)-positive malignancies. Trastuzumab emtansine is composed of trastuzumab, a humanized antibody directed against the extracellular region of HER2; DM1, an anti-microtubule agent derived from maytansine; and 4-[N-

maleimidomethyl]cyclohexane-1-carboxylate (MCC), derived from succinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate (SMCC), a thioether linker that conjugates DM1 to trastuzumab. Trastuzumab emtansine binds to HER2 with affinity similar to that of trastuzumab. After binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization, resulting in intracellular release of DM1 and subsequent cell death. DM1 is an inhibitor of tubulin polymerization. Its parent molecule, maytansine, was studied in approximately 800 patients who were administered maytansine every 3 weeks (q3w) either as a single dose or for 3 consecutive days. Responses were seen in patients with breast and lung cancer; however, because of its narrow therapeutic index, clinical development was not continued.

Trastuzumab emtansine recognizes an epitope on the extracellular domain (ECD) of HER2. Following antigen-specific binding of trastuzumab emtansine to HER2, it is hypothesized that the complex of receptor and ADC undergoes receptor-mediated internalization into endosomes. Following internalization, the endosome is fused with the lysosomal compartment, the ADC undergoes lysosomal degradation and the active metabolites lys-MCC-DM1 and DM1 are released [13,14]. DM1 is a highly potent thiolcontaining derivative of maytansine and is synthesized from ansamitocin P3. DM1 binds β-tubulin to inhibit tubulin polymerization, resulting in cell death [7]. In vitro studies of trastuzumab emtansine demonstrate enhanced cytotoxicity in HER2-overexpressing breast cancer cell lines compared to breast cancer cell lines with low HER2 expression.

The requirement for receptor binding for trastuzumab emtansine activity has been demonstrated in vivo where a non-HER2-binding isotype-matched ADC served as a control. In these experiments, the control antibody-MCC-DM1 had no anti-tumor activity in the HER2-positive for breast cancer model whereas trastuzumab emtansine exhibited significant anti-tumor activity.

9.1.3 Drug Metabolism, Pharmacokinetics and Toxicology

The recommended dose of trastuzumab emtansine for breast cancer is 3.6 mg/kg given as an IV infusion q3w. The PK analysis from the Phase I study (TDM3569g) following administration of 0.3 mg/kg to 4.8 mg/kg trastuzumab emtansine q3w showed that at the dose of 3.6 mg/kg q3w, the systemic clearance was approximately 12.7 mL/day/kg and the elimination half-life was approximately 3.1 days. The clearance of trastuzumab emtansine was nonlinear at doses less than or equal to 1.2 mg/kg. At all dose levels, clearance of trastuzumab emtansine was faster than that of trastuzumab. A qw dosing regimen was also evaluated in Study TDM3569g, and 2.4 mg/kg qw was identified as the MTD for qw dosing. Key trastuzumab emtansine PK parameters (ie, CL, Vss and t1/2) at 2.4 mg/kg qw were similar to those observed at 3.6 mg/kg q3w dosing.

There was no accumulation of trastuzumab emtansine when given q3w. The estimated volume of distribution was 30.7 to 58.4 mL/kg across all dose levels tested. Measurable levels of free DM1 were found, but are approximately 10,000 fold (by mass ratio) and approximately 50-fold (by molar ratio) lower than trastuzumab emtansine levels.

In the Phase II and III studies in MBC patients (TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976 and TDM4370g/BO21977), PK parameter values for trastuzumab emtansine after a 3.6 mg/kg dose given q3w were similar to those observed for the q3w dosing regimen in the Phase I study.

A robust population PK (popPK) model has been developed using the accumulated clinical data. The popPK model can predict trastuzumab emtansine exposure and interindividual variability in a large and representative patient population that has received prior trastuzumab-based therapy. The population parameter values for clearance and volume of distribution of the central compartment (Vc) for a typical person were estimated to be 0.68 L/day and 3.13 L, respectively. The popPK analysis showed a mean t½ of 3.94 days for trastuzumab emtansine. No adjustments in the starting dose of trastuzumab emtansine appear to be necessary in patient subpopulations based on data available to date, as it appears that dose adjustments would be unlikely to result in a meaningful reduction in inter-individual PK variability.

9.1.4 Management of Agent-Specific Adverse Events

The safety plan for patients in the trastuzumab emtansine treatment arm is based on nonclinical toxicities of trastuzumab emtansine, the clinical experience with this molecule in completed and ongoing studies, and clinical toxicities related to its components (trastuzumab and maytansine, the parent drug of DM1).

The following summarizes the important risks associated with trastuzumab emtansine identified in multiple breast cancer studies to date.

Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome have been reported in clinical trials with trastuzumab emtansine (Kadcyla® [trastuzumab emtansine]. Genentech, Inc. February 2013). Pneumonitis at an incidence of 0.8% (7 out of 884 treated patients) has been reported, with one case of grade 3 pneumonitis. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. In the randomized trial TDM 4370g/BO21977 (EMILIA) the overall frequency of pneumonitis was 1.2%. Treatment included administration of steroids, oxygen, and study drug discontinuation (Data on File. Genentech, Inc.)

Permanently discontinue treatment with trastuzumab emtansine in patients diagnosed with ILD or pneumonitis (Kadcyla® [trastuzumab emtansine]. Genentech, Inc. February 2013). Patients with dyspnea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary toxicity.

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic transient increases in the concentrations of serum transaminases (Grade 1 − 4 transaminitis), has been observed while on treatment with trastuzumab emtansine in clinical trials (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). A cumulative effect of trastuzumab emtansine on transaminases has been observed (Data on File. Genentech, Inc.)

Cases of severe hepatotoxicity, including death due to drug-induced liver injury (DILI) and hepatic encephalopathy, have been observed in patients treated with

trastuzumab emtansine (Trastuzumab Emtansine. Investigator's Brochure Version 7). While there is evidence of drug-induced liver toxicity (predominantly in the form of asymptomatic increases in the concentrations of serum transaminases) in patients treated with trastuzumab emtansine, its potential to cause liver injury with clinically meaningful changes in liver function is unclear as the observed cases were confounded by concomitant medications with known hepatotoxic potential and/or underlying conditions. Nevertheless, a contributory role of trastuzumab emtansine in these cases cannot be excluded.

Monitor serum transaminases and bilirubin prior to initiation of trastuzumab emtansine treatment and prior to each trastuzumab emtansine dose (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Reduce the dose or discontinue trastuzumab emtansine as appropriate in cases of increased serum transaminases and/or total bilirubin. Permanently discontinue trastuzumab emtansine treatment in patients with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN. Trastuzumab emtansine has not been studied in patients with serum transaminases > 2.5 x ULN or bilirubin > 1.5 x ULN prior to the initiation of treatment.

Cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). NRH was also observed in one fatal case of hepatic failure. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension. NRH should be considered in all patients with clinical symptoms of portal

hypertension and/or a cirrhosis-like pattern seen on computed tomography (CT) scan of the liver but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with trastuzumab emtansine. Diagnosis of NRH can be confirmed only by histopathology. Upon diagnosis of NRH, trastuzumab emtansine treatment must be permanently discontinued.

Left Ventricular Dysfunction

Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). A decrease of LVEF to < 40% has been observed in patients treated with trastuzumab emtansine. In the randomized trial, TDM 4370g/BO21977 (EMILIA), left ventricular dysfunction occurred in 1.8% of patients in the trastuzumab emtansine -treated group and 3.3% of patients in the lapatinib plus capecitabine-treated group.

Assess LVEF prior to initiation of trastuzumab emtansine and at regular intervals (e.g. every three months) during treatment to ensure the LVEF is within the institution's normal limits (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Treatment with trastuzumab emtansine has not been studied in patients with LVEF < 50% prior to initiation of treatment. If, at routine monitoring, LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold trastuzumab emtansine and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue trastuzumab emtansine if the LVEF has not improved or has declined further.

Infusion-related Reactions

Treatment with trastuzumab emtansine has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) and/or hypersensitivity; treatment with trastuzumab emtansine is not recommended for these patients (Kadcyla® Prescribing Information. Genentech, Inc. February 2013).

Infusion-related reactions, 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 (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). In the randomized trial, TDM 4370g/BO21977 (EMILIA), the overall frequency of IRRs in patients treated with trastuzumab emtansine was 1.4%. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Trastuzumab emtansine treatment should be interrupted in patients with severe IRR. Trastuzumab emtansine

treatment should be permanently discontinued in the event of a life-threatening IRR. Patients should be observed closely for IRR reactions, especially during the first infusion.

One case of a serious, allergic/anaphylactic-like reaction has been observed in clinical trials of single-agent trastuzumab emtansine (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

Thrombocytopenia

Thrombocytopenia, or decreased platelet count, was reported in clinical trials of trastuzumab emtansine (103 of 884 treated patients with ≥ Grade 3; 283 of 884 treated patients with any Grade) (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). The majority of these patients had Grade 1 or 2 events (< LLN to ≥ 50,000/mm3) with the nadir occurring by day 8 and generally improving to Grade 0 or 1 (≥ 75,000 /mm3) by the next scheduled dose. In clinical trials of trastuzumab emtansine, the incidence and severity of thrombocytopenia were higher in Asian patients. Cases of bleeding events with a fatal outcome have been observed. Severe cases of hemorrhagic events, including central nervous system hemorrhage, have been reported in clinical trials with trastuzumab emtansine; these events were independent of ethnicity. In some of the observed cases the patients were also receiving anti-coagulation therapy.

Patients with thrombocytopenia (≤100,000/mm3) and patients on anti-coagulant treatment should be monitored closely while on 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/mm3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (< 50,000/mm3) do not administer trastuzumab emtansine until platelet counts recover to Grade 1 (≥ 75,000/mm3).

Severe Hemorrhage

Severe hemorrhage with fatal outcomes including central nervous system bleeding has been reported in patients receiving trastuzumab emtansine. This drug should be used with caution in patients with thrombocytopenia (see above). Anti-coagulation therapy and anti-platelet agents may increase the risk of bleeding. Avoidance of these agents, or additional monitoring with concomitant use, may be indicated.

