Protocol number: 13-077

Official Title of the study: A Phase 2 Study of Eribulin in Patients with HER2-negative, Metastatic Breast Cancer: Evaluation of Efficacy, Toxicity, and Patient-Reported Outcomes

NCT number: NCT01827787

Date of the document: February 23, 2016

Status Page

PROTOCOL **13-077**

# Closed To New Accrual

Closure Effective Date: 04/15/2016
No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

*Date Submitted:* ***[09/04/13]***
*Date Posted:* ***[09/09/13]***

# Alert Page

## DF/HCC Protocol #: [13-077]

**Protocol Clarifications (non-drug related e.g. eligibility criteria, study assessments)**

**Protocol 5.5.2, Assessments in the Treatment Phase, page 22:** Provider Reported CTCAE Form should be completed by MD, NP /PA or Research Nurse the same day patients complete the QOL surveys (C1D1, C2D1, C3D1, and then day 1 of every other cycle). Please note:

1. Please include the following information when completing the Provider Reported CTCAE Form: **Subject MRN, subject initials, date, visit #, and provider name and signature.** This information is missing from the form on page 34 (table 2) and page 80 (Appendix 8). [Amendment forthcoming]
2. Provider reported CTCAE assessment is missing from Section 9, Table 3: Study Calendar. [Amendment forthcoming]

**Protocol Section 9, Table 3: Study Calendar, page 37:** Tumor assessment must be performed every 9 weeks (within 1 week prior to C4D1, C7D1, C10D1, etc) during study treatment until PD is documented. That is, Cycle 3 Day 15-21, Cycle 6 Day 15-21, Cycle 9 Day 15-21, etc. Study Calendar currently indicates tumor assessment should be done prior to C3D1, which is incorrect. [Amendment forthcoming]

**DFCI Protocol No: 13-077**

# Front Sheet

**Report Generated:** 11/10/2017 09:23 AM

**Title:** A Phase 2 Study of Eribulin in Patients with HER2-Negative, Metastatic Breast Cancer: Evaluation of Efficacy, Toxicity and Patient-Reported Outcomes

**Overall Institution:** Dana-Farber Cancer Institute

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| Sponsor Name | Sponsor Protocol No | Roles | Grant Number(s) |
|---|---|---|---|
| DF/HCC Investigator | | Regulatory | |
| Dana-Farber/Harvard Cancer Center | | Funding | |
| Eisai | | Funding | |

**Total Study-Wide Enrollment Goal:** 90 **Total DF/HCC Estimated Enrollment Goal:** 90

**Phase:** II

**Age:** Adults

**Age Ranges:** 18+

**Will all subjects be recruited from pediatric clinics?**

**CTEP Study:** No

**Management Group(s):** BIDMC Breast Cancer
DF/HCC Affiliate Site
DF/HCC Breast Cancer
DF/HCC Satellite Site
DFCI/BWH Breast Oncology
OTHER Registering Site

**Primary Management Group:** DF/HCC Breast Cancer

**Investigational Drug?** Yes

**Drug(s), Biologic(s):** E7389

**IND #:** 117840

**IND Holder Type:** DF/HCC Investigator

**IND Holder Name:** Erica Mayer, MD, MPH

**Investigational Device?** This study does not use an Investigational Device.

**IRB of Record:**

**Risk Category:** Greater Than Minimal Risk

**Protocol Involves:** Chemotherapy; Human Material Collection; Questionnaires/Surveys/Interviews; Radiological

Exams

**Date Range:** (Medical Record Review and Specimen Collection studies)

## Participating Sites under the DFCI IRB

**Institution:** Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Dana-Farber Cancer Institute
Dana-Farber Cancer Institute at Milford
Dana-Farber Cancer Institute at NHOH
Dana-Farber Cancer Institute at South Shore

## Participating Institutions Under Other IRB

**Institution:** Eastern Maine Medical Center **Location:** BANGOR, ME

**Protocol Number: 13-077**

**Approval Date:** 04/02/13 (IRB meeting date when protocol/consent approved or conditionally approved)

**Activation Date:** 05/14/13 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

| Date Posted | Revised Sections | IRB Approval Date | OHRS Version Date |
|---|---|---|---|
| 05/17/13 | Delayed Activation: BIDMC ready. All sites now active. | N/A | N/A |
| 06/27/13 | Front Sheet replaced due to Amendment # 3 | 06/20/13 | N/A |
| 08/06/13 | Front Sheet replaced due to Amendment # 4 | 08/05/13 | N/A |
| 09/09/13 | Alert Page added due to Amendment #5 | 09/04/13 | N/A |
| 10/03/13 | Protocol and Front Sheet replaced due to Amendment #6 | 09/26/13 | N/A |
| 03/05/14 | DF/BWCC at DFCI@Milford, DF/BWCC at DFCI @SSH, DFCI @NHOH sites added; DFCI @ FH removed; Consent Form and Front Sheet replaced due to Amendment #7 | 03/04/14 | 03/05/14 |
| 03/20/14 | Study renewal/ Consent Form footer replaced due to Continuing Review #1 | 03/13/14 | n/a |
| 04/14/14 | Front Sheet replaced due to Amendment #8 | 04/14/14 | n/a |
| 07/21/14 | Protocol and Front Sheet replaced due to Amendment #9 | 07/21/14 | N/A |
| 03/03/15 | Study renewal/ Consent Form footer replaced due to Continuing Review #2 | 02/26/15 | N/A |
| 03/03/15 | Partial Closure: Cohort 1 closed to New Accrual: accrual goal met (effective date: 02/27/15; Amendment #10; Cohort 2 remains open) | 02/27/15 | N/A |
| 04/14/15 | Protocol and Front Sheet replaced due to Amendment #11 | 04/03/15 | N/A |
| **Date Posted** | **Revised Sections** | **IRB Approval Date** | **OnCore Version Date** |
| 12/09/15 | Front Sheet replaced due to Amendment #12 | 12/08/15 | N/A |
| 02/25/16 | Study renewal/ Consent Form footer replaced due to Continuing Review #3 | 02/25/16 | 02/25/16 |
| 04/13/16 | Eligibility Checklist replaced due to Amendment #13 | 02/25/16 | n/a |
| 04/13/16 | Protocol, Eligibility Checklist and Front Sheet replaced due to Amendment #14 | 02/26/16 | n/a |
| 04/22/16 | Permanent Closure to New Accrual: slow accrual (effective date: 04/15/16; Amendment #18) | 04/14/16 | N/A |
| 01/19/17 | Study renewal, Consent Form removed due to Data Analysis Only per Continuing Review #4 | 12/29/16 | N/A |
| 11/14/2017 | Front Sheet replaced per Amendment #19 | 11/07/2017 | N/A |
| 11/16/2017 | Study Renewal per Continuing Review #5 | 11/09/2017 | N/A |
| | | | |
| | | | |

**Protocol Version Date: February 23, 2016**

**Local Protocol** #:13-077

**Title:** A Phase 2 Study of Eribulin in Patients with HER2-negative, Metastatic Breast Cancer: Evaluation of Efficacy, Toxicity, and Patient-Reported Outcomes

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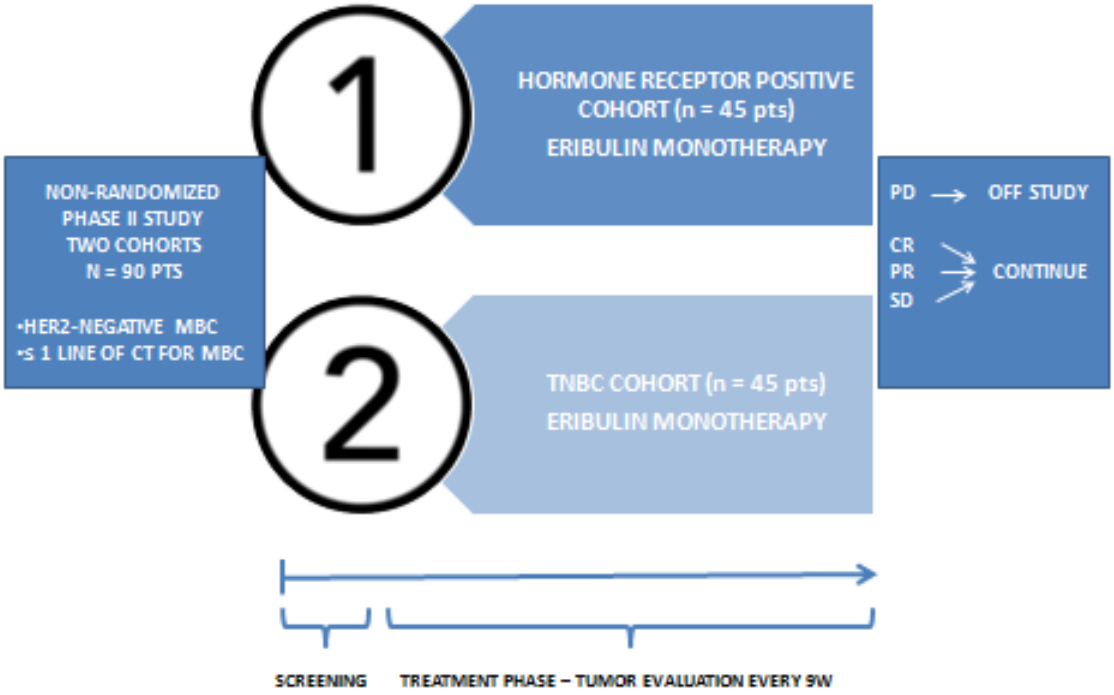
**Agent(s):** Eribulin mesylate (E7389)

## STUDY SCHEMA




Abbreviations: CR, complete response; CT, chemotherapy; MBC, metastatic breast cancer; PD, progressive disease; PR, partial response; SD, stable disease.

# Table of Contents

# 1. OBJECTIVES

## 1.1. Study Design

This is a non-randomized, open label study of eribulin monotherapy in the first or second line setting for metastatic HER2-negative breast cancer. Patients will be enrolled in 2 parallel cohorts. Cohort 1: Hormone receptor (HR)-positive /HER2-negative (HR+/HER2-). Cohort 2: HR-negative/HER2-negative (triple negative breast cancer [TNBC]). A total of 45 patients will be included in the HR-positive cohort and 45 in the TNBC cohort.

## 1.2. Primary Objectives

- To evaluate the antitumor activity of first-line treatment with single-agent eribulin mesylate in subjects with locally recurrent or metastatic HER2-negative breast cancer by determining overall response rate (ORR) (RECIST version 1.1). ORR will be estimated separately for the HR+/HER2- and the TNBC monotherapy cohorts.

## 1.3. Secondary Objectives

Efficacy Endpoints:

- Progression-free survival
- Time to first response
- Duration of response
- Time to first response and duration of response

Safety Endpoints

- To assess the safety and tolerability of single-agent eribulin mesylate (Both cohorts will be combined for these analyses)

Quality of Life (QOL) Analyses (Both cohorts will be combined for these analyses)

- To describe the adverse event (AE) profile of eribulin, according to provider-rated CTCAE v.4.0.
- To describe QOL at baseline and over time using the Functional Assessment of Cancer Therapy-Breast (FACT-B).
- To describe the impact of neurotoxicity on QOL at baseline and over time using the FACT-Neurotoxicity Subscale (FACT-Ntx).
- To describe the profile of patient-reported symptomatic toxicities experienced by patients receiving treatment with eribulin using the Patient Reported Outcome (PRO) Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

- To compare FACT-B, FACT-Ntx and PRO-CTCAE toxicity data with provider-reported CTCAE toxicity to determine degree of concordance or divergence for each class of toxicity.

Correlative Science:

- To explore the association between Single Nucleotide Polymorphisms (SNPs) and neurotoxicity. For this analysis, the two cohorts will be combined.
- To collect a repository of blood samples at baseline for future research.