Embryo-Fetal Toxicity

Trastuzumab emtansine can cause fetal harm when administered to a pregnant woman (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). There are no adequate and well-controlled studies of trastuzumab emtansine in pregnant women and no reproductive and developmental toxicology studies have been conducted with trastuzumab emtansine. Nevertheless, treatment with trastuzumab, the antibody component of trastuzumab emtansine, during pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. DM1, the cytotoxic component of trastuzumab emtansine, can be expected to cause embryo-fetal toxicity based on its mechanism of action.

If trastuzumab emtansine is used during pregnancy, or if the patient becomes pregnant while receiving trastuzumab emtansine, apprise the patient of the potential hazard to the fetus (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). Verify pregnancy status prior to the initiation of trastuzumab emtansine. Advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and after treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant. If trastuzumab emtansine is administered during pregnancy or if a patient becomes pregnant while receiving trastuzumab emtansine, immediately report exposure to the Genentech Adverse Event Line at 1-888-835-2555. Encourage women who may be exposed during pregnancy to enroll in the MotHER Pregnancy Registry by contacting 1-800-690-6720.

It is not known whether trastuzumab emtansine, specifically, is excreted in human milk, but IgG is known to be excreted in human milk (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). In lactating monkeys, trastuzumab was excreted in small amounts (about 0.3% of maternal serum concentrations) in breast milk after post-partum doses of 25 mg/kg (about 7 times the clinical dose of trastuzumab emtansine). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from trastuzumab emtansine, a decision should be made whether to discontinue nursing or discontinue trastuzumab emtansine, taking into account the importance of the drug to the mother.

Neurotoxicity

Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of trastuzumab emtansine (14 of 884 treated patients with ≥ Grade 3; 196 of 884 treated patients with any Grade) (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). In the EMILIA study, the overall frequency of peripheral neuropathy was 21.2% in the trastuzumab emtansine-treated group and 13.5% in the lapatinib plus capecitabine-treated group. The incidence of ≥ Grade 3 peripheral neuropathy was 2.2% in the

trastuzumab emtansine -treated group and 0.2% in the lapatinib plus capecitabine-treated group. Trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2. Patients should be clinically monitored on an ongoing basis for signs or symptoms of neurotoxicity.

Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed (Kadcyla® Prescribing Information. Genentech, Inc. February 2013). These reactions, observed more frequently within 24 hours of infusion, were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Specific treatment for trastuzumab emtansine extravasation is unknown. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

9.1.5 Composition

Trastuzumab emtansine is provided as a lyophilized product. The trastuzumab emtansine Drug Substance is produced in two steps from antibody (trastuzumab), drug (DM1), and linker (SMCC). A predefined molar ratio of SMCC is mixed with the antibody: the N-hydroxysuccinimide ester of SMCC reacts with antibody lysine residues to produce the maleimide-modified antibody (trastuzumab-MCC). Following purification by ultrafiltration/diafiltration (UF/DF), the sulfhydryl-containing cytotoxic drug (DM1) is added, and the subsequent reaction produces the thioether-linked conjugate. Trastuzumab emtansine conjugate is purified by UF/DF.

9.1.6 Storage Recommendations and Dosage Forms

Trastuzumab emtansine is supplied as a single-use lyophilized formulation in a colorless 20-mL Type I glass vial closed by means of a FluroTec-coated stopper and an overseal with flip-off cap. Upon receipt of trastuzumab emtansine, vials should be refrigerated at 2°C−8°C (36°F−46°F) until use. THE VIAL MUST NOT BE FROZEN OR SHAKEN.

Trastuzumab emtansine must be stored in the original carton to protect it from light. Do not use the product beyond the expiration date provided by the manufacturer. The reconstituted product contains no preservative and is intended for single use only. Any remaining medication should be discarded. All vials of trastuzumab emtansine should be handled by appropriately trained site staff wearing gloves and using appropriate procedures in place at the clinical site for preparation of chemotherapeutic drugs. Vials should be visually inspected upon receipt to ensure that they are intact without exterior contamination. Discard any cracked vials and report vials with surface contamination to the clinical site

manager for assessment. The lyophilized product should be reconstituted using Sterile Water for Injection (SWFI).

Using a new syringe, 8 mL of SWFI should be added to the vial and the vial swirled gently until the product is completely dissolved. The vial should not be shaken. The resulting product contains 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 60 mg/mL sucrose, and 0.02% (w/v) polysorbate 20. Each 20-mL vial contains enough trastuzumab emtansine to allow delivery of 160 mg trastuzumab emtansine.

The reconstituted product contains no preservative and is intended for single use only. The vial should be inspected to ensure the reconstituted product is a clear colorless solution, and is free of particulates before proceeding. Drug from any vial that appears abnormal upon inspection should not be administered to patients. Using a new syringe, the indicated volume of trastuzumab emtansine solution should be removed from the vial(s) and added to the IV bag containing at least 250 mL of 0.45% sodium chloride (preferred) or 0.9% sodium chloride injection and gently inverted to mix the solution. A 0.22-µm non-protein adsorptive polyethersulfone in-line filter is recommended when using 0.45% sodium chloride and required when using 0.9% sodium chloride injection. The solution of trastuzumab emtansine should not be shaken. The solution of trastuzumab emtansine for infusion should be used immediately. If not used immediately, storage times should not be longer than 24 hours at 2°C−8°C (36−46°F) for solutions of trastuzumab emtansine diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin, polypropylene, or polyethylene bags containing 0.45% or 0.9% Sodium Chloride for Injection, USP.

Formulation:

Trastuzumab emtansine single-use vials contain 100 mg per vial or 160 mg per vial of trastuzumab emtansine as lyophilized powder.

Preparation:

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is trastuzumab emtansine and not trastuzumab.

Administration:

• Administer trastuzumab emtansine as an intravenous infusion only with a 0.22 micron in-line non-protein adsorptive polyethersulfone (PES) filter. Do not administer as an intravenous push or bolus.

• Do not mix trastuzumab emtansine, or administer as an infusion, with other medicinal products.

Reconstitution:

• Use aseptic technique for reconstitution and preparation of dosing solution. Appropriate procedures for the preparation of chemotherapeutic drugs should be used.

• Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg trastuzumab emtansine vial, or 8 mL of Sterile Water for Injection into the 160 mg trastuzumab emtansine vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do not shake. Inspect the reconstituted solution for particulates and discoloration.

• The reconstituted solution should be clear to slightly opalescent and free of visible particulates. The color of the reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particulates or is cloudy or discolored.

• The reconstituted lyophilized vials should be used immediately following reconstitution with Sterile Water for Injection. If not used immediately, the reconstituted trastuzumab emtansine vials can be stored for up to 4 hours in a refrigerator at 2ºC to 8ºC (36°F to 46°F); discard unused trastuzumab emtansine after 4 hours. Do not freeze.

• The reconstituted product contains no preservative and is intended for single-use only.

Dilution:

Determine the correct dose (mg) of trastuzumab emtansine.

• Calculate the volume of the 20 mg/mL reconstituted trastuzumab emtansine solution needed.

• Withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Do not use Dextrose (5%) solution.

• Gently invert the bag to mix the solution in order to avoid foaming.

• The diluted trastuzumab emtansine infusion solution should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 4 hours prior to use. Do not freeze or shake.

9.1.7 Dispensation and Accountability

Trastuzumab emtansine will be supplied by **Genentech, Inc.** for the phase 1 portion of the study. For the phase 2 portion of the study, drug supply will be determined after the outcome of the phase 1 study.

Reconciliation: **Genentech, Inc.** agrees to conduct reconciliation for the product, reconciliation periodicity and format, but agree at minimum to exchange quarterly (no less frequently than monthly) line listings of cases received by the other party. If discrepancies are identified, **Genentech, Inc**. will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

9.2 **Vinorelbine**

[Refer to the FDA-approved package insert for more information.]

9.2.1 Other name(s)

Vinorelbine tartrate, NAVELBINE®

9.2.2 Mechanism of Action

Vinorelbine (NAVELBINE®) is a vinca alkaloid that interferes with microtubule assembly. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Vinorelbine may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca++-transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. Vinorelbine inhibited mitotic microtubule formation in intact mouse embryo tectal plates at a concentration of 2 μM inducing a blockade of cells at metaphase, but produced depolymerization of axonal microtubules at a concentration 40 μM, suggesting a modest selectivity of vinorelbine for mitotic microtubules.

9.2.3 Drug Metabolism, Pharmacokinetics and Toxicology

The pharmacokinetics of vinorelbine (NAVELBINE®) were studied in 49 patients who received doses of 30 mg/m administered as 15- to 20-minute constant-rate infusions. Vinorelbine concentrations in plasma decay in a triphasic manner. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr/kg.

Distribution

Steady-state volume of distribution (V_{ss}) values range from 25.4 to 40.1 L/kg. Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in human plasma over a concentration range of 234 to 1169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

Metabolism
Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces.

Two metabolites of vinorelbine have been identified in human blood, plasma, and urine; vinorelbine Noxide and deacetylvinorelbine. Deacetylvinorelbine has been demonstrated to be the primary metabolite of vinorelbine in humans, and has been shown to possess antitumor activity similar to vinorelbine. Therapeutic doses of vinorelbine (30 mg/m) yield very small, if any, quantifiable levels of either metabolite in blood or urine. The metabolism of vinorelbine is mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily.

Excretion
After intravenous administration of radioactive vinorelbine, approximately 18% and 46% of administered radioactivity was recovered in urine and feces, respectively. In a different study, 10.9% + 0.7% of a 30-mg/m intravenous dose was excreted as parent drug in urine.

Specific Populations
Elderly: Age has no effect on the pharmacokinetics (CL, V and t) of vinorelbine.

Drug Interactions
The pharmacokinetics of vinorelbine are not influenced by the concurrent administration of cisplatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of NAVELBINE has not been studied. Vinorelbine has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay.

Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m , approximately one third the human dose) or alternate-day schedule (4.2 mg/m, approximately 0.14 times the human recommended dose) prior to and during mating. In male rats, administration of vinorelbine twice weekly for 13 or 26 weeks at dose levels of 2.1 and 7.2 mg/m (approximately 0.07 and 0.24 times the recommended human dose), respectively, resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

9.2.4 Management of Agent-Specific Adverse Events

The results of clinical studies show that treatment with vinorelbine (NAVELBINE®) is associated with relatively mild or moderate side-effects, the most frequent side effect being neutropenia. Apart from hair loss, nausea and

vomiting, which are typical side-effects of treatment with cytostatic agents, gastrointestinal side-effects are also frequently seen; however, these are rarely of a serious nature. In one study, Grade 3 or 4 nausea and vomiting were reported in 4% of the patients. 30% of patients experienced mild or moderate constipation and neurotoxicity was observed in 20% of patients. Those AEs were reversible and seldom serious. Other side-effects such as chest pain and respiratory problems are relatively rare among patients treated with vinorelbine. The most frequently observed abnormal laboratory value is increased ALP levels, which may be related to both vinorelbine treatment or a high incidence of liver or bone metastases in the patients treated (Pierre Fabre).

Myelosuppression

Myelosuppression manifested by neutropenia, anemia and thrombocytopenia occur with NAVELBINE® as a single agent and in combination with cisplatin. Neutropenia is the major dose-limiting toxicity with NAVELBINE. Grade 3-4 neutropenia occurred in 53% of patients treated with NAVELBINE at 30 mg/m per week. Dose adjustment due to myelosuppression occurred in 51% of patients. In clinical trials with NAVELBINE administered at 30 mg/m per week, neutropenia resulted in hospitalizations for pyrexia and/or sepsis in 8% of patients. Death due to sepsis occurred in 1% of patients. Neutropenia nadirs occur between 7 and 10 days after dosing with neutropenia count recovery usually occurring within the following 7 to 14 days. Monitor complete blood counts prior to each dose of NAVELBINE. Do not administer NAVELBINE to patients with neutrophil counts <1,000 cells/mm. Adjustments in the dosage of NAVELBINE should be based on neutrophil counts obtained on the day of treatment.

Hepatic Toxicity

Drug-induced liver injury manifest by elevations of aspartate aminotransferase and bilirubin can occur in patients receiving NAVELBINE alone or in combination with cytotoxic agents. Assess hepatic function prior to initiation of NAVELBINE and periodically during treatment. Reduce the dose of NAVELBINE for patients who develop elevations in total bilirubin > 2 times upper limit of normal.

Severe Constipation and Bowel Obstruction

Severe and fatal paralytic ileus, constipation, intestinal obstruction, necrosis, and perforation occur with NAVELBINE administration. Institute a prophylactic bowel regimen to mitigate potential constipation, bowel obstruction and/or paralytic ileus, considering adequate dietary fiber intake, hydration, and routine use of stool softeners.

Extravasation and Tissue Injury

Extravasation of NAVELBINE can result in severe irritation, local tissue necrosis and/or thrombophlebitis. If signs or symptoms of extravasation occur, immediately stop administration of NAVELBINE and institute recommended management procedures.

Neurologic Toxicity

Sensory and motor neuropathies, including severe neuropathies, occur in patients receiving NAVELBINE. Monitor patients for new or worsening signs and symptoms of neuropathy such as paresthesia, hyperesthesia, hyporeflexia and muscle weakness while receiving NAVELBINE. Discontinue NAVELBINE for NCI CTCAE Grade 2 or greater neuropathy.

Pulmonary Toxicity and Respiratory Failure

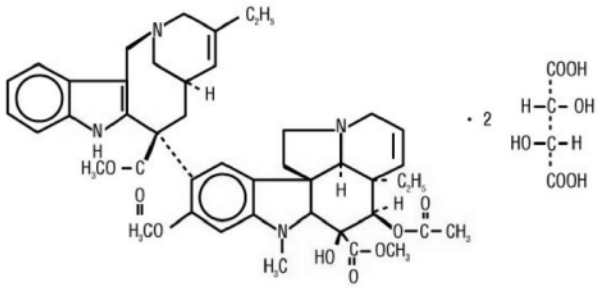
Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS) occurs with use of NAVELBINE. Interstitial pneumonitis and ARDS included fatalities. The mean time to onset of interstitial pneumonitis and ARDS after vinorelbine administration was one week (range 3 to 8 days). Interrupt NAVELBINE in patients who develop unexplained dyspnea, or have any evidence of pulmonary toxicity. Permanently discontinue NAVELBINE for confirmed interstitial pneumonitis or ARDS.

Embryo-Fetal Toxicity

NAVELBINE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies in mice and rabbits, embryo and fetal toxicity were observed with administration of vinorelbine at doses approximately 0.33 and 0.18 times the human therapeutic dose, respectively. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during therapy with NAVELBINE.

9.2.5 Composition

Vinorelbine (NAVELBINE®, vinorelbine tartrate) is a semi-synthetic vinca alkaloid for intravenous injection. Chemically, vinorelbine tartrate is 3',4'-didehydro-4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2, 3-dihydroxybutanedioate (1:2)(tartrate)] and has the following structure:



$C_{45}H_{54}N_4O_8 \bullet 2C_4H_6O_6$

M.W. 1079.12

NAVELBINE® Injection is a sterile nonpyrogeinc aqueous solution. Each milliliter of solution contains vinorelbine tartrate equivalent to 10 mg vinorelbine in Water for Injection. The pH of NAVELBINE Injection is approximately 3.5.

9.2.6 Storage Recommendations and Dosage Forms

Vinorelbine (NAVELBINE®) is delivered in vials containing 10 mg/ml and must be stored at 2-8 degrees celsius. Vinorelbine is prepared with a minimum of 50 ml sterile saline solution (sodium chloride) 0.9% or glucose 5%. After preparation vinorelbine must be used within 12 hours; however, 24 hours if the solution is stored in refrigerator.

NAVELBINE Injection is a clear, colorless to pale yellow aqueous solution available in single-dose vials with royal blue caps, individually packaged in a carton as:

- 10 mg/1 mL (NDC 64370-532-01).
- 50 mg/5 mL (NDC 64370-532-02).

Store the vials at 2° to 8°C (36° to 46°F) in the carton. Protect from light. DO NOT FREEZE. Unopened vials of NAVELBINE are stable at 25°C (77°F) for up to 72 hours.

NAVELBINE is a cytotoxic drug. Follow applicable special handling and disposal procedures.

9.2.7 Dispensation and Accountability

Vinorelbine (NAVELBINE®) will be commercially supplied. **This product is for intravenous (IV) use only. NAVELBINE® must only be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any NAVELBINE® is injected. Intrathecal administration of other vinca alkaloids has resulted in death.**

Syringes containing this product should be labeled "WARNING – FOR IV USE ONLY. FATAL if given intrathecally."

10.0 TREATMENT/ DOSE MODIFICATIONS/ DOSE DELAYS

10.1 Unacceptable Toxicity

If a treatment-related (possible, probable, or definite) death occurs, enrollment will be suspended and continuation of the study will be reassessed by the DSMC (see Section 16.0).

For the purposes of safety monitoring, we define unacceptable toxicity to be any of the following treatment-related (possible, probable, or definite) adverse events:

- Grade 3 neuropathy which does not resolve to grade 2 or less within two cycles of treatment
- Grade 4 neutropenia which does not resolve to grade 2 or less within 14 days
- Grade 3 elevation of liver function tests (LFTs) that does not resolve to grade 2 or less within 14 days
- Re-occurrence of grade 4 neutropenia or grade 3 elevation of LFTs despite 2 dose modifications or one dose medication and one protocol specified dose delay.
- Grade 3 left ventricular systolic dysfunction that does not resolve to grade 2 or less within one cycle of treatment

NOTE: Grade 5 (death) not related to treatment will not be considered an unacceptable adverse event.

10.2 Dose Modification/ Dose Delay Guidelines for Trastuzumab emtansine

10.2.1 Phase I

There will be no dose modifications of trastuzumab emtansine permitted for the phase I portion of the study (fixed dose of 3.6mg/kg for all cohorts).

10.2.2 Phase II

Once the RP2D dose of the combination of vinorelbine and trastuzumab emtansine is determined in the phase I portion of the protocol, it will be the starting dose used to treat all patients during phase II. However, modifications in both drugs will be permitted, as detailed below.

Trastuzumab emtansine dose will not be re-escalated after a dose reduction is made.

If a planned dose is delayed or missed, it should be administered as soon as possible; do not wait until the next planned cycle. The schedule of administration should be adjusted

to maintain a 3- week interval between doses. The infusion may be administered at the dose and rate the patient tolerated in the most recent infusion.

The infusion rate of trastuzumab emtansine should be slowed or interrupted if the patient develops an infusion-related reaction. Permanently discontinue trastuzumab emtansine for life-threatening infusion related reactions, and discontinue participation on protocol.

Management of increased serum transaminases, hyperbilirubinemia, left ventricular dysfunction, thrombocytopenia, pulmonary toxicity or peripheral neuropathy may require temporary interruption, dose reduction or treatment discontinuation of trastuzumab emtansine as per guidelines provided in Tables 4 to 7.

Table 4: Recommended Dose Reduction Schedule for Adverse Events

Dose Reduction Schedule	**Dose Level**
Starting dose	3.6 mg/kg
First dose reduction	3 mg/kg
Second dose reduction	2.4 mg/kg
Requirement for further dose reduction	Discontinue treatment

Hepatotoxicity

Serious hepatotoxicity has been reported, including liver failure and death in patients treated with trastuzumab emtansine. Monitor serum transaminases and bilirubin prior to initiation of trastuzumab emtansine treatment and prior to each trastuzumab emtansine dose.

Patients with increased total bilirubin because of Gilbert syndrome are allowed to continue trastuzumab emtansine dosing without a dose hold or dose modification if the direct (conjugated) bilirubin level is within the normal reference range.