# 2. BACKGROUND

## 2.1. Study Agent - Eribulin

Eribulin mesylate is a synthetic derivative of the natural product halichondrin B, a large polyether macrolide isolated from a marine sponge (*Halichondria okadai*). Halichondrin B exhibits anti-cancer activity through a microtubule-destabilizing anti-mitotic mechanism of action.[1,2] Eribulin exerts its effects by binding to the plus end of microtubules, leading to tubulin sequestration into nonproductive aggregates, preventing tubulin polymerization and microtubule dynamics. Suppression of microtubule growth interferes with normal mitotic spindle formation, and blocks the prometaphase portion of mitosis,[3] leading to irreversible cell cycle blockade at G2/M, disruption of mitotic spindles, and cell death via apoptosis after prolonged mitotic blockage.[4] *In vitro* studies demonstrate that analogues of halichondrin B inhibit cell growth at nanomolar concentrations in a wide variety of cancer cell types, including breast, ovary, colon and melanoma.[5]

The dosing regimen for eribulin selected based on results of Phase 1 studies is 1.4 mg/m$^2$ administered i.v. on Days 1 and 8 of a 3-week cycle. In an early Phase 2 trial, E7389-A001-201, the response rate (RR) in patients with breast cancer previously treated with anthracycline and taxanes was 11.5%. [6] Based on these results, the effectiveness and safety of eribulin were further explored in Study E7389-A001-211, which included patients with locally advanced or metastatic breast cancer who had received between two to five prior chemotherapy regimens, including an anthracycline, taxane, and capecitabine, and who had progression on or within 6 months of their last chemotherapy regimen. The response rate for eribulin was 9.3% in these heavily pretreated subjects.[7]

In a Phase 3 trial, E7389-G000-305 ("EMBRACE"), eribulin (1.4 mg/m$^2$ on Days 1 and 8 of a 3-week cycle) was compared with treatment of the physician's choice (TPC; any cytotoxic or hormonal agent) in subjects heavily pre-treated for locally advanced or metastatic breast cancer (MBC). [8] In the analysis of the primary endpoint of overall survival, patients receiving eribulin had a longer median overall survival of 13.1 months compared with 10.7 months for TPC ($P = 0.04$, stratified log-rank test; hazard ratio = 0.81). Objective RR was 12% for eribulin mesylate and 5% for TPC ($P = 0.005$). Grade 3 or 4 eribulin-related adverse events (AEs) included asthenia/fatigue (7.6%), neutropenia (44%), and peripheral neuropathy (8.4%). Twelve

percent of eribulin-treated subjects and 7% of TPC-treated subjects experienced treatment-related serious AEs. Based on the results of this Phase 3 trial, eribulin was approved by the FDA in November 2010 for metastatic breast cancer pre-treated with at least 2 prior regimens including anthracycline and taxane.

The tolerability of eribulin and its ease of use suggest possible treatment advantages in comparison to other available agents for advanced disease (i.e. taxanes). Preclinical and clinical data suggest that eribulin mesylate may exhibit less neurotoxicity, myalgia/arthralgia, and hypersensitivity than other chemotherapeutic agents. The most common AEs with single-agent eribulin mesylate are asthenia/fatigue and neutropenia. In addition, eribulin requires minimal preparation, can be administered quickly, and does not require premedication to prevent hypersensitivity.

The current study will evaluate the safety and efficacy of eribulin for the treatment of HER2-negative advanced breast cancer in the first- or second-line settings.

## 2.2. Study Disease

Breast carcinoma is the leading cause of cancer-related mortality in women worldwide, with an estimated 1.38 million new cases and 458,000 deaths in 2008 alone.[9] The American National Cancer Institute estimates that approximately 2.4 million women with a history of breast cancer were alive in 2004.[10] Approximately 10% of patients with breast cancer have *de novo* metastatic disease from diagnosis, and another 10 to 20% present with locally advanced breast cancer. Additionally, up to one third of patients with early stage breast cancer cases will develop metastatic disease in the course of their lives.[11]

Improvements in outcomes with MBC have been observed in the last 30 years, however overall prognosis remains poor with a median survival of 2 to 3 years.[12] Long term complete responses are observed only for a minority of MBC patients (2% to 5%), and MBC remains an incurable disease for most of patients.[13] The possibility of offering multiple lines of treatment to a particular patient makes the treatment decision process a difficult task. A balance between treatment response and quality of life should be pursued, as the great majority of MBC patients remain incurable. Response rate to first-line chemotherapy ranges from 30% to 60%, with an associated time to progression (TTP) of 7 to 10 months. [14] Treatment of MBC after progression on first-line treatment is associated with a lower response rate (20% to 30%) and subsequent shorter TTP in the range of 6 months. [14]

Despite significant advances in the field of targeted therapies for the treatment of advanced breast cancer, there has been little improvement in the development of novel cytotoxics. Eribulin is a novel chemotherapeutic agent with proven activity in advanced breast cancer patients previously treated with at least two regimens in the advanced setting. The present study aims to evaluate the ORR and safety profile of eribulin in the first and second-line treatment of advanced breast cancer.

## 2.3. Rationale for Correlative Studies – Patient Reported Outcomes

When treating metastatic breast cancer, the dual goals of care are prolonging survival and optimizing QOL. Treatment selection requires consideration not only of potential anti-neoplastic activity, but also of possible toxicities. Neuropathy is a common side effect of many of the major chemotherapeutics with activity in MBC, including taxanes, vinorelbine, ixabepilone, and eribulin. This toxicity is of particular interest, as it can be cumulative and, if severe, preclude further administration of potential active therapy. Although ongoing studies will provide initial description of the activity of eribulin in less heavily pretreated patients, these trials are not designed to capture the full effect of treatment on the patient aside from response rate. In the present study, recommended instruments based on the available evidence supporting their psychometric properties and past use in cancer research will be evaluated at baseline, during treatment and upon treatment completion.[15]

Patient-reported outcomes (PRO) are an important part of new drug evaluation, and may play a role in regulatory approval of novel agents in oncology.[16] PROs are the consequences of disease and/or its treatment as reported by the patient. PROs are evaluated through the use of questionnaires developed to assess topics a patient can report about his or her own health. This includes symptoms (i.e. nausea, fatigue, diarrhea), physical functioning (difficulty climbing stairs or fastening buttons), and mental health (i.e. anxiety, fear or worry).

Previous studies have demonstrated that patient and clinician reports of symptoms during cancer treatment provide discrepant but complimentary information. [17-19] The current standard mechanism for reporting toxicities in cancer research is clinician-only reporting using items from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). In a retrospective analysis of 14 randomized clinical trials, PRO measures improved the predictive accuracy of clinician CTCAE reporting.[20] In a prospective study including lung cancer patients PRO measurements of toxicities better reflected patients' underlying state and functional status than clinician's evaluation.[18]

In the current study, we will assess quality of life through validated questionnaires (FACT-B and FACT-Ntx) and the newly developed items of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).[15]

The FACT-B is a 44-item self-report questionnaire designed to measure multidimensional quality of life in patients with breast cancer.[21] The FACT-B consists of the FACT-General (FACT-G) plus the Breast Cancer Subscale (BCS), which adds items specific to QOL in breast cancer. Reliability and validity have been demonstrated in multiple patient samples. The Physical Well-Being (PWB), Functional Well-Being (FWB) subscales are sensitive to change in performance status rating. Sensitivity to change has also been demonstrated compared to the Functional Living Index-Cancer (FLIC) on the FACT-B total score, PWB, FWB, and Emotional Well-Being subscales. Internal consistency is high (alpha = 0.90) for the total score, with subscale alpha ranging from 0.63 to 0.86. QOL analyses using the Functional Assessment of

Cancer Therapy-Breast (FACT-B) have been presented from E2100, and are available as comparison data reflecting paclitaxel monotherapy.[22]

FACT-Neurotoxicity Subscale (FACT-Ntx) is aimed at the evaluation of quality of life of cancer patients suffering from neurotoxicity. [23] FACT -Ntx is a reliable and valid instrument for assessing the impact of neuropathy on health-related quality of life and has the sensitivity to detect meaningful clinical distinctions and change over time.

The PRO-CTCAE items have been developed under a contract between the National Cancer Institute (NCI) and clinical investigators with the intention that they will be available in future studies to allow patients to self-report their own adverse symptoms. The PRO-CTCAE item bank (i.e., lexicon of available questions) consists of five "types" of items (present/not present, frequency, severity, interference with usual or daily activities, and amount) which can be associated with any given symptom. The wording and response options for each type of item are as follows ("XXXX" represents the given symptom):

PRESENT/NOT PRESENT: In the last 7 days, did you have any XXXX:
• Yes / No

FREQUENCY:
In the last 7 days, how OFTEN did you have XXXX:
• Never / Rarely / Occasionally / Frequently / Almost constantly

SEVERITY:
In the last 7 days, what was the SEVERITY of your XXXX at its worst:
• None / Mild / Moderate / Severe / Very severe

INTERFERENCE:
In the last 7 days, how much did XXXX INTERFERE with your usual or daily activities:
• Not at all / A little bit / Somewhat / Quite a bit / Very much

AMOUNT:
In the last 7 days, did you have any XXX:
• Not at all / A little bit / Somewhat / Quite a bit / Very much

For each symptom, the types of items used to assess the symptom were previously agreed in the development process of the National Cancer Institute's PRO-CTCAE project. For example, for the symptom of "pain", the PRO-CTCAE includes three items:

In the last 7 days, how OFTEN did you have PAIN:
• Never / Rarely / Occasionally / Frequently / Almost constantly

In the last 7 days, what was the SEVERITY of your PAIN at its worst:
• None / Mild / Moderate / Severe / Very severe

In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities:
• Not at all / A little bit / Somewhat / Quite a bit / Very much

Whereas, for the symptom of "shortness of breath", the PRO-CTCAE includes only two items:

In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its worst:
• None / Mild / Moderate / Severe / Very severe

In the last 7 days, how much did SHORTNESS OF BREATH INTERFERE with your usual or daily activities:
• Not at all / A little bit / Somewhat / Quite a bit / Very much

and for the symptom of "constipation", the PRO-CTCAE includes only one item:

In the last 7 days, what was the SEVERITY of your CONSTIPATION at its worst:
• None / Mild / Moderate / Severe / Very severe

In total, the current version of the PRO-CTCAE has 126 items to assess 81 symptoms (Appendix 6). There are 45 symptoms which are assessed using one item, 27 symptoms which are assessed using two items, and 9 symptoms which are assessed using three items. The types of items in order of prevalence include severity (used to assess 52 symptoms), frequency (used to assess 26 symptoms), interference (used to assess 25 symptoms), present/not present (used to assess 21symptoms), and amount (used to assess 2 symptoms).

There are 20 symptoms (39 items in total) which were identified as "core" symptoms by the PRO-CTCAE development team in collaboration with NCI and FDA advisors based on their frequency in cancer patients and prior NCI trials, importance in monitoring, and/or inherent patient-reported nature. These symptoms include: Anxiety; arm or leg swelling; constipation; decreased appetite; loose or watery stools (diarrhea); dry mouth; fatigue, tiredness, or lack of energy; hair loss; headache; insomnia; mouth or throat sores; nausea; numbness or tingling in your hands or feet; pain; problems with concentration; problems with tasting food or drink; rash; sad or unhappy feelings; shortness of breath; and vomiting.

## 2.4. Rationale for Correlative Studies – Single Nucleotide Polymorphisms and Neurotoxicity

Both preclinical and clinical data suggest eribulin may lead to less neuropathy than other commonly used breast cancer chemotherapeutics. In mouse models, exposure to eribulin appears to cause less neuropathy in comparison to exposure to paclitaxel or ixabepilone.[24] In the clinical setting, rates of significant neuropathy have only been described in heavily pretreated patients. In the EMBRACE study, with a median duration of drug exposure of 4 months, 8% of the pretreated population experienced grade 3/4 neuropathy.[8] In contrast, in E2100, which included an arm evaluating first line weekly paclitaxel, the rate of grade 3/4 sensory neuropathy was 18%, with a median duration of therapy of 5.1 months.[25] In CALGB 40502, which also included an arm evaluating first-line weekly paclitaxel, the rate of grade 3/4 sensory neuropathy was 16%.[26] Additionally, in RIBBON-2, which enrolled patients in the second line setting, the rate of grade 3-4 sensory neuropathy was 13% in the chemotherapy alone arm (which included paclitaxel, gemcitabine, capecitabine, or vinorelbine).[27] It is possible that rates of significant neuropathy and subsequent detrimental effect on QOL with eribulin may be lower than those observed with other agents, especially in less heavily pretreated patients.