A reduction in the dose of trastuzumab emtansine is recommended in the case of hepatotoxicity exhibited as increases in serum transaminases and/or hyperbilirubinemia (see Tables 5 and 6).

Table 5: Dose Modification Guidelines for Increased Serum Transaminases (AST/ALT)

Grade 2 (> 2.5 to ≤ 5 × ULN)	**Grade 3 (> 5 to ≤ 20 × ULN)**	**Grade 4 (> 20 × ULN)**
Treat at same dose level.	Do not administer trastuzumab emtansine until AST/ALT recovers to Grade ≤ 2, and then reduce one dose level.	Permanently discontinue trastuzumab emtansine.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

Table 6: Dose Modification Guidelines for Hyperbilirubinemia

Grade 2 (> 1.5 to ≤ 3 × ULN)	**Grade 3 (> 3 to ≤ 10 × ULN)**	**Grade 4 (> 10 × ULN)**
Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1, and then treat at same dose level.	Do not administer trastuzumab emtansine until total bilirubin recovers to Grade ≤ 1, and then reduce one dose level.	Permanently discontinue trastuzumab emtansine.

Permanently discontinue trastuzumab emtansine treatment in patients with serum transaminases > 3 x ULN and concomitant total bilirubin > 2 x ULN.

Permanently discontinue trastuzumab emtansine in patients diagnosed with nodular regenerative hyperplasia (NRH).

Thrombocytopenia

Patients receiving trastuzumab emtansine who experience any of the following events listed below, after adequate recovery to a platelet count of Grade ≤ 1 (≥ 75,000/μL), may continue treatment with trastuzumab emtansine at one dose level reduction in subsequent treatment cycles (see Table 4). Patients who experience any event listed below while receiving the 2.4 mg/kg dose will be discontinued from study treatment. A dose delay of up to 42 days from the last dose received is permitted. Platelet counts should be obtained no less frequently than every week to evaluate recovery whenever any of the events listed below occur. If platelet counts do not recover to Grade ≤ 1 within 42 days from the last dose received, the patient will be discontinued from study treatment. No re-escalation of the trastuzumab emtansine dose is allowed.

Note: although CBCs with platelets are required within 72 hours prior to study treatment administration at each cycle, the investigator may monitor platelet counts (or any other laboratory test) more frequently as clinically indicated. Dose reduce in subsequent treatment cycles in the event of:

• Platelet count < 10,000/μL of any duration

• Platelet count of Grade 4 (< 25,000/μL) that does not recover to Grade ≤ 1 after 7 days from the onset date of the Grade 4 event

• For patients on anticoagulation therapy, platelet count of Grade ≥ 3 (< 50,000/μL) of any duration.

Left Ventricular Dysfunction (LVEF) (See Appendix E for Management Algorithm)

Patients without significant cardiac history and with a baseline LVEF ≥ 50% as determined by ECHO or MUGA scan are eligible for study participation. Ejection fractions will be monitored prior to cycle 3 and every four cycles thereafter (at any timepoint within respective cycles) until the assessment at the Study Treatment Discontinuation Visit. Table 7 and Appendix E summarizes the management of trastuzumab emtansine on the basis of measured LVEF and changes in LVEF from baseline in patients. If the LVEF is reported as a range, the median of the range should be taken. If an investigator is concerned that an AE may be related to cardiac dysfunction, an additional LVEF measurement may be performed. Trastuzumab emtansine will be discontinued in any patient who develops symptomatic CHF. CHF should be treated and monitored according to standard medical practice.

The decision to stop or continue trastuzumab emtansine should be based on the algorithm shown in Table 7. Trastuzumab emtansine must be discontinued in all patients for whom a confirmed drop of LVEF to below 40% is documented (with a repeat assessment within 21 days). For patients whose LVEF drops to values between 40% and 45% with an absolute decrease in LVEF of ≥ 10% points from baseline, trastuzumab emtansine should be held. For these patients, the LVEF should be repeated in 21 days, and trastuzumab emtansine should be discontinued if the LVEF has not recovered to within 10% absolute difference below baseline. If clinically significant cardiac dysfunction or cardiac failure develops or persists or if significant medical management is required to maintain ejection fraction, the patient should be discontinued from study treatment.

Table 7: Dose Modifications for Left Ventricular Dysfunction

Symptomatic CHF	**LVEF < 40%**	**LVEF 40% to ⩽ 45% and decrease is ⩾ 10% points from baseline**	**LVEF 40% to ⩽ 45% and decrease is < 10% points from baseline**	**LVEF > 45%**
Discontinue trastuzumab emtansine	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue trastuzumab emtansine.	Do not administer trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue trastuzumab emtansine.	Continue treatment with trastuzumab emtansine. Repeat LVEF assessment within 3 weeks.	Continue treatment with trastuzumab emtansine.
CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction				
See also Appendix E for Management Algorithm				

Pulmonary Toxicity

Trastuzumab emtansine should be permanently discontinued in patients diagnosed with interstitial lung disease (ILD) or pneumonitis.

Peripheral Neuropathy

Trastuzumab emtansine should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2.

Trastuzumab emtamsine overdosage

There is no known antidote for overdose of trastuzumab emtansine. In clinical trials, overdose of trastuzumab emtansine has been reported at approximately two times the recommended dose which resulted in Grade 2 thrombocytopenia (resolved 4 days later) and one death. In the fatal case, the patient incorrectly received trastuzumab emtansine at 6 mg/kg and died approximately 3 weeks following the overdose; a cause of death and a causal relationship to trastuzumab emtansine were not established.

10.3 **Dose Modification/ Dose Delay Guidelines for Vinorelbine**

There will be no dose modification of vinorelbine during the phase I portion of the protocol.

10.3.1 Phase I Dose Delays

If neutrophils < 1.5 x 10^9/L or platelets < 75 x 10^9/L when measured on the **Day 1** of any given cycle of treatment, the treatment will be postponed for 1 week until the blood counts have returned to normal levels (neutrophils > 1.5 x 10^9/L and thrombocytes >75x10^9/L). In this instance the administration of both drugs should be postponed. However if neutrophils < 1.5 x 10^9/L or platelets < 75 x 10^9/L when measured on the **Day 8** of any given cycle of treatment, the day 8 dose of vinorelbine should be skipped and another cycle will be started 3 weeks from the last dose of trastuzumab emtansine. If on the date the next cycle is due, neutrophils have not recovered to ≥1.5 x 10^9/L, **prophylactic use of growth factor support** will be permitted to allow dosing of the next cycle. In this case, for future cycles growth factor support will be permitted. If with the use of growth factor support, neutropenia has not resolved to grade 2 or less within 14 days, this will be considered a DLT. See also Section 7.3.

10.3.2 Phase II

Once the RP2D dose of the combination of vinorelbine and trastuzumab emtansine is determined in the phase I portion of the protocol, it will be the starting dose used to treat all patients during phase II. However, modifications in both drugs will be permitted, as detailed below.

<u>Hematological toxicity and Use of Growth Factor Support</u>

Vinorelbine dose must be adjusted if neutropenia and thrombocytopenia occur. If neutrophils < 1.5 x 10^9/L or platelets < 75 x 10^9/L when measured on the **Day 1** of any given cycle of treatment, the treatment will be postponed for 1 week until the blood counts have returned to normal levels (neutrophils > 1.5 x 10^9/L and thrombocytes >75x10^9/L). (In this instance trastuzumab emtansine should also be postponed.) However if neutrophils < 1.5 x 10^9/L or platelets < 75 x 10^9/L when measured on the **Day 8** of any given cycle of treatment, the day 8 dose of vinorelbine should be skipped and another cycle will be started 3 weeks from the last dose of trastuzumab emtansine. If on the date the next cycle is due, neutrophils have not recovered to ≥1.5 x 10^9/L, prophylactic use of growth factor support will be permitted to allow dosing of the next cycle. In this case, for future cycles growth factor support will be permitted.

In the event of Grade 4 toxicity, or in the event of Grade 3 or 4 toxicity associated with febrile neutropenia, there will be a dose reduction in Vinorelbine permitted. These dose level reductions will be supplied in an amendment once the MTD has been determined in the phase I portion of the study.

Neurological toxicity

In the event of neurological toxicity, including abdominal inflation due to obstipation, at NCI-CTCAE Grade 3 or 4, treatment with vinorelbine will be suspended until improvement to Grade 2 or less. The dose will then be reduced by 20%.

Liver toxicity

If during treatment with vinorelbine bilirubin increases to more than twice the ULN or ALT/AST increases to more than 3 x ULN (not related to liver metastases), the dose will be reduced by 50%.

Other toxicity

Symptoms estimated as NCI-CTCAE Grade 3 or 4 against the background of the vinorelbine treatment entail a dose reduction of 20%.

Treatment with vinorelbine must be discontinued for the following reasons:

• Respiratory insufficiency requiring bronchodilation in spite of extensive premedication

• Generalized urticaria

• Termination of vinorelbine at hypersensitivity reactions others than hypotension, angioedema, respiratory insufficiency or generalized urticaria is done at the investigator's discretion.

11.0 TREATMENT DISCONTINUATION

Treatment may be discontinued for any of the following reasons:

- The patient experiences a DLT (see Section 7.3)
- The patient demonstrates progression of disease (Exception: Patients may remain on the study if in the opinion of the Investigator, he/she is deriving clinical benefit from study treatment)
- The patient withdraws consent from the study
- The patient has not received study treatment for 2 cycles (42 days) due to an adverse event (toxicity)
- The patient experiences an adverse event that in the opinion of the Investigator makes continued study treatment an unacceptable risk (also see Section 10.0)
- The patient becomes pregnant (also see Section 14.7 Expedited Adverse Event Reporting Requirements)
- The patient requires continuous treatment with a prohibited concomitant drug(s) for which no safe alternatives can be substituted
- The patient is significantly noncompliant with the requirements of the protocol

Should discontinuation of study therapy occur, all efforts should be made to execute/ report End-of-Treatment and Follow-up Evaluations as completely as possible and to determine/ document the reason for discontinuation (unless the patient withdraws consent for follow-up).