There is increasing interest in host factors, for example genetic polymorphisms that may be associated with neurotoxicity and other adverse effects. In the E2100 trial (paclitaxel chemotherapy backbone), genome wide association studies led by Dr. Bryan Schneider have identified 6 single nucleotide polymorphisms (SNPs) with minor allele frequency > 5% which were associated with neuropathy.[28] The strongest association was found for RWDD3, where the incidence of grade 2-4 neuropathy at any time point was 27% in homozygous wild-type patients versus 40% in heterozygous and 60% in homozygous variant patients. It would be of interest to explore whether the same SNPs are predictive of toxicity of other potentially neurotoxic agents. In addition, capturing neurotoxicity with both traditional physician-rated CTCAE grading and with PROs may explore associations between host factors and toxicity in a more comprehensive fashion.

In this study we will evaluate whether previously described SNPs are able to predict the observed neurotoxicity reported by patients in a specific PRO assessment of neurotoxicity, but also physicians' reported toxicity.

### 2.5. Rationale for Study

Eribulin has a well-demonstrated and approved role in the treatment of pretreated patients with metastatic HER2- breast cancer. In this setting, the phase 3 EMBRACE study demonstrated improved survival outcomes with eribulin monotherapy in comparison to treatment of physician choice, and the toxicity profile was predictable and manageable.[8] However, in view of its activity in the challenging setting of late-line treatment, eribulin merits assessment in this earlier-line setting, as greater clinical activity may be observed in a less heavily pretreated population.

We propose to expand the experience with eribulin in the first and second line MBC settings through a phase 2 trial designed to better define drug activity, with a focus on HR-positive and TNBC. An additional goal of the trial is to provide novel PRO-CTCAE data describing the effect

of eribulin on patient quality of life (QOL), compare toxicity evaluation by PRO-CTCAE versus provider-reported symptoms and validated QOL surveys (FACT-B, FACT-Ntx), and provide samples for exploration of host polymorphisms on the development of chemotherapy-related toxicity.

# 3. PARTICIPANT SELECTION

## 3.1. Eligibility Criteria

Subjects who meet all of the following criteria may be included in this study:

- Female or male age 18 years or older at the time of informed consent
- Have histologically or cytologically proven invasive breast cancer, locally recurrent or metastatic, with at least one measurable lesion according to RECIST v 1.1 (Appendix 1). Measurable disease is defined as: At least one lesion of ≥10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node which is serially measurable according to RECIST criteria, using CT or MRI
- Patients may have hormone receptor positive or hormone receptor negative HER2-negative disease. Hormone receptor positivity (ER and/or PR) is defined by at least 1% of positive tumor cells in the sample by immunohistochemistry (IHC). “Triple negative” is defined by the lack of estrogen and progesterone receptor and by HER2-negative status. HER2-negative disease can be determined by FISH or IHC. Negativity by IHC is defined as scores of 0 or 1+. Borderline IHC results (i.e., 2+) should undergo FISH testing; subjects with an HER2 FISH ratio $\leq$ 2.0 are eligible.
- Prior therapies
    - Up to one prior line of chemotherapy for advanced disease is allowed. If received, prior chemotherapy must be discontinued at least 14 days prior to initiation of protocol therapy.
    - Prior bevacizumab in the neo/adjuvant or metastatic setting is acceptable.
    - No limit on prior lines of endocrine therapy or biologic therapy. Endocrine therapy and biologic thearpy must be discontinued at least 7 days prior to initiation of protocol therapy.
    - Patients must have completed any prior radiotherapy at least 2 weeks prior to initiation of protocol therapy.
    - Patients must have recovered from any reversible effects of prior therapies to no more than Grade 1 toxicity, with the exception of alopecia.
- ECOG PS score of 0, 1 or 2 (see Appendix 2)
- Participants must have normal organ and marrow function as defined below

- Creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula (Appendix 3)
- Absolute neutrophil count ≥1.5 x $10^9$/L
- Hemoglobin ≥9 g/dL
- Platelet count ≥100 x $10^9$/L
- Bilirubin ≤1.5 times (x) the institutional ULN
- ALT and AST ≤3 x ULN, or ≤ 5 x institutional ULN in subjects with liver metastasis.
- ECG QTC interval < 470ms

- The effects of eribulin on the developing human fetus are unknown. For this reason, women of child-bearing potential or men must agree to use adequate contraception (barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

- Subjects willing and able to comply with all aspects of the protocol for the duration of the study and provide written informed consent before any study-specific screening procedures are performed, with the understanding that the subject may withdraw consent at any time without prejudice

### 3.2. Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

- Prior treatment with eribulin
- Subjects who have had a prior malignancy other than carcinoma in situ of the cervix or nonmelanoma skin cancer, unless the prior malignancy was diagnosed and definitively treated 1.5 or more years before enrollment in this study, with no subsequent evidence of recurrence
- Clinically significant cardiovascular impairment (history of congestive heart failure greater or equal to NYHA Class II (Appendix 4); unstable/active angina or MI ≤6 months before Day 1 of this study, or serious cardiac arrhythmia)
- Active brain metastases or unevaluated neurologic symptoms suggestive of brain metastases. Subjects with brain metastasis and documented stable disease for > 6 weeks may be included in this study. Brain metastases will not be considered measureable lesions for the purposes of this trial.

- Subjects with metastatic disease limited to bone are ineligible unless at least one lytic lesion with identifiable soft tissue components that can be evaluated by MRI or CT, that is measurable (≥15 mm at Baseline) and can be followed serially by RECIST v 1.1 (Appendix 1).
- Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring the use of oxygen
- Currently pregnant or breast-feeding. All females must have a negative serum or urine pregnancy test at the Baseline visit. Females of childbearing potential must agree to use a medically acceptable method of contraception (e.g., abstinence, an intrauterine device, a double-barrier method such as condom + spermicidal or condom + diaphragm with spermicidal, a contraceptive implant, an oral contraceptive or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after discontinuation of study treatment. Subjects who will be exempt from this requirement are postmenopausal women (defined as women who have been amenorrheic for at least 12 consecutive months, in the appropriate age group, without other known or suspected primary cause) or subjects who have been sterilized surgically or who are otherwise proven sterile (i.e., bilateral tubal ligation, hysterectomy, or bilateral oopherectomy)
- Subjects with organ allograft requiring immunosuppression
- HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with eribulin. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated
- Subjects with pre-existing Grade 3 or 4 neuropathy. Any peripheral neuropathy must recover to Grade ≤1 before enrollment
- Subjects with a hypersensitivity to halichondrin B or halichondrin B chemical derivative
- Uncontrolled intercurrent illness including, but not limited, to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
- Inability to read in English

### 3.3. Inclusion of Minorities and Other Underrepresented Populations

Both men and women are eligible for this protocol. Every effort will be made to include patients from minority populations. Because breast cancer predominantly affects females, it is anticipated that male enrollment will be < 5% of the overall study population.

# 4. REGISTRATION PROCEDURES

## 4.1. General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator(PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study may be cancelled. Notify the QACT Registrar of registration cancellation as soon as possible.

## 4.2. Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2. Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol, and reflected on the eligibility checklist.**

   **Reminder:** Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.
3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.
4. The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.
5. An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the lead site, treating investigator

and registering person immediately following the registration and/or randomization.

### 4.3. Registration Process for Other Investigative Sites

To register a participant, the appropriate documents should be completed by the research nurse or data manager and faxed *[Fax 617-632-5152]* or e-mailed *[CTOPM@dfci.harvard.edu]* to the Study Project Managers.

Please refer to Appendix 9: Section 3.7.1 for a complete list of appropriate documents.

The research nurse or data manager at the participating site will then e-mail *[CTOPM@dfci.harvard.edu]* the Project Manager to verify eligibility. To complete the registration process, the Project Manager will

- register the participant on the protocol with the QACT
- fax or e-mail the participant study number, and if applicable the dose treatment level to the participating site
- call the research nurse or data manager at the participating site and verbally confirm registration

**NOTE: Registration and randomization with the QACT can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday.** Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

## 5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for eribulin are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

### 5.1. Overall Study Design and Plan

This is a non-randomized, open label study of eribulin monotherapy in the first or second line setting for metastatic HER2-negative breast cancer. Each subject will be assigned a unique identification number during screening, which will be used on all CRFs and correspondence regarding the subject.

Patients receiving monotherapy will be enrolled in 2 parallel cohorts:

- Cohort 1: HR+/HER2-negative (n = 45 pts)

- Cohort 2: TNBC (n= 45 pts)

| Treatment Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-medications** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Eribulin | none | 1.4 mg/m$^2$ | IV over 2 to 5 minutes | Days 1, 8 | 21 days (3 weeks) |

The starting dosage of eribulin mesylate in this study, 1.4 mg/m$^2$ administered as an i.v. infusion over approximately 2 to 5 minutes on Days 1 and 8 of a 3-week cycle, is based on results of four Phase 1 and four Phase 2 clinical studies. Four Phase 1 dose-finding studies were conducted to evaluate escalating doses of eribulin mesylate and determine the maximum tolerated dose (MTD) of eribulin mesylate as: (1) a 1-hour i.v. infusion on Days 1, 8 and 15 of a 28-day cycle (E7389-A001-101); (2) a 1-hour i.v. infusion on Day 1 of a 21-day cycle (E7389-A001-102); (3) an i.v. bolus on Days 1, 8 and 15 of a 28-day cycle (National Cancer Institute [NCI] Study 5730); and (4) a bolus infusion on Days 1 and 8 of a 21-day cycle (E7389-J081-105). The MTD was determined to be 1.4 mg/m$^2$ for the bolus injection and 1.0 to 2.0 mg/m$^2$ for the infusion.

Eribulin mesylate 1.4 mg/m$^2$ i.v. bolus was tested as the starting dose in four Phase 2 studies. In the first two Phase 2 studies, subjects initially received eribulin mesylate on Days 1, 8 and 15 in 28-day cycles. Because the majority of subjects receiving the 28-day dosing schedule experienced dose delays, reductions, or omissions due to neutropenia on Day 15 of the cycle, an additional cohort of subjects who received eribulin mesylate 1.4mg/m$^2$ on Days 1 and 8 in 21-day cycles was added. This schedule appeared to be better tolerated than the 28-day schedule and demonstrated antitumor activity in all four Phase 2 studies. Thus, the optimal schedule of eribulin mesylate based on the four studies appears to be 1.4 mg/m$^2$ administered on Days 1 and 8 in 21-day (3-week) cycles.

## 5.2. Pretreatment Criteria

Pretreatment criteria will be assessed within 21 days of the first dose of study treatment to establish eligibility and baseline values.

Informed consent will be obtained after the study has been fully explained to the subject and before the conduct of any screening procedures or assessments. If screening assessments occur within 3 days before start of study treatment, then they may serve as the baseline Cycle 1 Day 1 visit and screening tests do not need to be repeated.

Demographic information and baseline characteristics will be collected at the Screening Visit. Standard demographic parameters include age, sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include ECOG PS (Appendix 2), NYHA cardiac disease classification (Appendix 4), disease status, medical histories, prior and concomitant medications, and PE findings. Relevant hormone receptor status will be collected.

Within the 21 days prior to therapy initiation patients will undergo baseline clinical evaluation (including history, physical evaluation, vital signs, and performance status). Subsequent changes from screening PE findings that meet the definition of an AE will be recorded on the AE page of the eCRF.

Additional pre-treatment evaluations include: CBC with differential, chemistries, pregnancy test (if indicated), tumor measurements by staging studies and concomitant medication assessmentIf eligible and registered, blood collection for correlative studies will occur at Cycle 1 Day 1.

### 5.3. Treatment Phase

Treatment cycles will begin with the first dose of administration of study treatment on Cycle 1, Day 1 and continue in 3-week (21-day) cycles. Subjects will continue to receive study treatment until the development of Progressive Disease (PD) or the subject meets another withdrawal criterion as described in Section 15. All subjects will receive eribulin mesylate 1.4 mg/m$^2$ on Day 1 and Day 8 of each cycle. Subjects will undergo tumor response assessments every 9 weeks.

After PD is documented or if subject is withdrawn from study, study treatment must be discontinued; all enrolled subjects will then be treated according to prevailing local standards at the investigator's discretion. Subjects who discontinue study therapy without PD will continue to undergo tumor response assessments every 9 weeks (from the date of the last tumor assessment) until PD is documented. All subjects will undergo an End-of-Treatment visit within 21 days after the final dose of study treatment.

### 5.4. Agent Administration

Eribulin Mesylate

Eribulin mesylate 1.4 mg/m$^2$ will be administered on an outpatient basis via i.v. infusion over approximately 2 to 5 minutes on Days 1 and 8 of each 3-week cycle. Therapy will continue until PD is documented or another withdrawal criterion is met as specified in Section 5.9. All subjects will receive the same starting dosage of eribulin mesylate, based on BSA.

Please note that minor variations in treatment dates (+/-3 days) may occur depending on physician and patient scheduling, observed holidays, inclement weather, etc. Regardless of the time of administration, toxicity from previous treatment must be within acceptable ranges as described below:

**Criteria for Eribulin administration**

- Absolute Neutrophil Count $\geq$1,000/mm$^3$ or $\geq$1.0×10$^9$/L
- Platelet Count $\geq$75,000/ mm$^3$ or $\geq$75×10$^9$/L
- Non-hematologic toxicity CTCAE $\leq$ Grade 3 or 4

Before dose administration, the amount of eribulin mesylate needed for each subject must be calculated in the following manner:

1. Scheduled dose (mg/$m^2$) x body surface area ($m^2$) = Dose (mg)
2. Dose (mg) x 2 = the number of mL of eribulin mesylate to withdraw from vials for administration

Body surface area (BSA) will be calculated using any method that is accepted and customarily used by the investigational site, such as the Mosteller formula:

BSA ($m^2$) = ([Height ([cm) x Weight (kg)]) ÷ 3600)$^{½}$

Height and body weight will be recorded at the screening visit. Thereafter, body weight will be recorded on each treatment day and dosing BSA will be calculated accordingly.

The amount of eribulin mesylate required (as calculated above) will be withdrawn from the appropriate number of vials into a syringe. This may be injected directly as an i.v. infusion over approximately 2 to 5 minutes or diluted in up to 100 mL 0.9% saline for i.v. infusion over approximately 2 to 5 minutes. No special tubing is required for the i.v. administration of eribulin mesylate.

## 5.5. Schedule of Visits and Procedures

### 5.5.1. Pre-treatment phase

Day -21 to Day 0

Before performing any procedures or assessments, the investigator's staff will explain the nature of the study and the potential risks associated with the study to all subject candidates and their respective partners where applicable, and obtain written informed consent from both if required. Once the IRB/IEC-approved ICF has been signed, the following procedures and evaluations will be performed:

- Determination of eligibility (inclusion/exclusion criteria, Section 3):
- Record demographic data
- Evaluate ECOG PS score (must be 0, 1 or 2 for subject to be eligible) (Appendix 2) and cardiovascular status per NYHA criteria (Appendix 4)
- Record medical and surgical history
- Record all prior and concomitant medication use (prescription and nonprescription medications as well as transfusions) beginning 30 days before the start of study treatment (except record all previous breast cancer treatments)
- Perform physical examination

- Obtain vital signs (BP, HR, respiratory rate, and body temperature), weight, and height.
- Perform tumor assessments to identify target and nontarget lesions. Computed tomography or MRIs are to be obtained between Day -21 and Day 1. Confirm the presence of at least one measurable lesion ≥10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node
- Obtain bone scan within 6 weeks before start of study treatment.
- Perform a 12-lead ECG
- Collect serum or urine sample for β-hCG pregnancy testing from all premenopausal and any postmenopausal women who have been amenorrheic for <12 months
- Collect blood samples for clinical chemistry and hematology analyses (see Table 4) for a list of tests to be performed).
- Collect blood samples for whole blood for germline DNA SNP analysis
- Record any AEs (from the time of the first dose of study treatment)
- Schedule Cycle 1 Day 1 Visit: Screening assessments may serve as baseline assessments if they are performed within 3 days before the first dose of study treatment.

### 5.5.2. Assessments in the Treatment Phase

Reasonable effort should be made to conduct study visits on the day scheduled (±3 days). The Study Calendar is provided in Table 3.

Day 1 of Treatment

- Record ECOG PS score (for Cycle 1: record if not done at Baseline visit)
- Record weight (for Cycle 1: record if not done at Baseline visit)
- Record vital signs (BP, HR, respiratory rate, body temperature) before administration of eribulin mesylate.
- Perform one post baseline 12-lead ECG on Day 1 of Cycle 2 before administration of study treatment
- Perform physical exam
- Collect blood samples for clinical chemistry and hematology analyses within 3 days before the scheduled visit (see Table 4 for a list of tests to be performed). Laboratory assessments are not required on Day 1 of Cycle 1 if already performed at Baseline (within 3 days before study administration)
- Review all laboratory results before administering study treatment

- Record all concomitant medication use
- Cycle 1 D1, cycle 2 D1, cycle 3 D1, and every other cycle (i.e., cycles 5, 7, 9 until treatment discontinuation) - Administer QOL surveys (FACT-B, FACT-Ntx, and PRO-CTCAE) and complete physicians reported CTCAE as detailed below:
  - Administer the QOL surveys (FACT-B, FACT-Ntx, and PRO-CTCAE). Assessments may be performed within 3 days before the scheduled
  - Record selected provider-reported CTCAE (detailed in Table 3). Adverse events should be graded as the worst grade in the last 7 days, which is different from standard CTCAE grading which typically spans the duration of time since the prior clinical assessment or treatment. Attempts should be made to have provider-reported CTCAE and QOL surveys performed on the same day.
- Administer study treatment:
- Eribulin mesylate 1.4 mg/m$^2$ as an i.v. infusion over approximately 2 to 5 minutes
- Record any AEs or SAEs

Day 8 of Treatment

- Record weight
- Record vital signs (BP, HR, respiratory rate, body temperature) before the administration of eribulin mesylate
- Collect blood samples for hematology and chemistry analyses within 24 hours before the scheduled visit (see Table 4 for the tests to be performed).
- Review all laboratory results before administering study treatment.
- Administer study treatment:
- Eribulin mesylate 1.4 mg/m$^2$ as an i.v. infusion over approximately 2 to 5 minutes

Tumor Assessments Interval

Tumor assessments will be performed every 9 weeks, up to 1 week before the administration of the first dose of study treatment in the next treatment cycle as indicated in the Study Calendar (Table 3):

- Confirm Complete Response (CR) or Partial Response (PR) a minimum of 4 weeks after initial response assessmentBone scan and brain CT/MRI at treating physician discretion. Scans can also occur as clinically indicated for new symptoms or to confirm disease response. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.

End-of-Treatment Visit in the Treatment Phase

Subjects will continue to receive study treatment until PD or another withdrawal criterion is met, as described in Section 5.9. If a subject develops PD study treatment must be discontinued and end-of-treatment assessments be performed within 21 days of discontinuation of study treatment. If study treatment is discontinued without the subject having PD, the subject will undergo end-of-treatment assessments and enter the posttreatment Follow-up Period for tumor response assessment.

### 5.5.3. End-of-Treatment Procedures

All subjects will be asked to return to the site for a final, End-of-Treatment visit, if possible. The End-of-Treatment visit must be performed within 21 days of final administration of study treatment. End-of-treatment assessments will not have to be repeated if the same assessments were performed within 7 days of this visit.

End-of-Treatment Visit

- Perform tumor assessments as indicated in the Study Calendar (Table 3). If study treatment is discontinued due to PD, then tumor assessments are not required for that subject.
- Evaluate ECOG PS
- Perform physical exam
- Record vital signs (BP, HR, respiratory rate, body temperature) and weight
- Collect blood samples for hematology and serum chemistry analyses (see Table 4 for a list of tests to be performed)
- Record all concomitant medication use. Concomitant medications should be collected for 30 days after the last dose of study treatment.
- End of treatment visit - Administer QOL surveys (FACT-B, FACT-Ntx, and PRO-CTCAE)and complete physicians reported CTCAE as detailed below:
  - Administer the QOL surveys (FACT-B, FACT-Ntx, and PRO-CTCAE) survey. Assessments may be performed within 3 days before the scheduled clinic visit.
  - Record selected physicians reported CTCAE (detailed in table 2). Adverse events should be graded as the worst grade in the last 7 days, which is different from standard CTCAE grading which typically spans the duration of time since the prior clinical assessment or

treatment. Physicians reported CTCAE and QOL surveys should be performed in the same day.

- Record any AEs or SAEs

All AEs, regardless of relationship to study treatment or procedure or grade, will be collected from the time the subject signs the study ICF until 30 days after discontinuation of study treatment. Any AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. However, treatment-emergent peripheral neuropathy and alopecia will be followed until resolution or another anticancer agent is started, whichever occurs first. Serious AEs will be collected for 30 days posttreatment and followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize or returns to baseline levels.

#### 5.5.4. Follow-up Period Procedures

Subjects who do **not** have PD upon discontinuation of study treatment are to have tumor assessments during the post treatment Follow-up Period (using the same methodology and acquisition techniques as were used for previous assessments) every 9 weeks from the date of the last tumor assessment until PD is documented (see the Study Calendar in Table 3. During the Follow-up Period, subjects who have treatment-emergent peripheral neuropathy during the study will be followed until resolution of the neuropathy, or until another anticancer therapy is started, whichever occurs first.

### 5.6. General Concomitant Medication and Supportive Care Guidelines

All diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded in the electronic case report form (eCRF), including the date, indication, description of the procedure(s), and any clinical findings. All previous treatments for breast cancer should be included.

All prior treatment or medication administered during the 30 days preceding the first dose of study treatment and any concomitant therapy administered to the subject throughout the study until 30 days after the final dose of study treatment must be recorded on the Prior and Concomitant Therapy page of the eCRF. The generic name of the drug (or trade name for combination drugs) must be specified along with the duration of treatment and indication for use. If concomitant medication/therapy is administered for an adverse event (AE), investigators will record that AE on the AE page of the eCRF.

Any medication that is considered necessary for the subject's welfare and that is not expected to interfere with the evaluation of study treatment may be given at the discretion of the investigator. Ancillary treatments will be given as medically indicated.

Any changes in documented, permitted concomitant treatment already being taken at the start of the clinical study must be recorded on the eCRF, noting the type of medication, duration of use, and indication.

### 5.6.1. Premedication

Premedications (anti-emetics) may be administered before eribulin mesylate administration, but are not required. Premedication with steroids or antihistamines to prevent hypersensitivity reactions is not required.

### 5.6.2. Permitted concomitant Therapies and Medications

The following agents are permitted, except as noted:

- Antiemetics
- Antidiarrheal therapy
- Antiallergic measures such as corticosteroids and antihistamines
- Granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin in accordance with American Society of Clinical Oncology guidelines and local standard practice.
- Bisphosphonates: Subjects being treated with bisphosphonates when they enter the study may continue the medication as long as the dose is stable. Subjects may also initiate bisphosphonate therapy while on protocol therapy if it is thought to be medically necessary.
- Palliative radiotherapy may be given for bone pain or for other reasons (i.e., bronchial obstruction, ulcerating skin lesions). The irradiated area should be limited and should not involve more than 10% of the bone marrow. The irradiated area cannot be used for tumor response assessment.
- During palliative radiotherapy, treatment with study treatment should be held. Treatment with study treatment may be resumed within 14 days after completion of radiotherapy if the subject has recovered from any radiation-associated toxicity.
- Ovarian suppression with goserelin or leuprolide are allowed on study.