Although unexpected termination of study treatment may occur, it is possible the subject may still agree to follow-up. In such a scenario, the EOT visit and procedures shall occur but it is important to understand that the subject is still in Follow-up.

If however a subject withdraws consent to participate in the study, this constitutes the End of Study for the patient. Even so attempts should be made to obtain permission to record at least Survival Data up until the protocol-specified end of Follow-up period. Methods used for attempted contact must also be documented properly (e.g. number of telephone calls to subject, certified letters, etc.).

If a patient wishes to withdraw consent from the study, the PI must be notified. The information regarding withdrawal (i.e. subject identifiers and date of withdrawal) should be documented in the subject's record and updated within any other research database(s).

12.0 SCHEDULE OF CLINICAL & LABORATORY EVALUATIONS

Prior to performing any study-specific procedures or evaluations, written informed consent and authorization for the use of protected health information (HIPAA) must be obtained in accordance with all applicable policies, regulations and laws.

If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that precludes the procedure within the allotted window, the procedure should be performed within 3 days, unless otherwise specified.

12.1 Pre-Treatment Evaluations (Screening)

The following must be collected/ performed within 28 days prior to Cycle 1, day 1 of treatment. Clinical and laboratory evaluations performed as part of routine standard of care do not need to be repeated if performed within the appropriate window.

- Medical history
  - Documented HER-2 status
- Complete physical examination to include:
  - Evaluation of the presence/absence of enlarged lymph nodes, hepatomegaly and splenomegaly,
  - Head, eye, ear, nose and throat,
  - Cardiovascular,
  - Musculoskeletal,
  - Respiratory,
  - Gastrointestinal, and

  - Neurological systems
- ECOG Performance Status (ECOG PS); see also Appendix C
- Weight (wt)
- Height (ht)
- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT
- Comprehensive metabolic panel (CMP), including:
  - Sodium,
  - Potassium,
  - Chloride,
  - Bicarbonate,
  - Glucose,
  - Blood urea nitrogen (BUN),
  - Creatinine,
  - Calcium,
  - Phosphorus,
  - Magnesium,
  - Total bilirubin,
  - Direct bilirubin,
  - Total protein,
  - Albumin,
  - Alanine aminotransferase (ALT),
  - Aspartate aminotransferase (AST), and
  - Alkaline phosphatase (alk phos)
- Urinalysis (U/A)
- Urine or serum Pregnancy test (for women of child-bearing potential or WoCBP), within 3 days prior to Day 1 of study treatment
- INR (for patients on coumarin anticoagulants)
- 12-Lead Electrocardiogram (ECG)
- Echocardiogram or Multiple Gated Acquisition Scan (ECHO or MUGA) the same procedure used at Screening must be used throughout the study
- Imaging studies; the same radiographic procedure(s) used at Screening must be used throughout the study (for tumor evaluation; measurable and unmeasurable disease of all known and/or suspected sites of disease)
  - Brain MRI/ CT, if patient has documented brain metastases
  - CT or MRI of the chest, abdomen and pelvis (C/A/P)

  - Bone scan (if an isotope-based bone scan was performed >28 days but ≤60 days prior to enrollment, the bone scan does not need to be repeated and non-isotopic radiographic modalities should be utilized to document the extent of bone metastases)
- Tumor sample(s) for local HER-2 testing, requested **but not required** as per local/ institutional guidelines

12.2 **Evaluations on Treatment**

Collection of Concomitant Medications and Adverse Events (AEs) should occur throughout the study, as described. 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.

Tumor assessments (including Bone Scan as needed) will be conducted every 6 weeks (±7 days) from the date of Randomization to Cycle 6. Thereafter, these assessments will be done every 12 weeks (± 7 days). These shall occur regardless of dose delays or dose interruptions, until Investigator-assessed progressive disease (PD), early treatment discontinuation or death, whichever occurs first. More frequent tumor assessments may be performed as clinically indicated, at the discretion of the treating Investigator. See also section 13.0 for details.

After screening/baseline, ejection fractions will be monitored by ECHO or MUGA prior to cycle 3 and every four cycles (i.e. every 12 weeks, ±7 days) thereafter (at any timepoint within respective cycles) until the assessment at the Study Treatment Discontinuation Visit. See also section 10.2.2, Table 7 and Appendix E.

Patients taking anticoagulants or starting anticoagulants while on study should have weekly platelet counts monitored for at least 2 cycles in order to assess whether a trastuzumab emtansine dose reduction may be necessary.

12.2.1 **All Cycles, day 1** (±3 days)

- Complete physical examination to include:
  - Evaluation of the presence/absence of enlarged lymph nodes, hepatomegaly and splenomegaly,
  - Head, eye, ear, nose and throat,
  - Cardiovascular,
  - Musculoskeletal,
  - Respiratory,
  - Gastrointestinal, and
  - Neurological systems
- ECOG Performance Status (ECOG PS); see also Appendix C
- Weight (wt)
- Vital signs
  - Blood pressure (BP)

- Heart rate (HR)
- Respiratory rate (RR)
- Oral temperature (temp)

- Complete blood count (CBC)
  - diff and PLT
- Comprehensive metabolic panel (CMP)
  - Sodium,
  - Potassium,
  - Chloride,
  - Bicarbonate,
  - Glucose,
  - Blood urea nitrogen (BUN),
  - Creatinine,
  - Calcium,
  - Phosphorus,
  - Magnesium,
  - Total bilirubin,
  - Direct bilirubin,
  - Total protein,
  - Albumin,
  - Alanine aminotransferase (ALT),
  - Aspartate aminotransferase (AST), and
  - Alkaline phosphatase (alk phos)
- INR (for patients on coumarin anticoagulants)

12.2.2 Cycle 1, day 8 (±3 days)

- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT

12.2.3 Cycle 2, day 8 (±3 days)

- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT

12.2.4 Cycle 3, day 8 (±3 days)

- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT
- Urine or serum Pregnancy test (for women of child-bearing potential or WoCBP)

12.2.5 Cycle 4, day 8 (±3 days)

- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT

12.2.6 Cycle 5, day 8 (±3 days)

- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT

12.2.7 Cycle 6, day 8 (±3 days)

- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT
- Urine or serum Pregnancy test (for women of child-bearing potential or WoCBP)
- Comprehensive metabolic panel (CMP)

12.2.8 Subsequent Cycles, **Days 1 and 8 (as specified)**

- Complete physical examination to include:

  - Evaluation of the presence/absence of enlarged lymph nodes, hepatomegaly and splenomegaly,
  - Head, eye, ear, nose and throat,
  - Cardiovascular,
  - Musculoskeletal,
  - Respiratory,
  - Gastrointestinal, and
  - Neurological systems
- ECOG Performance Status (ECOG PS); see also Appendix C
- Weight (wt)
- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)
  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT
- Comprehensive metabolic panel (CMP)
- Urine or serum Pregnancy test (for women of child-bearing potential or WoCBP)
- INR (for patients on coumarin anticoagulants)

12.3 **Off-Treatment Evaluations (End of Treatment or EOT visit)**

The following assessments must be performed at the EOT visit and should occur 30-days (±5 days) after the last dose of study treatment.

- Complete physical examination to include:
  - Evaluation of the presence/absence of enlarged lymph nodes, hepatomegaly and splenomegaly,
  - Head, eye, ear, nose and throat,
  - Cardiovascular,
  - Musculoskeletal,
  - Respiratory,
  - Gastrointestinal, and
  - Neurological systems
- ECOG Performance Status (ECOG PS); see also Appendix C
- Weight (wt)
- Vital signs
  - Blood pressure (BP)
  - Heart rate (HR)
  - Respiratory rate (RR)

  - Oral temperature (temp)
- Complete blood count (CBC)
  - diff and PLT
- Comprehensive metabolic panel (CMP)
- INR (for patients on coumarin anticoagulants)

12.4 **Follow-up Evaluations**

After treatment completion the following assessments should be performed as indicated.

Patients (regardless of reason for treatment discontinuation) will then be followed for survival every 12 weeks (±2 weeks) for at least 3 years, until death, lost to follow-up, withdrawal of consent*, or study termination by the Principal Investigator. A telephone call to the patient and/or the patient's family may be made to evaluate the patient's status on the following:

- Post-study anticancer therapy status
- Survival status

Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments approximately every 6 weeks (±7 days) from the date of enrollment for the first year (first 12 months after End of Treatment), then every 12 weeks (±7 days) thereafter for at least 3 years, until Investigator-assessed disease progression, death, lost to follow-up, or withdrawal of consent*. Once patient meets all eligibility criteria, the date of first dose is considered the enrollment date.

*Note: Some patients may withdraw their consent from study *treatment* but still agree to participate in survival follow-up. For these patients survival follow-up shall occur every 12 weeks (±7 days) until death, lost to follow-up or withdrawal from study.

A telephone call to the patient and/or the patient's family may also be made to evaluate the patient's status on the following:

- Post-study anticancer therapy status
- Survival status

12.5 **Calendar of Clinical and Laboratory Evaluations**

	Screening	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Subsequent Cycles**		**End of Treatment (EOT)**	**Follow-Up**
	≤28 days prior [A]	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	Day 1 (±3 days unless specified)	Day 8 (±3 days unless specified)	30-days (+5 days) after EOT	every 12 (±2) weeks [J]
ICF	X																
Eligibility	X																
Medical History [B]	X																
(Request tumor samples for local Her2 testing; **not required**)	X																
Height	X																
Weight	X	X		X		X		X		X		X		X	X	X	
Vital Signs [C]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete PE [C]	X	X		X		X		X		X		X		X	X	X	
ECOG PS	X	X		X		X		X		X		X		X	X	X	
12-Lead ECG	X																
CBC with diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Comp Metabolic Panel [D]	X	X		X		X		X		X		X	X	X	X	X	
INR [E]	X	X		X		X		X		X		X		X	X	X	
Urine or serum pregnancy test [F]	X						X						X	X	X		
Urinalysis	X																
Imaging studies [G]	X	(X) [G]			(X) [G]				(X) [G]				(X) [G]	(X) [G]		(X) [G]	(X) [G]
ECHO or MUGA [H]	X				(X) [H]								(X) [H]	(X) [H]			

Trastuzumab emtansine IV		X		X		X		X		X		X		X			
Vinorelbine direct IV push		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Baseline Symptoms	X																
Adverse Events		X															(X) [I]
Concomitant Medications		X															
Telephone Call [K]																	X

[A] Screening evaluations should be done within 28-days prior to enrollment unless otherwise specified.