### 5.6.3. Prohibited Concomitant Therapies and Drugs

The use of investigational or other antitumor therapies, other than eribulin mesylate is prohibited during this study. If subjects receive additional antitumor therapies such as chemotherapy, hormone therapy (tamoxifen, aromatase inhibitors, fulvestrant), radiation therapy other than required for palliation, gene therapy, biologics, or immunotherapy, irrespective of the reason for which they are being given, this will be judged to represent evidence of progressive disease (PD) and study treatment will be discontinued. These subjects will complete all end-of-treatment assessments.

### 5.6.4. Drug-Drug Interactions

The weak inhibitory effect on cytochrome P450 enzymes exhibited by eribulin mesylate in vitro suggests a low risk of eribulin mesylate interaction with the pharmacokinetics of other drugs coadministered in usual clinic practice. Eribulin mesylate exposure (area under the curve and

maximal concentration) was bioequivalent when administered in combination with ketoconazole, a potent CYP3A4 inhibitor, compared with administration of eribulin mesylate alone.

#### 5.6.5. Treatment Compliance

Eribulin mesylate will be administered by trained medical personnel at the investigational site. Treatment compliance will be monitored through documentation of study treatment administration in the subject's medical record.

### 5.7. Duration of Therapy

Duration of therapy with eribulin will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Development of progressive disease by clinical evaluation or as documented by RECIST v 1.1 (Appendix 1)
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

### 5.8. Duration of Follow Up

Participants will be followed for 30 days after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

### 5.9. Criteria for Removal from Study

The investigator may withdraw a subject from the study at any time for safety or administrative reasons. A subject may stop study treatment at any time for safety or personal reasons.

Subjects who withdraw after signing the informed consent form (ICF) but before receiving study treatment will be replaced.

Participants will be removed from study when any of the criteria listed in Section 5.7 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with and, if necessary, provided for the participant.

All subjects who withdraw from the study will be required to complete protocol-specified end-of-treatment assessments within 21 days after the last dose of study treatment (end-of-treatment assessments will not have to be repeated if same assessments were done within 7 days of last dose). Subjects who do not have progression upon discontinuation of study treatment will have tumor assessments every 9 weeks from the date of the last tumor assessment until PD is documented. A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of AEs, the clinical course of signs and symptoms, and survival.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Erica L. Mayer MD MPH at 617-632-2335.

# 6. EXPECTED TOXICITIES AND DOSE/DELAYS MODIFICATION

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

## 6.1. Eribulin – Expected toxicities

In a completed Phase 3 trial, E7389-G000-305, eribulin (1.4 mg/m$^2$ on Days 1 and 8 of a 3-week cycle) was compared with treatment of the physician's choice (TPC; any cytotoxic or hormonal agent) in subjects heavily pre-treated for locally advanced or metastatic breast cancer. Grade 3 or 4 eribulin-related AEs were asthenia/fatigue (7.6%), neutropenia (44%), and peripheral neuropathy (8.4%). Twelve percent of eribulin-treated subjects and 7% of TPC-treated subjects experienced treatment-related SAEs.

Refer to Section 5.2 of the Investigator's Brochure for complete details on toxicity in previous clinical trials conducted with eribulin.

### 6.2. Eribulin - Toxicity Management

Subjects should be carefully monitored for toxicity. If Grade 3 or 4 toxicities are present, then treatment should be delayed to allow for recovery (see instructions for dose delay below). If toxicities recur, the dose of eribulin should be reduced. In the setting of neutropenia, growth factor support may be added instead of a dose reduction at time of first occurrence of neutropenia at the discretion of the investigator. Once the dose of eribulin is reduced, it may not be increased at a later date. Dose adjustment recommendations for eribulin are shown in Table 1.

**Eribulin Dose Levels**

| **Starting dose** | **1.4 mg/m2** |
|---|---|
| 1st dose reduction | 1.1 mg/m2 |
| 2nd dose reduction | 0.7 mg/m2 |

**Table 1:** Dose adjustment recommendations for eribulin

| **Adverse reaction/Toxicity[a]** | **Grade/Details** | **Eribulin dose modification** |
|---|---|---|
| ANC | < 500 cells/mm3 lasting > 7 days in the previous cycle without use of growth factors | Hold eribulin until recovery to grade ≤ 2. Eribulin may be resumed at the same dose with growth factor support, or it may be reduced by one dose level, per investigator discretion. |
| | < 500 cells/mm3 lasting > 7 days in the previous cycle despite use of growth factors | Hold eribulin until recovery to grade ≤ 2, and reduce by 1 dose level. |
| | <1000 /mm3 with fever or infection without use of growth factors | Hold eribulin until recovery to grade ≤ 2. Eribulin may be resumed at the same dose with growth factor support, or it may be reduced by one dose level, per investigator discretion. |
| | <1000 /mm3 with fever or infection despite use of growth factors | Hold eribulin until recovery to grade ≤ 2, and reduce by 1 dose level. |
| | <1000 /mm3 without fever or infection without use of growth factors | Hold eribulin until recovery to grade ≤ 2 then resume at the same dose with growth factor support.<br><br>If uncomplicated neutropenia lasting < 1 week (<1000 /mm3 without fever or infection) occurs/recurs despite growth factor support, then hold eribulin until recovery to grade ≤ 2 . Eribulin may be then be resumed at the same dose with growth factor support, or it may be reduced by one dose level, per investigator discretion. |

| | | |
|---|---|---|
| | | If uncomplicated neutropenia lasting > 1 week (<1000 /mm3 without fever or infection) occurs/recurs despite growth factor support, then hold eribulin until recovery to grade ≤ 2 and reduce by 1 dose level. |
| Platelets | Grade 2 | Hold eribulin until recovery to grade 1 |
| | Grade 3 | Hold eribulin until recovery to grade 1 then reduce by 1 dose level. |
| | Grade 4 | Hold eribulin until recovery to grade 1 then reduce by 1 dose level. |
| Anemia | Grade 4 | Hold eribulin until recovery to grade ≤ 2 then reduce by 1 dose level. PRBC transfusions are permitted to treat anemia. |
| Peripheral neuropathy | Grade 2 | For intolerable (as determined by physician and patient) grade 2, decrease chemotherapy by one dose level. |
| | Grade 3 | Hold eribulin until recovery to grade ≤ 2 then reduce by 1 dose level. |
| | Grade 4 | Treatment discontinuation. |
| Non-hematologic toxicity | Grade 3, first occurrence | Hold eribulin until recovery to grade ≤ 2. Maximize supportive care measures. If symptom recovery occurs within 1 week, then eribulin may be resumed at the same dose if deemed appropriate by the investigator, otherwise, reduce by 1 dose level. |
| | Recurrent grade 3, or any grade 4 toxicity | Hold eribulin until recovery to grade ≤ 2 then reduce by 1 dose level. |
| Recurrence of any Grade 3 or 4 event despite reduction to 0.7 mg/m$^2$, or persistent grade 3 or 4 toxicity lasting more than 3 weeks despite maximal supportive measures | | Treatment discontinuation |
| ANC = absolute neutrophil count<br>a: Toxicities graded in accordance with National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0, Appendix 5 | | |

**Instructions for Dose Delay**

Criteria to continue treatment

- Absolute Neutrophil Count $\geq$ 1000/mm$^3$ or $\geq$1.0×10$^9$/L
- Platelet Count $\geq$ 75,000/mm$^3$ or $\geq$75×10$^9$/L
- Non-hematologic toxicity $\leq$ grade 2

Eribulin will NOT be administered if any of the following values are present on Day 1 or 8 prior to treatment administration:

- Absolute Neutrophil Count <1,000/mm$^3$ or <1.0×10$^9$/L
- Platelet Count <75,000/ mm$^3$ or <75×10$^9$/L
- Non-hematologic toxicity CTCAE Grade 3 or 4

If the dose of eribulin cannot be administered as planned due to treatment-related toxicity, the dose should be delayed according to the following instructions:

**Day 1 of each cycle:** If eribulin cannot be administered on Day 1, the dose should be delayed until recovery to above mentioned values (criteria for eribulin administration). The Day 1 dose will be rescheduled for when the criteria for eribulin administration are being met. The dose of eribulin may have to be reduced following a dose delay in accordance to the instructions for dose reduction (Table 1). A maximum of 3 weeks are allowed for a delay in therapy. If the patient fails to meet the criteria to continue treatment within 3 weeks, they will be removed from the protocol.

**Day 8 of each cycle:** If eribulin cannot be administered on Day 8, the dose should be delayed until recovery to above mentioned values (criteria for eribulin administration). The Day 8 dose will be **delayed for a maximum of 7 days** and as follows:

- If the criteria for eribulin administration are met on, or before Day 15 of a cycle, administer eribulin as recommended inTable 1; this dose is still called Day 8.
- Eribulin administration on Day 1 of the next cycle should be no sooner than 14 days later.
- If the criteria for eribulin administration are NOT being met by Day 15 of a cycle, omit the Day 8 dose of eribulin for that cycle. Eribulin should be administered as recommended in Table 1 on Day 1 of the next scheduled cycle assuming criteria to continue treatment are met within a maximum 3 week delay in therapy from originally planned day 8.

# 7. DRUG FORMULATION AND ADMINISTRATION

## 7.1. Eribulin

Refer to the Investigator's Brochure for detailed agent information and Havalen® FDA approved package for more information.

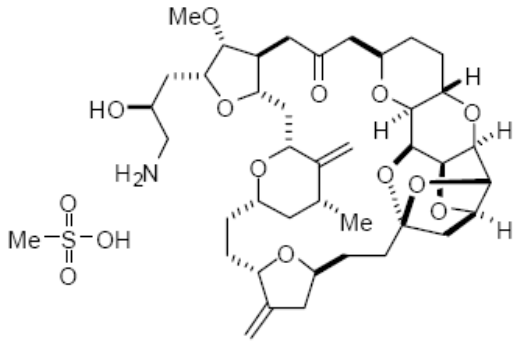
Description

**Chemical name:** 11,15:18,21:24,28- Triepoxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-*b][1,4]dioxacyclopentacosin-5(4H)-one,*2-[(2S)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)(2R,3R,3aS,7R,8aS,9S,10aR,11S,12R,13aR,13bS,15S,18S,21S,24S,26R,28R,29aS)-, methanesulfonate (salt)

**Empirical formula:** C40H59NO11•CH4O3S

**Molecular weight:** 826.0 (729.9 for free base).

Structural formula:




**Other name:** E7389, Halaven®

**Mode of action:** Eribulin injection is a non-taxane microtubule dynamics inhibitor.

**Manufacturer:** Eisai

**Molecular weight:** 826.0 (729.9 for free base).

**Distribution:** Vd: 43-114 L/m2

**Protein binding:** 49% to 65%

**Metabolism:** Negligible

**Half-life, elimination:** ~40 hours

**Excretion:** Feces (82%; predominantly as unchanged drug); urine (9%, primarily as unchanged drug)

**Form**

Eribulin is clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin as a 0.5 mg/mL solution in ethanol: water (5:95).Eribulin is manufactured by Eisai.

**Storage and Stability**

Store undiluted eribulin in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or/ 4°C). Store diluted solutions of eribulin for up to 4 hours at room temperature or up to 24 hours under refrigeration. Discard unused portions of the vial.

**Compatibility**

Eribulin is compatible with saline (0.9% Sodium Chloride Injection). It is not compatible with solutions with dextrose.

**Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

**Availability**

Eribulin is a commercially available agent but will be supplied free-of-charge from Eisai.

**Preparation**

The amount of eribulin required will be withdrawn from the appropriate number of vials into a syringe. This may be injected directly as an i.v. infusion over approximately 2 to 5 minutes or diluted in up to 100 mL 0.9% saline for i.v. infusion over approximately 2 to 5 minutes. Do not dilute in or administer through an intravenous line containing solutions with dextrose. Do not administer in the same intravenous line concurrent with the other medicinal products.

**Administration**

It will be administered over approximately 2-5 minutes. Do not administer in the same intravenous line concurrent with the other medicinal products.

**Ordering**

Eribulin will be provided by Eisai and stored in the site research pharmacy. Under no circumstances will the investigator allow the study treatment(s) to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study. Please refer to Appendix 9: Section 4.0 for additional ordering information.

**Accountability**

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form.

**Destruction and Return**

At the end of the study, unused supplies of eribulin should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

# 8. CORRELATIVE STUDIES

## 8.1. Patient-Reported Outcomes Assessment

QOL surveys (PRO-CTCAE, FACT-B, FACT-Ntx) surveys will be administered at cycles 1, 2 and 3, every other cycle in subsequent cycles, and End-of-Treatment visit (detailed in Table 3 and Appendix 6).

In order to minimize incomplete data, which can be a major issue in survey research, surveys will be administered using electronic tablets at the specified study visits listed above. This will be performed via wireless tablet computers brought to patients by study staff. This is a well-established method of administering electronic questionnaires to patients. No data will be stored on these tablets, and data will be transmitted securely and in de-identified form in real-time to a server at the DFCI, where the data will be stored on highly secure servers. As a backup, paper copies of QOL surveys will be available at all sites. The PRO-CTCAE Software System will be used in this study to administer PRO-CTCAE items to enrolled patients at designated clinic visits. Items of the PRO-CTCAE system defined as core symptoms will be used in the present study (Appendix 6).

If a participant is unable to fill out the survey using the electronic tablet, the survey may be filled out on paper with the patient ID, date, and timepoint clearly recorded. These paper surveys should be returned to the participating site, and a copy stored in the patient research record. The original survey should be mailed to:Survey and Data Management Core

RE: Eribulin Trial

Dana-Farber Cancer Institute

450 Brookline Avenue, LW 601

Boston, MA 02215

Selected provider-reported CTCAE (detailed in Table 2, also attached as Appendix 8) will be collected on day 1 of cycles 1, 2 and 3, every other cycle in subsequent cycles, and off study visit for the purpose of assessing agreement between PRO-CTCAE and provider reported CTCAE. Data collection will occur using a form (Appendix 8) to be completed by the provider after the patient encounter. Adverse events will be graded as the worst grade in the last 7 days, which is different from standard CTCAE grading which typically spans the duration of time since the prior clinical assessment or treatment. This adverse event data collection is in addition to routine comprehensive adverse event reporting performed at every encounter and detailed in Table 3, the Study Calendar.

**Table 2:** Selected provider-reported CTCAE adverse events to be collected at cycles 1, 2 and 3, every other cycle in subsequent cycles, and off study visit.

| System Organ Class (SOC) | Adverse event | None | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| **Gastrointestinal Disorders** | Constipation | | | | | |
| | Diarrhea | | | | | |
| | Dry mouth | | | | | |
| | Mucositis | | | | | |
| | Nausea | | | | | |
| | Vomiting | | | | | |
| **General disorders and administration site conditions** | Hair Loss | | | | NA | NA |
| | Edema limbs | | | | | |
| | Fatigue | | | | | |
| | Pain | | | | | |
| **Metabolism and nutrition disorders** | Anorexia | | | | | |
| **Nervous system disorders** | Concentration impairment | | | | | |
| | Dysgeusia | | | | | |
| | Headache | | | | | |
| | Peripheral sensory neuropathy | | | | | |
| **Psychiatric disorders** | Anxiety | | | | | |
| | Depression | | | | | |
| | Insomnia | | | | | |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea | | | | | |
| | Abbreviations: Not applicable | | | | | |

We expect that this study will provide supportive data as part of an accumulating body of evidence for the psychometric integrity of the PRO-CTCAE.

## 8.2. Correlative Neurotoxicity Analysis

Previous analysis has identified single nucleotide polymorphisms (SNPs) that predicted likelihood of experiencing taxane-induced peripheral neuropathy in the adjuvant breast cancer trial; E5103.[29] In this study, we plan to explore whether these SNPs also predispose patients to peripheral neuropathy from eribulin.

*DNA sample preparation from whole blood*

Whole blood samples (10 ml) are collected in a tube containing a standard anticoagulant, such as ACD, EDTA, or heparin. Samples are then stored in a -70°C freezer until they are ready to be shipped. The frozen blood samples are shipped on dry ice to Schneider`s lab at Indiana University.

The blood samples are thawed in a water bath at 37°C and gently agitated. Buffy coat samples are prepared by centrifuging the blood sample at 3300 g for 10 minutes at room temperature and the intermediate clear layer of sample are collected for DNA extraction. QIAamp DNA Blood

Mini Kit is used to isolate DNA from the buffy coat samples. Steps in this process include lysis and digestion of the sample with a protease, a simple bind-wash-elute procedure, and finally precipitation of the DNA for future use.

**Methods:**

DNA from buffy coat will be used to genotype candidate SNPs. The candidates will include those SNPs that had a provocative association with peripheral neuropathy from prior work with paclitaxel in E5103. We will compare candidate genotypes with the likelihood of developing clinically significant peripheral neuropathy in this trial.

***Shipping address for Schneider lab***

Schneider Lab
980 W. Walnut Street
Walther Hall C246
Indianapolis, IN 46202
Tel: (317)274-4646
Fax: (317)274-0396

## 9. STUDY CALENDAR

**Table 3** summarizes the Study Calendar. Visits should occur within +/- 3 days of the scheduled day. If a subject fails to appear for a scheduled study visit, the investigator will make every attempt to contact the subject and determine the reason(s) for the missed visit as completely and accurately as possible. Subjects will only be judged as lost to follow-up if they cannot be reached after three documented attempts (1 week apart) by the site to contact them.

## Table 3:

| | Pre-Tx | Treatment Phase (cycles 1 to 3 and subsequent cycles) | | | | | | | | End of tx. | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Cycle 1 | | Cycle 2 | | Cycle 3 | | Cycle 4 [b] | | | |
| **Day(D) Assessments** | **D –21 to D 0** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **D1** | **D8** | **Within 21 days of final dose [c]** | **Every 9 weeks [d]** |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | |
| Demographic Data | X | | | | | | | | | | |
| ECOG PS | X | X | | X | | X | | X | | X | |
| Medical / Surgical History | X | | | | | | | | | | |
| Prior Medications / Procedures | X | | | | | | | | | | |
| Physical Examination | X[e] | X[e] | | X[e] | | X[e] | | X[e] | | X[e] | |
| Vital Signs | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | |
| Tumor Assessments | X[a] | | | | | | | X[a] | | X[a] | X[a] |
| 12-Lead ECG[g] | X[g] | | | X[g] | | | | | | | |
| Pregnancy Test (if applicable) | X[h] | | | | | | | | | | |
| Hematology | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | X[i] | |
| Blood Sampling | | X[j] | | | | | | | | | |
| Chemistry | X[k] | X[k] | X[k] | X[k] | X[k] | X[k] | X[k] | X[k] | X[k] | X[k] | |
| QOL assessments | | X[l] | | X[l] | | X[l] | | | | X[l] | |
| Eribulin mesylate | | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | |
| Adverse Events | | X[n] | | X[n] | | X[n] | | X[n] | | X[n] | X[n] |
| Provider CTCAE form | | X[o] | | X[o] | | X[o] | | | | X[o] | |

**Footnotes**

Clinical chemistry and hematology analyses screening assessment may serve as the baseline assessment if performed within 3 days (72 hours) before the first dose of study treatment. Assessments on Day 1 of each cycle may be performed within 3 days of administration of study treatment, except vital signs (which are measured before administration of eribulin mesylate).

a: Screening: Baseline tumor assessments of the chest, abdomen, pelvis and other areas of known or newly suspected disease should be performed within 21 days before start of treatment. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT (Chest x-ray not permitted for tumor assessment). CT scans should be performed with oral and iodinated i.v. contrast and MRI scans with i.v. gadolinium chelate unless there is a medical contraindication to contrast. If i.v. contrast is contraindicated, chest CT should be done without i.v. contrast. Skin lesions should be clinically assessed using a metric ruler to calibrate

lesion size. A bone scan should be performed on all subjects within 6 weeks before start of treatment.

Treatment Phase: Tumor assessments of the chest, abdomen and other areas of known disease that were scanned at Baseline, or newly suspected disease, must be performed every 9 weeks during study treatment until PD is documented. If treatment is delayed due to toxicity, tumor assessments will remain on a 9 week schedule. Tumor assessment must be performed within 1 wk of administration of the first dose of study treatment in the next treatment cycle, and should use the same methodology (CT/MRI) and scan acquisition techniques (including use or nonuse of i.v. contrast) as was used for the baseline assessments. Possible PR and CR (according to RECIST v 1.1,Appendix ) must be confirmed at no less than 4 weeks after the initial response assessment. If a subject withdraws from the study for radiographic evidence of PD, tumor assessments are not required at the End-of-Treatment visit.

Posttreatment Follow-up Period: Subjects without PD at the time study treatment is discontinued should have tumor assessments every 9 wks from the date of last tumor assessment until PD is documented.

Brain scans are at treating physician discretion. Scans can also occur as clinically indicated for new symptoms or to confirm disease response. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.

Bone Scans: Screening bone scans will be performed within 6 weeks before the start of treatment. Post screening bone scans are at treating physician discretion. Scans can also occur as clinically indicated for new symptoms or to confirm disease response. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.

The same methodology and scan acquisition techniques used at screening should be used throughout the study.

b: Assessments in the subsequent treatment cycles should follow assessments specified in cycles 1 to 4.

c: These assessments will also be conducted upon early discontinuation from the study.

d: Subjects who discontinue study treatment without having PD will return to the clinic for disease evaluation every 9 weeks until PD is documented.

e: Physical examination to be done at Screening, Day 1 of each cycle, and End-of-Treatment visit. PE on Day 1 of each cycle may be done within 3 days before the scheduled visit.

f: Height recorded at Screening. Weight to be recorded on Days 1 and 8 of each cycle and End of Treatment. Other vital signs (BP, HR, respiratory rate, and body temperature) will be recorded before administration of eribulin mesylate on Days 1 and 8 of each cycle.

g: ECG evaluations will be performed for all subjects at Screening and during the Treatment Phase before starting the second cycle of eribulin mesylate (recommended to be on Day 1 of Cycle 2 before administration of eribulin mesylate).

h: Females of childbearing potential must undergo a urine or serum β-hCG pregnancy test at screening.

i: Hematology will be measured on Day 1 and Day 8 of each cycle. Hematology assessments are not required on Day 1 of Cycle 1 if performed within 3 days before study administration. Hematology assessments must be reviewed before administration of study treatment.

j: Collection of whole blood for germline DNA and SNP analysis. If for any reason this sample is missed at baseline, or sample is insufficient; this may be redrawn at any timepoint before participant is removed from the study. Refer to Appendix 7 for additional information.

k: Serum chemistry parameters will be measured on Day 1 and day 8 of each cycle. Assessments are not required on Day 1 of Cycle 1 if performed within 3 days before study administration. Serum chemistry assessments must be reviewed before administration of study treatment.

l: FACT-B, FACT-Ntx and PRO-CTCAE questionnaires to be recorded at Day 1 Cycles 1, 2 and 3, every other cycle in subsequent Cycles, and End-of-Treatment visit. Assessments may be performed within 3 days before the scheduled visit.

m: Eribulin mesylate 1.4 mg/m2 given via i.v. infusion over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle.

n: All AEs, regardless of relationship to study treatment or procedure or grade, will be collected from the time the subject initiated therapy until 30 days after discontinuation of study treatment. All AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first. However, treatment-emergent peripheral neuropathy

of any grade will be followed until resolution or until another anticancer therapy is started, whichever occurs first. Serious AEs will be collected for 30 days post treatment and followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize.

O: Adverse event assessments will be graded as the worst grade in the last 7 days and recorded on Day 1 of Cycles 1, 2 and 3, every other cycle in subsequent Cycles, and End-of-Treatment visit.. Complete form in Appendix 8.