[B] Medical History includes documented HER2 status.

[C] Vital signs include oral temperature, blood pressure, respiratory rate and heart rate. Complete PE includes: evaluation of the presence/absence of enlarged lymph nodes, hepatomegaly and splenomegaly, Head, eye, ear, nose and throat, Cardiovascular, Musculoskeletal, Respiratory, Gastrointestinal, and
Neurological systems

[D] Comprehensive Metabolic Panel (CMP) Sodium,Potassium, Chloride, Bicarbonate, Glucose, Blood urea nitrogen (BUN), Creatinine, Calcium, Phosphorus, Magnesium, Total bilirubin, Direct bilirubin, Total protein, Albumin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Alkaline phosphatase (alk phos).

[E] International Normalized Ratio (INR) for patients on coumarin anticoagulant.

[F] Urine or serum (beta-HCG) pregnancy test is required for women of childbearing potential **within 3-days prior to Day 1** of trial treatment.

[G] Imaging studies for tumor assessment for all known sites of disease (including CT or MRI of abdomen with contrast, Brain MRI/ CT, if patient has documented brain metastases, and Bone scan (if an isotope-based bone scan was performed >28 days but ≤60 days prior to enrollment, the bone scan does not need to be repeated and non-isotopic radiographic modalities should be utilized to document the extent of bone metastases)): the same method of assessment and technique used at baseline will be used during treatment and follow-up. Imaging studies will be done every 2 cycles (**every 6 weeks, ±7 days**) from the date of Enrollment to Cycle 6. After Cycle 6, imaging studies are to be done every 4 cycles (every 12 weeks, ±7 days) timed to coincide with the end of the prior treatment cycle.)

[H] Echocardiogram or Multiple Gated Acquisition Scan (ECHO or MUGA) the same procedure used at Screening must be used throughout the study. After screening/baseline evaluation, ejection fractions will be monitored by ECHO or MUGA prior to cycle 3 and every four cycles thereafter (at any time point within respective cycles) until the assessment at the Study Treatment Discontinuation Visit. See also 10.2.2, Table 7 and Appendix E for details.

[I] AE/SAE collections should continue for at least 90-days post EOT visit. All subjects with SAEs must be followed up for outcome. (See Section 14.0 and Appendix A for details).

[J] Follow-up for patients without documented objective disease progression shall occur every 12 weeks (+/- 2 weeks) for at least 3 years, until documented disease progression, death, withdrawal of consent, or End of Study, whichever occurs first

[K] Telephone call may be made to patient or patient's family to follow-up on patients' post-study anticancer therapy and survival status.

13.0 MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks (±7 days) before Cycle 6 and every 12 weeks (±7 days) after Cycle 6. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with trastuzumab emtansine and vinorelbine.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

13.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.*

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

13.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment 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 follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.1.4 Response Criteria – Evaluation of Target Lesions

Table 8: Response Criteria - Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

13.1.5 Response Criteria – Evaluation of Non-Target Lesions

Table 9: Response Criteria - Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

13.1.6 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease):

Table 10: Best Overall Response - Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Table 11: Best Overall Response - Non Measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

13.1.7 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.1.8 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13.1.9 Other Response Parameters

For other response parameters, refer to Section 15.0 for details.

14.0 **ADVERSE EVENTS**

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs) that are considered related to trastuzumab emtansine and vinorelbine, all events of death, and any study specific issue of concern. These will include but not be limited to: measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of trastuzumab emtansine when given in combination with vinorelbine.

14.1 **Purpose**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies, as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care.

14.2 **Adverse Event**

Adverse Event (AE): Can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, medical treatment, or procedure without judgment about causality. An adverse event can arise from any use and from any route of administration, formulation, or dose including an overdose. This includes any newly occurring event or a previous condition that has increased in severity or frequency since initiation of a drug, medical treatment, or procedure.

Abnormal Findings

In any clinical assessment, a value outside the normal or reference range (such as a clinical laboratory, vital sign, or ECG) will not be reported or assessed as an AE unless that value is considered to be of clinical significance by the investigator. A value of clinical significance is one that leads to discontinuation or delay in protocol treatment, dose modification, therapeutic intervention*, or is considered to be a clinically significant new finding or change from baseline by the investigator.

*Transfusion support administered to offset clinical symptoms of anemia or thrombocytopenia will not be considered therapeutic intervention.

Signs and Symptoms

Signs/symptoms resulting from an underlying clinical diagnosis should be documented as one comprehensive AE. If no underlying clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event. (A new or worsening event resulting from an underlying clinical diagnosis or a reaction to concurrent medications should be documented as a separate independent AE unless it is within the normal range of fluctuation for that patient.)

Grade Changes/Fluctuations

AEs will be reported at the maximum grade/severity experienced for the duration of the event. Should one particular event warrant further investigation, additional details may be collected at the discretion of the Principal Investigator.

Progression of Disease

Progression of disease, if documented in accordance to standard of care, should not be reported as an AE.

Tests and Procedures

Tests and procedures should not be reported as AEs. The underlying clinical diagnosis (or sign/symptom in the event an underlying clinical diagnosis is not known) requiring testing or a procedure, should be reported as an adverse event if it meets criteria for reporting.

14.3 **Serious Adverse Events (see also Appendix A)**

Serious AE (SAE) means any untoward medical occurrence that occurs at any dose:

1. **Results in death.**
2. **Is life-threatening.**
   The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
3. **Requires inpatient hospitalization or prolongation of present hospitalization.**
   Elective hospitalization to simplify protocol treatment/evaluations or to treat a baseline condition that did not worsen from baseline will not be considered an SAE.
4. **Results in persistent or significant disability/incapacity.**
   Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect**.
6. **Is a medically important event.**
   A medically important event may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT synonymous. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.4 **Adverse Event Collection Period**

All adverse events that occur after informed consent is obtained and within ≤ 30 days of the last dose of study therapy (or study discontinuation/termination, whichever is earlier), will be reported and followed until resolution. Resolution is defined as a return to baseline status or the stabilization of an event with the expectation that it will remain chronic. After this period, investigators should only report SAEs that are attributed to prior study treatment.

14.5 **Adverse Event Reporting Requirements**

The information to be reported in AEs will be assessed by and assigned severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. The NCI CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the NCI CTCAE v4.03 can be downloaded from the CTEP home page (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

Information to be reported in the description of each adverse event may be included, but is not limited to:

1. Clinical Diagnosis of the event as determined by NCI CTCAE, Version 4.03 descriptive terminology. If no clinical diagnosis can be identified, each sign/symptom should be reported as a separate independent event.
2. Date of onset of the AE (start date).
3. Date of resolution of the AE (end date).
4. Severity of the event determined by NCI CTCAE, Version 4.0 grading scale.
5. Relationship of the AE to study therapy. Categorized as follows:

Definite	The adverse event is clearly related to the investigational agent(s)
Probable	The adverse event is likely related to the investigational agent(s)
Possible	The adverse event may be related to the investigational agent(s)
Unlikely	The adverse event is doubtfully related to the investigational agent(s)
Unrelated	The adverse event is clearly not related to the investigational agent(s)

6. Whether or not the AE is Serious or Not Serious as defined in Section 14.3 Serious Adverse Events.

7. Whether the AE is Suspected and/or Unexpected.

Suspected	Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE.
Unexpected	Any AE for which the nature or severity of the event is not consistent with the applicable product information, e.g., the Investigator's Brochure or Package Insert.

8. Action taken as a result of the AE.
9. Outcome.

14.6 **Additional General Guidelines for Consistent Causality Assessments**

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline(s):

Yes
There is a plausible temporal relationship between the onset of the SAE or AE and administration of the trastuzumab emtansine, and the SAE or AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the SAE or AE follows a known pattern of response to the trastuzumab emtansine; and/or the SAE or AE abates or resolves upon discontinuation of the trastuzumab emtansine or dose reduction (applicable to phase II portion only) and, if applicable, reappears upon re-challenge.

No
Evidence exists that the SAE or AE has an etiology other than the trastuzumab emtansine (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the SAE or AE has no plausible temporal relationship to trastuzumab emtansine administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the current Investigator Brochure, included at the end of the current protocol.

Unexpected adverse events are those not listed in the current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

14.7 **Expedited Adverse Event Reporting Requirements**

All AEs, regardless if serious or not, will be described in the source documents, reported on the applicable AE page of the CRFs, and entered into *Velos*. However,

certain adverse events must also be reported in an expedited manner for more timely monitoring of patient safety and care. Appendix A provides information about these expedited reporting requirements.

14.8 **Alternate Definitions**

The alternate definitions shown below in Table 12 should be used ONLY when the reported AE is not in the above referenced grading scale.

Table 12: Adverse Event Grading (Severity) Scale

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

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

Note: Regardless of severity, some events may also meet regulatory seriousness criteria. Refer to the definition of a serious AE (see Section 14.3)

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

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

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

15.0 **STATISTICAL CONSIDERATIONS**

15.1 **Patient enrollment and follow-up**

Based on the estimated number of potentially eligible patients seen at University of Miami, enrollment period for this phase I/II study is estimated to be about 2 years. The expected accrual period for the phase I component of study is about 6 months and for

the phase II about 1.5 years. To gather data on disease relapse/progression and survival, all patients will be under follow up for a minimum of 3 years, unless they withdraw consent or die within that time. Thus, expected total study duration is 4.5 to 5 years.