Abbreviations: BP = blood pressure; CBC = complete blood count; CNS = central nervous system; CR = complete response; CT = computed tomography; ECG = electrocardiogram; HR = heart rate; i.v. = intravenous; MRI = magnetic resonance imaging; PD = disease progression; PE = physical exam; PR = partial response; PS = performance status; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; Tx = treatment

# 10. MEASUREMENT OF EFFECT

## 10.1. Efficacy Assessments (Antitumor Activity)

Tumor response assessments

All tumor assessments will be performed and analyzed based on RECIST v 1.1 (refer to Appendix 1 for details). Eligible subjects for this study must have measurable disease at Baseline, determined by the presence of at least one measurable target lesion. To assess best response (CR, PR, stable disease [SD], PD, not evaluable [NE]), each subject's overall tumor burden at Baseline will be compared with subsequent measurements of lesions. Tumor response is to be assessed every 9 weeks. The same modality and contrast agent should be used for each measurement.

Timing and Method of Tumor Assessments

Baseline tumor assessments must be performed within 21 days before the first infusion of study treatment during the Pretreatment Phase to confirm subject eligibility and to identify target and nontarget lesions to be followed during the study. Baseline tumor assessments will consist of radiographic evaluation (CT or MRI scans) of the chest, abdomen, pelvis, and any other areas of known or suspected disease, along with clinical assessment of skin lesions, if applicable, using a metric ruler in the field and measured using calipers. A bone scan should also be performed on all subjects within 6 weeks before the first infusion of study treatment.

Radiologic tumor assessments of the chest, abdomen, pelvis and other areas of known disease that are scanned at screening, or areas of newly suspected disease, must be performed every 9 weeks. During treatment, tumor assessments should be performed any time within 1 week of administration of the first dose of study treatment in the next treatment cycle. Tumor assessments may be performed sooner than every 9 weeks if there is symptomatic evidence of PD upon clinical examination of the subject.

For subjects with a possible PR or CR (according to RECIST v 1.1), changes in tumor measurements must be confirmed by repeat evaluations, to be performed not less than 4 weeks after the response criteria are first met. **The same imaging modality and image-acquisition protocol (including use or nonuse of i.v. contrast) should be used across all time points to allow consistent comparison of lesions**.

The preferred type of **CT scan** is a diagnostic quality spiral or multi-detector CT with i.v. and oral contrast. If iodinated i.v. contrast is contraindicated, it is recommended that the chest evaluation be done with noncontrast CT and the abdomen and pelvis evaluation be performed using either CT with oral contrast (without i.v. contrast) or MRI with gadolinium chelate i.v. contrast. Low-dose noncontract CT transmission scans from a positron-emission tomography (PET)-CT combination scanner are **not** acceptable. Spiral/multidetector CT and MRI body scans should be performed using ≤5 mm contiguous slices. **Skin lesions** should be clinically assessed using a ruler with millimeter subdivisions in the field and measurement performed using calipers. Ultrasound and low-dose noncontract CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are **not** acceptable methods of radiographic tumor assessment. However, a fluorodeoxyglucose positron emission tomography (FDG-PET) scan, chest x-ray or skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document PD in lieu of the CT/MRI scans.

Post screening **bone scans** will be performed at treating physician discretion. Scans can also occur as clinically indicated for new symptoms or to confirm disease response. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.
The recommended bone scan technique is 99m-technetium-labeled methylene diphosphonate (99m-Tc-MDP) scintigraphy or whole-body bone MRI. If an alternative scanning method is used, it should be continued throughout the rest of the study.

**The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.**

A **brain scan** by CT or MRI will only be performed at treating physician discretion. Scans can also occur as clinically indicated for new symptoms or to confirm disease response. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated. Brain scans should be performed with contrast-enhanced CT or MRI with ≤5-mm contiguous slices. **Skin lesions** should be clinically assessed using a metric ruler in the field and measured using calipers. If **subcutaneous masses or nodes** are palpable (e.g., bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of these lesions, whether target or nontarget.

If study treatment is discontinued due to radiographic evidence of PD, the subject does not have to undergo tumor assessments at the End-of-Treatment visit. Follow-up disease evaluation is not required for subjects who have radiographic evidence of PD at the time of discontinuation of treatment or for those subjects who withdraw consent before developing PD.

### 10.2. Baseline Identification of Target and Nontarget Lesions

At Baseline, the investigator is to select up to a total of five measurable lesions (two per organ) that are representative of all involved organs as **target lesions**. Target lesions are to be selected on the basis of their size (the lesion with the longest diameter) and suitability for accurate repeated measurements (either by imaging techniques or clinically). To be considered a **target lesion** at Baseline, the lesion must be measurable and have a minimum size of ≥10 mm in the longest diameter for non-lymph node lesions or ≥15 mm in the short-axis for a lymph node.

All other lesions (or sites of disease), both measurable and nonmeasurable, will be identified as **nontarget lesions** and will be recorded at Baseline. Nontarget lesions will be evaluated at the same assessment time points as target lesions. However, measurements will not be required, and these lesions will be followed as "present" or "absent."

Refer to Appendix 1 for further details on the evaluation of target and nontarget lesions.

### 10.3. Primary efficacy variable/endpoint

The antitumor activity of eribulin mesylate monotherapy will be assessed by determining ORR based on RECIST v 1.1 (Appendix 1). For analysis purposes, ORR is defined as the proportion of subjects who achieve a CR plus those who achieve a PR. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat evaluations, to be performed not less than 4 weeks after the response criteria are first met.

### 10.4. Secondary efficacy variables

The secondary efficacy endpoints for this study are time to first response, duration of response and PFS, defined as follows:

- Time to first response will be defined for subjects whose best overall response (OR) is a CR or PR. The time to first response will be measured from the date of first dose of study treatment until the earliest date that CR or PR is objectively documented.
- Duration of overall response will be defined for subjects whose best OR is CR or PR. The duration of OR will be measured from the time that response criteria for CR or PR (whichever is recorded first) are first met until the date that PD or death from any cause is first objectively documented). Subjects who do not have PD will be censored on the day of their last tumor assessment.
- Progression-free survival will be defined as the time from the date of the first dose of study treatment until the date of first documentation of PD or date of death from any cause (whichever occurs first). Subjects who die without reported PD are considered to have progressed on the day of their death. Subjects who are alive at the end of study without reported PD will be censored on the date of their last tumor assessment**.**

### 10.5. Laboratory measurements

Clinical laboratory tests will be performed at the investigational sites. Screening assessments of laboratory parameters may be used as Baseline assessments if they are performed within 3 days before the start of study treatment.

Table 4 presents the clinical laboratory tests to be performed at various time points during the study. **All results from laboratory assessments obtained at a scheduled visit must be reviewed before administration of study treatment.**

The Study Calendar (Table 3) shows the visits at which blood will be collected for clinical laboratory tests.

Hematology assessments will be performed at Screening, Day 1 and Day 8 of each treatment cycle, and the End-of-Treatment visit.

Clinical chemistry assessments will be performed at Screening, Day 1 and Day 8 of each treatment cycle, and the End-of-Treatment visit.

**Table 4: Clinical Laboratory Tests**

| Category | Tests |
|---|---|
| **Hematology**[a] | 1. Hematocrit, hemoglobin, RBC, platelet count, WBC with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC |
| **Clinical Chemistry**[b] **Screening/Baseline Panel** | 2. Pregnancy test (serum or urine β-hCG), chloride, potassium, sodium, BUN, serum creatinine, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, magnesium |
| **Treatment Panel** | 3. Chloride, potassium, sodium, BUN, serum creatinine, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, magnesium |

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; RBC = red blood cells; WBC = white blood cells

a: Hematology assessments obtained at Screening/Baseline, Days 1 and 8 of each treatment cycle

b: Chemistry assessments obtained at Screening/Baseline, and Day 1 and Day 8 of each treatment cycle

### 10.6. Vital signs and weight measurements

Vital sign measurements (blood pressure [BP], heart rate [HR], respiratory rate, oral body temperature [°C]) and weight will be obtained at the time points designated on the Study Calendar. Height will be measured at the Screening Visit only. Weight will be recorded on Day 1 and 8 of each cycle, before the subject receives study treatment, for calculation of BSA.

### 10.7. Electrocardiograms

Standardized, 12-lead ECGs will be performed at Screening, Baseline, once during Cycles 1 or 2 (preferably on Day 1 of Cycle 2 before administration of study treatment), and at the End-of-Treatment visit. The Screening assessment may be used as the Baseline assessment if the ECG is performed within 3 days before the start of study treatment.

An ECG abnormality may meet AE criteria as described in Section 11 of this protocol and the CRF completion guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Event page of the eCRF. For ECG abnormalities meeting SAE criteria, the study site must fax the SAE report, including the ECG report, to the Eisai Drug Safety Department using the SAE reporting form.

# 11. ADVERSE EVENT REPORTING REQUIREMENTS

## 11.1. Definitions

### 11.1.1. Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

### 11.1.2. Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. 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.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

### 11.1.3. Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a description of expected adverse events associated with eribulin.

Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

### 11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

### Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.
A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

**Reporting Requirements**

Each investigative site will be responsible to report SAEs that occur at that institution to the Overall Primary Investigator , Dr Erica Mayer and to their own Institutional IRB. DF/HCC sites will report to Dr Erica Mayer, and the DFCI/HCC IRB. Complete reporting instructions are described below.

**Reporting to the Study Sponsor**

Serious Adverse Event Reporting

Serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the following criteria:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 business hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 business hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Erica L. Mayer, MD MPH
Telephone: 617-632-2335
Fax: 617-632-1930
emayer@partners.org

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

### 11.2. Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

| Attribution | DF/HCC Reportable AEs | | | | |
|---|---|---|---|---|---|
| | **Gr. 2 & 3 AE Expected** | **Gr. 2 & 3 AE Unexpected** | **Gr. 4 AE Expected** | **Gr. 4 AE Unexpected** | **Gr. 5 AE Expected or Unexpected** |
| Unrelated Unlikely | Not required | Not required | 5 calendar days# | 5 calendar days | 24 hours* |
| Possible Probable Definite | Not required | 5 calendar days | 5 calendar days# | 5 calendar days | 24 hours* |
| # If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported. | | | | | |

* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

### 11.3. Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

### 11.4. Reporting SAEs to EISAI

All SAEs, as defined in Section 11.1.2, will be reported to EISAI on a Medwatch 3500A form within one business dayof the event. The reports will be sent to EISAI at the number listed below:

EISAI safety fax number (732-791-1111) Email: ESI_Safety@eisai.com

External participating sites will send Medwatch 3500A reports directly to EISAI, and a copy will be sent to the DFCI project manager: CTOPM@dfci.harvard.edu

DF/HCC sites will send the Medwatch 3500A reports directly to EISAI and file a copy in the study regulatory documents.

### 11.5. Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the investigator or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse

event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

## 12. DATA AND SAFETY MONITORING

This study will be organized, performed, and reported in compliance with the protocol, standard operating practices, working practice documents, and applicable regulations and guidelines. Site visit audits may be made periodically by a qualified compliance auditing team, which is an independent function from the study conduct team.

### 12.1. Data Reporting

Method

The QACT will collect, manage, and monitor data for this study.

Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

| **Form** | **Submission Timeline** |
|---|---|
| Eligibility Checklist | Complete prior to registration with QACT |
| On Study Form | Within approximately 14 days of registration |
| Baseline Assessment Form | Within approximately 14 days of registration |
| Treatment Form | Within approximately 10 days of the last day of the cycle |
| Adverse Event Report Form | Within approximately 10 days of the last day of the cycle |
| Response Assessment Form | Within approximately 10 days of the completion of the cycle required for response evaluation |
| Off Treatment/Off Study Form | Within approximately 14 days of completing treatment or being taken off study for any reason |
| Follow up/Survival Form | Within approximately 14 days of the protocol defined follow up visit date or call |

### 12.2. Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## 12.3. Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements. Please refer to Appendix 9: Section 5.0 for additional information.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

## 12.4. Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix F.

The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

# 13. REGULATORY CONSIDERATIONS

## 13.1. Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

## 13.2. Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

## 13.3. Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

### 13.4. Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

### 13.5. Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

# 14. STATISTICAL METHODS

## 14.1. Statistical and Analytical Plans

Statistical programming and analyses will be performed using SAS and other validated statistical software as required.