In general, patient enrollment during phase I will be spaced at least 3 weeks apart to allow for evaluation of DLT. Simultaneous enrollment is only permitted if the first patient to receive a dose level does not experience DLT within 2 cycles, patients 2 and 3 may be enrolled simultaneously at the same dose level.

15.1.1 Analysis sets

All study-eligible patients who start the proposed treatment will be considered evaluable for purposes of analyzing data on safety and toxicity. For the phase I component of study, if a patient withdraws from study during the treatment for reasons other than toxicity, then the next patient shall be treated at the same dose as the withdrawn patient. Analysis of efficacy endpoints for the phase II, that is, PFS, treatment response (CR, PR, PD, or SD), and OS will be based on 35 patients enrolled on the phase II portion of the study.

15.1.2 Exclusions

Patients who are enrolled on study but not treated with at least 2 cycles (do not start treatment with vinorelbine and trastuzumab emtansine) are not considered evaluable and will be excluded from all efficacy analyses. Reasons for such exclusions will be characterized, but could include reasons such as: consent withdrawn or eligibility subsequently not confirmed. Any patient who initiates treatment and is later found to be ineligible for the study will be withdrawn from treatment (stop receiving study treatment) and excluded (not evaluable) from the main analyses of safety and treatment efficacy. Such patients, however, would be followed for overall survival. The experience of any treated patients who are not “study eligible” will be characterized separately from that of evaluable patients, whose experience will represent the main basis for evaluating the proposed combined treatment effect in this trial.

15.1.3 Study size justification

The objective of the phase I component of study is to determine recommended dose phase II dose of vinorelbine with trastuzumab emtansine. Patients will be treated at one of 4-5 dose levels according to the standard dose escalation/de-escalation scheme detailed in Section 7.1. In accordance with this scheme, the recommended phase II dose of vinorelbine with trastuzumab emtansine (vinorelbine on day 1 and 8 and trastuzumab emtansineon day 1) will be established as the highest dose level tested for which no more than 1 out of 6 patients experiences DLT. The number of patients for phase I component will be between 15 and 21 assuming four dose levels are tested.

The objective of the phase II component of study is to obtain preliminary evidence of the therapeutic efficacy of a combination regimen consisting of vinorelbine and

transtuzumab emtansine in HER2-positive MBC patients. The primary endpoint is progression-free survival (PFS). Secondary endpoints are objective response rate, clinical benefit rate, and overall survival. Analysis of these endpoints will be based on all evaluable patients as defined in Section 3.0. The study treatment will be of further interest if the median PFS is ≥12 months, and will be considered ineffective if the median PFS is ≤9 months. With 35 patients and a significance level of 10%, statistical power of the study will be 81.1%, assuming no patients are dropped out.

15.1.4 Planned statistical analysis

Demographic and baseline characteristics: Patient demographics and disease characteristics will be summarized using descriptive statistics: counts and percentages, range, median, mean, and standard deviation, as appropriate.

Safety: Toxicities will be tabulated by type, grade, duration, and attribution to treatment. A patient-level summary by worst grade toxicity will be included.

Efficacy: Preliminary evidence of treatment efficacy will be assessed by progression-free survival (PFS) and treatment response (CR, PR, SD, or PD) by RECIST1.1 criteria – see appendix B. In addition, the experience of patients in each category will be summarized by descriptive statistics (median and range) for time to onset of response or progression, and duration of benefit if achieved. The Kaplan-Meier method will be used to estimate progression-free survival and overall survival and corresponding medians. Point estimates with corresponding 95% confidence intervals for the proportion of progression-free/surviving patients will be given for selected times, such as 6, 12, 18, 24 and 36 months following the initiation of treatment, as well as for median times. For purposes of these analyses, progression-free survival (PFS) will be measured from date from first treatment received on study to date of documented disease progression, or death due to cancer, whichever occurs first. Patients who do not experience progression and those who die from causes other than cancer will be censored at the date of last known progression free date. Overall survival (OS) will be measured from date from first treatment received on study to date of death from any cause. Survival time will be censored at the date of last contact for patients who remain alive.

16.0 **DATA REPORTING**

Data must be submitted according to the protocol requirements for all patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

16.1 **Data and Safety Monitoring**

The Sylvester Comprehensive Cancer Center (SCCC) Data and Safety Monitoring Committee (DSMC) will monitor this clinical trial according to the Cancer Center's

DSM Plan. In its oversight capacity, the DSMC bears responsibility for suspending or terminating this study. DSMC oversight of the conduct of this trial includes ongoing review of accrual and adverse event (AE) data, and periodic review of the study therapy. The guidelines appearing in this section are offered for DSMC consideration in assessing AEs, and response to study treatment. In addition, the DSMC will review reports from all audits, site visits, or study reviews pertaining to this clinical trial and take appropriate action. The SCCC DSM Plan to which this study is subject can also be found at www.sylvester.org.

16.1.1 Early stopping guidelines for phase II component of study

NOTE: During phase I component, toxicity will be monitored by research team following escalation/de-escalation rules presented in Section 7.2.

We propose the following guidelines for the DSMC in its review of accumulating data on toxicity and response to treatment during the phase II component of study. The proposed guidelines were developed using Bayesian methods, which can be applied at any stage of enrollment without advance specification of the number of interim analyses to be performed, or the number of patients evaluable for toxicity, or response, at the time such assessments are made.

Under the Bayesian method, we assign a prior probability (level of belief at the start of the trial) to a range of possible values for the true toxicity rate. As data on treated patients become available, each of these probability distributions is revised and the resulting posterior probability becomes the basis for recommending either early termination or continuation of the study. In the sections that follow, we provide specific stopping guidelines based on posterior probabilities for monitoring toxicity and efficacy over the course of this trial. Underlying assumptions for the prior distributions are also presented.

16.1.2 Safety: Early Stopping Due to Toxicity

(As described in Section 10.1) If a treatment-related (possible, probable, or definite) death occurs, enrollment will be suspended and continuation of the study will be reassessed by the DSMC.

For the purposes of safety monitoring, we define unacceptable toxicity to be any of the following treatment-related (possible, probable, or definite) adverse events:

- Grade 3 neuropathy which does not resolve to grade 2 or less within two cycles of treatment
- Grade 4 neutropenia which does not resolve to grade 2 or less within 14 days
- Grade 3 elevation of liver function tests (LFTs) that does not resolve to grade 2 or less within 14 days

- Re-occurrence of grade 4 neutropenia or grade 3 elevation of LFTs despite 2 dose modifications or one dose medication and one protocol specified dose delay.
- Grade 3 left ventricular systolic dysfunction that does not resolve to grade 2 or less within one cycle of treatment

NOTE: Grade 5 (death) not related to treatment will not be considered unacceptable adverse event.

Unacceptable toxicity is expected to occur in no more than 10% of patients within the phase II component of the study in the whole cohort (up to 35patients). In other words no more than 4 patients. If there is evidence that the true rate of this toxicity exceeds 20% (i.e. more than 7 patients), then the study should be suspended or possibly terminated early. Specifically, we suggest as a guideline for early termination a posterior probability of 90% or higher that the true rate exceeds 20%. Table 13 details specific instances where this guideline is met. In this setting, early termination due to evidence of excessive toxicity would be warranted.

Table 13 Early Stopping Guidelines due to toxicity for phase II

Early Stopping Guidelines due to toxicity for phase II.

Patients with unacceptable toxicity	***Patients evaluated for toxicity***	***Observed toxicity rate ≥***
3	3 to 4	75%
4	5 to 6	67%
5	7 to 9	56%
6	10 to 11	55%
7	12 to 14	50%
8	15 to 17	47%
9	18 to 19	47%
10	20 to 22	45%
11	23 to 25	44%
12	26 to 28	43%
13	29 to 31	42%
14	32 to 33	42%
15	35	42%

Early Stopping Guidelines due to toxicity for phase II.

Patients with unacceptable toxicity	*Patients evaluated for toxicity*	*Observed toxicity rate ≥*

Unacceptable toxicity: any of the following **treatment-related (possible, probable, or definite)** adverse events:

- Grade 3 or higher non-hematologic toxicity, excluding fatigue, or toxicity attributed to androgen deprivation;
- Grade 4 or higher hematologic toxicity, excluding lymphopenia, leucopenia, and neutropenia lasting ≤ 7 days, and anemia.
    - **In patients with Grade 4 neutropenia**, a follow up CBC will be checked within 7 days. However, if CBC results cannot be obtained due to patient non-compliance or sample errors and a subsequent CBC results show resolution of Grade 4 neutropenia, this will be reported and not considered unacceptable toxicity.

16.1.3 Early Stopping Due to Lack of Efficacy: Monitoring the Overall Response Rate (ORR)

While both drugs are highly active in MBC (see sections 1.3, 1.4 and 1.5) and we expect synergy, it is not anticipated that this study will be stopped due to lack of efficacy. However, the DSMC should consider stopping the study early if accumulating data suggest that the true ORR is no better than 15%. Table 14 shows specific instances where this guideline is met, thus suggesting early termination due to evidence that treatment is ineffective.

Table 14 Early Stopping Guidelines for lack of efficacy

Early Stopping Guidelines for lack of efficacy.

No. of Patients with response	*Patients evaluated for response**	*Observed overall response rate ≤*
0	11 to 21	0%
1	22 to 30	5%
2	31 to 35	6%

* Evaluable and assessed for response under inclusion criteria.

For example, if 11 to 21 evaluable patients have been assessed for response and none has achieved criteria for response, then recommendation should be made to stop the study early for lack of efficacy. Likewise, if only one responder among the first 22 to 30 evaluable patients, then recommendation should be made to stop the study early for lack of efficacy.

Posterior probabilities used to derive the stopping guidelines shown above are calculated under a prior beta distribution with parameters $\beta 1=0.8$ and $\beta 2=1.2$, which corresponds to an expected overall response rate of 40% based on very limited information, roughly equal to having studied 2 patients. Equivalently, this prior distribution implies that there only 25.3% chance that the true overall response rate (ORR) is no better than 15%.

16.1.4 No Early Stopping for Better than Expected Treatment Efficacy

We do not intend to stop the study early if the proposed treatment appears to be overly effective. Under such circumstance, continuation of the trial will yield additional information regarding the magnitude of the true objective overall response rate and progression-free survival. Moreover, if results from this study are promising, further studies will be needed to fully assess the benefits and risks of vinorelbine with trastuzumab emtansine in pre-treated HER2-positive MBC.

17.0 **STUDY MONITORING**

This study will be audited and/or monitored (as applicable) according to the University of Miami requirements. See also http://uresearch.miami.edu/regulatory-compliance-services/rcqa and http://research.med.miami.edu/clinical-research/crors.

18.0 **INVESTIGATOR RESPONSIBILITIES**

18.1 **Investigator Responsibility/Performance**

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects. The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

18.2 **Confidentiality**

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study entry and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence.

18.3 **Informed Consent and Permission to Use Protected Health Information**

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The

investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate). For subjects not qualified or able to give legal consent, consent must be obtained from a parent, legal guardian, or custodian. The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

18.4 **Source Documentation and Investigator Files**

The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents may include hospital/clinic patient records; physician's and nurse's notes; appointment book; original laboratory, ECG, EEG, radiology, pathology, and special assessment reports; pharmacy dispensing records; subject diaries; signed informed consent forms; and consultant letters. When the CRF or any form is used as the source document, this must be clearly stated in the investigator study file. Minimally, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit
- Documentation of treatment
- Laboratory test results
- Adverse events (action taken and resolution)
- Condition and response of subject upon completion of or early termination from the study

18.5 **Recording and Processing of Data**

If using hard copies of CRF's, study center personnel will complete individual CRF's in ink. All corrections to entered data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated and explained, if necessary. The use of "white-out" or obscuring correction tape

will be prohibited. A CRF is required for every patient who received any amount of study treatment. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries except those for which use of the CRF as source document is clearly allowed per note in the investigator study file.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

Data must be submitted according to the protocol requirements for ALL patients registered. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

A list of forms to be submitted, as well as expectation dates may be found in Appendix B.

18.6 **Reports to Sponsor**

Any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study: Email: strauss.ross@gene.com or Fax: 973-252-7618.

18.7 **Non-Protocol Research**

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

18.8 **Ethics**

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics.

UM Ethics Programs' Research Ethics Consultation Service (RECS) is a free resource for UM Researchers. See the website for further information: http://www.miami.edu/index.php/ethics/projects/recs/

18.9 **Essential documents for the conduct of a clinical trial**

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The following documents should be on file: 1) CV's and license of all Investigators; 2) IRB documentation/correspondance and 3) Documentation of IRB certification

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APPENDIX A: EXPEDITED ADVERSE EVENT (AE) REPORTING REQUIREMENTS

For all AEs that meet criteria for expedited reporting, the Principal Investigator (PI) is obligated to pursue and provide follow-up reporting information until the event has resolved or until an acceptable medical endpoint has been reached (i.e. for the duration specified in the protocol), or the patient is lost to follow-up.

The PI and all applicable research study team members should become familiar with the safety profile of the investigational agent(s) and/or intervention at the start of the study and for the duration of the research, e.g. by reviewing the Investigator's Brochure (IB) and any Safety Reports released, by the Sponsor as applicable.

A. IRB Expedited Reporting

   a. All Investigators should also be aware of local Institutional requirements for AE reporting. For more information regarding the IRB policy, please refer to the UM HSRO's Investigator Manual: http://hsro.med.miami.edu/documents/HRP-103_-_INVESTIGATOR_MANUAL_4.11.2014.docx and the UM HSRO SOP on New Information (HRP-024) https://eprost.med.miami.edu/eProst/Doc/0/HLJ5OTJVQEH419E0I6QPT3B199/HRP-024%20-%20SOP%20-%20New%20Information.docx

   b. All AEs that are serious, unanticipated and possibly related will be reported to the IRB within ten (10) working days of being made known to the PI.

   c. Events that are more frequent than anticipated or more severe than expected must be reported to the IRB within ten (10) working days of being made known to the PI.

   d. All unanticipated deaths must be reported to the IRB within 24 hours of being made known to the PI.

B. Sponsor Expedited Reporting – **Genentech, Inc.**

   a. The PI is also required to comply with all reporting requirements as supplied by the Investigational Drug Sponsor(s).

   b. Investigators must report all SAEs within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to **Genentech Drug Safety** at: (650) 225 4682 *OR* (650) 225 4630. Please use the "Genentech Safety Reporting Fax Cover Sheet" provided at the end of the protocol.

   c. Relevant follow-up information should be submitted to **Genentech Drug Safety** as soon as it becomes available and/or upon request.

d. Serious AE reports that are related to the trastuzumab emtansine and AEs of Special Interest (regardless of causality) will be transmitted within fifteen (15) calendar days of the Awareness Date.

e. Serious AE reports that are unrelated to the trastuzumab emtansine will be transmitted within thirty (30) calendar days of the Awareness Date.

f. Additional Reporting Requirements include the following:
• All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report.

- Pregnancy: If a female subject becomes pregnant while receiving the study drug(s) or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted. Any reports of pregnancy following the start of administration with the trastuzumab emtansine will be transmitted within thirty (30) calendar days of the Awareness Date. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the trastuzumab emtansine should be reported as an SAE.

  Additional information on any trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e. after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

g. Post-Study Adverse Events: The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior trastuzumab emtansine exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should (also) be reported as an SAE.

h. AEs of Special Interest (AESIs): AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the product. The trastuzumab emtansine Events of Special Interest are:
   • Cardiac events
   • Thrombocytopenia (Grade ≥ 3)
   • Hepatic events (Grade ≥ 3 AST, ASLT or total bilirubin elevations or rug-Inducted Liver injury (non-serious and serious))
   • Infusion Associated Reactions, Hypersensitivity
   • Embryofetal Toxicity or Birth Defects

APPENDIX B: DATA SUBMISSION SCHEDULE

CASE REPORT FORM(S)	TIMEPOINT TO BE COMPLETED
Pre-Treatment	
ICF, including HIPAA signed/dated	Prior to registration
Eligibility Checklist	
SCCC Protocol Enrollment Form	
On-study Form	Within 30 days of registration/ enrollment
On Treatment	
Treatment Form Cycle X, Day Y	Due every week for phase I studies, every cycle for phase II
End of Treatment	
Off Treatment Form	Within 14 days of discontinuation/completion of protocol therapy
Follow-Up (for studies with long term follow-up)	
Follow-up Form	Every 3 months if < 3 years from study entry
Progression/Relapse	Within 4 weeks of knowledge of progression/relapse
Notice of Death Form	Within 4 weeks of knowledge of death
Subsequent Malignancy	Within 4 weeks of knowledge of another malignancy

APPENDIX C: PERFORMANCE STATUS SCALES

PERFORMANCE STATUS CRITERIA					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to a bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.
5	Dead	0	Dead	0	Dead

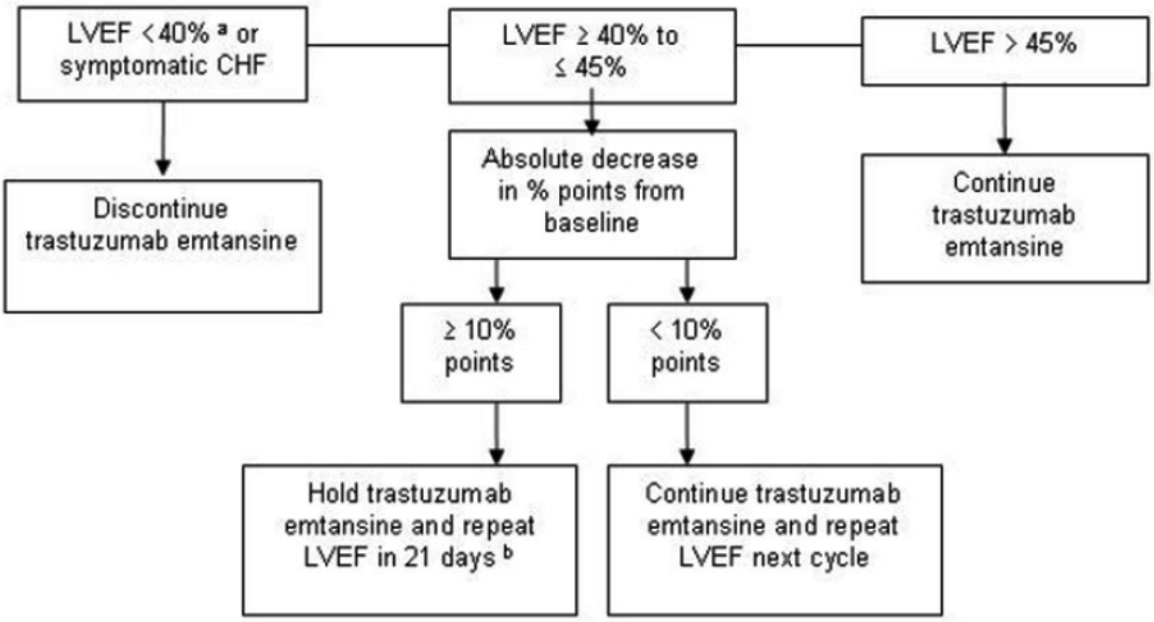
As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX D: NYHA CLASSIFICATION OF HEART DISEASE

New York Heart Association (NYHA) classification of heart disease

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

APPENDIX E: ALGORITHM FOR CONTINUATION & DISCONTINUATION OF TRASTUZUMAB EMTANSINE BASED ON LEFT VENTRICULAR EJECTION FRACTION ASSESSMENTS IN PATIENTS



CHF = congestive heart failure; LVEF = left ventricular ejection fraction.

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

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

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

Genentech
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APPENDIX F: SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Version 1, 31-May-2012