The primary analyses of efficacy endpoints that are related to tumor assessment will be performed using investigator-assessed data.

The full analysis dataset will include all subjects who receive at least one dose of study treatment. Objective response will be assessed according to RECIST 1.1. All patients who receive at least one dose of therapy will be included in the calculation of objective response rate. Patients who, in retrospect, do not have measurable disease, and patients with no follow up evaluation of response, will be considered non-responders for the purpose of analysis of the primary endpoint. Confirmation of response is required to assign a status of best overall response of CR or PR.

Patients who have developed metastatic disease within 12 months of last dose of (neo) adjuvant chemotherapy who enroll on protocol will be considered in the analysis as a second-line patient, even if no prior chemotherapy was received in the metastatic setting.

Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be listed, and summarized for the full analysis dataset. For continuous demographic/baseline variables such as age, weight, and vital signs, results will be summarized and presented as number (N), mean, median, and range. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

Subject Disposition

The number and percentage of subjects, who complete or prematurely withdraw from the study, as well as the reason for discontinuation, will be summarized.

## 14.2. Determination of sample size

The historical ORR data for chemotherapy in the first-line metastatic setting indicated a 33% ORR for anthracycline and 38% ORR for taxanes. For patients treated beyond first-line, the historical data indicate an approximate 20% ORR. This trial will be open for treatment in either the first- or second-line setting. The study primary endpoint is the ORR of eribulin given as monotherapy. ORR defined as the proportion of subjects who achieve a confirmed CR or PR (RECIST 1.1), will be evaluated for each cohort separately using investigator-assessed data (Appendix 1).

Statistical considerations for eribulin monotherapy cohorts (cohort 1 and 2)

ORR will be estimated separately for the HR+/HER2- and the TNBC monotherapy cohorts. For the TNBC cohort, it is assumed there will be a 50-50 allocation between first- and second-line patients. For the HR-positive cohort, it is assumed there will be a 40-60 allocation between first- and second-line patients. The primary objective is to estimate the response rate (by RECIST 1.1) to eribulin.

From the meta-analysis of O'Shaughnessy *et al*, the ORR in TNBC in the first-line setting was approximately 23%, and was 18% in the second-line setting based on the results of the TNBC subgroup of patients in the RIBBON-2 trial. With a 50-50 allocation between first- and second-line patients, we would assume a response rate of approximately 21-22% in the cohort of TNBC. For patients with HR-positive disease, the estimated ORR from RIBBON-2 was 29.6% in the second-line setting and has been reported to be between 33-38% for first-line therapy. We assume a 40-60 allocation between first- and second-line patients in the HR-positive cohort, and conservatively estimate a response rate of 30% in this protocol.

Our response rate assumptions for this protocol are 22% in the TNBC cohort and 30% in HR-positive cohort. Because eribulin has already demonstrated activity, including an overall survival advantage in the refractory setting, this study will utilize a single-stage design. The sample sizes of each cohort were based on the lower bounds of the 90% exact confidence intervals (CI) around possible observed response rates, as shown in the Table 5.

**Table 5: Eribulin Sample Size Table**

***Confidence intervals estimated using exact binomial methods.**

| ***Sample Size (per cohort)*** | ***Number responses*** | ***Observed response rate*** | ***Lower end 90% CI**** | ***Upper end 90% CI**** | ***Width 90% CI*** |
|---|---|---|---|---|---|
| 45 | 9 | .200 | .109 | .323 | .215 |
| | 11 | .244 | .144 | .372 | .228 |
| | 13 | .289 | .180 | .420 | .239 |
| | 14 | .311 | .199 | .443 | .244 |
| | 15 | .333 | .218 | .466 | .248 |
| | 16 | .356 | .237 | .489 | .252 |
| | 17 | .378 | .257 | .511 | .254 |
| | 18 | .400 | .277 | .534 | .257 |
| | 19 | .422 | .297 | .555 | .258 |
| | 20 | .444 | .317 | .578 | .261 |
| | 21 | .467 | .338 | .599 | .261 |

For TNBC (orange) cohort, if 16 or more women of 45 have a response, then the lower bound of the 90% exact confidence interval of the observed response rate exceeds 22%.

For ER+ (yellow) cohort, if 20 or more women of 45 have a response, the lower bound of the 90% exact confidence interval of the observed response rate exceeds 30%, which is the historical response rate of the combined 1st and 2nd line groups.

In the TNBC cohort, there will be 90% power to detect a 22% percent improvement in response (22% vs. 44%) assuming an equal allocation of first- and second-line patients. In the HR-positive cohort, there will be 90% power to detect a 23 percent improvement in response (30% vs. 53%) assuming first- and second-line patients are allocated approximately 40-60. Both calculations assume a two-sided, 0.1 type-1 error and an exact binomial test.

### 14.3. Safety analysis

All patients who receive at least one dose of the study regimens will be included in the assessment of adverse events (full analysis population). Adverse event information for the two cohorts will be combined. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, and ECGs. Abnormal laboratory values will be flagged.

Adverse event information will be collected from the time the subject signs the ICF until resolution or for 30 days after the subject's last study visit, whichever comes first. Treatment-emergent AEs (TEAEs) will be analyzed. Adverse events will be regarded as TEAEs if they started on or after the date and time of administration of the first dose of study treatment or if they were present before the administration of the first dose of study treatment and increased in severity during the study. Treatment-emergent peripheral neuropathy will be followed until resolution or until the start of another anticancer therapy post treatment, whichever occurs first.

Adverse events will be graded using CTCAE v 4.0 (Appendix 5). Investigators will collect all CTCAE grades for all AEs (to assess both increasing and decreasing severity). Events will be summarized by frequency and percentage.

The incidence of TEAEs and relatedness to study treatment will be summarized. Although an adverse event may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that adverse event term by the highest CTCAE grade (in the summary by CTCAE grade) and by the closest causal relationship to study treatment (in the summary by relatedness to study treatment).

### 14.4. Analysis of Secondary Efficacy Variables

Progression-free survival (PFS) will be analyzed using Kaplan-Meier product-limit estimates and presented separately for each cohort. Median PFS and the cumulative probability of PFS at 6 and 12 months will be presented with two sided 90% CIs derived using log(-log(survival)) methodology. Time to first response and duration of response will be summarized for the responders using the Kaplan-Meier method. The cumulative PFS, time to first response, and duration of response probabilities will be plotted over time. Median and first and third quartiles from Kaplan-Meier estimation for PFS, time to first response, and duration of response will be provided with 90% CIs.

### 14.5. Analysis of Quality of Life Assessments

Patient reported outcome data will be combined for the monotherapy cohorts. QOL surveys (FACT-B, FACT-Ntx, and PRO-CTCAE) questionnaires will be obtained at baseline, C2D1,

C4D1, C7D1, and at the off-study visit. Quality of life (QoL) data will be combined for the monotherapy cohorts (Cohorts 1 and 2).

FACT-B: At each assessment time, subscale scores for physical well-being, emotional well-being, social well-being, functional well-being, and relationship with doctor will be scored per standardized scoring algorithms and will be presented individually and combined to obtain the FACT-G total score. In addition, the breast cancer subscale score will be summarized separately and combined with the FACT-G to obtain the summary score of the FACT-B. For all subscales and total scores, a higher score reflects better QoL. Descriptive statistics will be presented for each subscale and total score. We will also summarize changes in scores between baseline and C2D1 to assess the effect of treatment upon QoL. Change scores will be compared with zero using the Wilcoxon signed-rank test. For the combined monotherapy cohort, a sample of size 90 will have 80% power to detect a mean change score that is 0.28 times the common standard deviation (i.e., effect size of 0.28), when tested at a two-sided 10% significance level. Scores will also be summarized graphically over the repeated assessment times to derive a QoL response profile over the course of treatment.

FACT-NTX: The effect of peripheral neuropathy upon QoL will be summarized using the 11-item FACT-NTX assessment. At each assessment time, scores will be summarized descriptively. Changes in score between baseline and C2D1 will also be summarized descriptively on a continuous scale, in addition to the proportion of patients who have clinically meaningful changes in score of 3 points or greater. The proportion will be presented with a 90% confidence interval estimated using exact binomial methods. For a sample of size 90, the confidence interval will be no wider than 0.18.

The primary purpose of the inclusion of PRO-CTCAE is to evaluate the performance of an electronic-based system for patient self-reporting of AEs, and assess whether PRO data collection improves the accuracy and description of each class of AEs. PRO-CTCAE data will also be compared with provider-reported CTCAE toxicity data to estimate the degree of concordance or divergence for each class of toxicity. The PRO-CTCAE data evaluation will also focus on accurate description of incidence and severity of neuropathy in this patient population. The PRO-CTCAE data presentation and analysis will be descriptive and exploratory in nature.

### 14.6. Neuropathy Analysis

Comparison of candidate genotypes with the likelihood of developing clinically significant peripheral neuropathy in this trial will be exploratory in nature.

## 15. PUBLICATION PLAN

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation. The Primary Investigator will be the final arbiter of the manuscript content.

The outcome results of this trial will be made public within 24 months of the end of data collection. Interim accrual and toxicity results of this trial may also be periodically presented at meetings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium. A full report of the outcomes will be made public no later than two (2) years after the end of data collection.

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# 17. APPENDICES

## 17.1. Appendix 1 - Overview of RECIST v 1.1 for Evaluation of Tumor Response

Tumor response assessments in this clinical study will use RECIST v 1.1 based on the 2009 article by Eisenhauer et al. entitled, *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)*.**Error! Bookmark not defined.** This Appendix contains an overview of the RECIST v 1.1 guidelines. For complete details, the Eisenhauer article, published in the *European Journal of Cancer*, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

**Baseline Tumor Assessment**

Subjects are required to have **measurable disease**, defined as the presence of at least one measurable lesion, to be eligible for entry into the study. Measurable and nonmeasurable lesions are defined as:

- **Measurable lesions**: Lesions that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) with a **minimum** size of >10 mm based on CT (CT slice thickness of ≤5 mm; for slice thicknesses >5 mm, measurable lesions must have a longest diameter ≥2 times the slice thickness) or caliper measurement by clinical exam.

  A lymph node will be considered pathologically enlarged and measurable if its short axis is ≥15 mm; the short axis should be measured and followed throughout. Nodes with a short axis ≥10 mm and <15 mm will be considered pathologically enlarged but nonmeasurable.

  Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft-tissue components will be considered measurable if the soft-tissue component can be evaluated by cross-sectional imaging (i.e., CT scan) and meets the general definition of measurability. Blastic bone lesions are nonmeasurable.

  A lesion located in a previously irradiated area, or in an area previously subjected to any locoregional therapy, will be considered measurable only if there has been a documented increase in lesion size subsequent to prior treatment but before study entry.

  Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules) and should be assessed using a metric ruler to estimate the size of the lesion. The minimum lesion size is ≥10 mm.
- **Nonmeasurable lesions**: All other lesions, including small lesions (LD <10 mm or pathological lymph nodes with a short axis of ≥10 mm to <15 mm), lesions that cannot be accurately measured with calipers, and truly nonmeasurable lesions: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Lymph nodes with a short axis <10 mm are considered nonpathological and should not be recorded or followed.

  Simple cysts (cystic lesions) will not be considered malignant, and will be neither measurable nor nonmeasurable. Cystic lesions believed to be metastases may be considered measurable if they meet the general definition of measurability, but noncystic lesions are preferred as target lesions.

Baseline evaluations should be performed as closely as possible to the start of treatment and within 21 days before the first dose of study treatment (bone scans should be performed within 6 weeks of start of treatment).

**Methods of Tumor Measurement**

The same imaging modality and the same technique (including use or nonuse of oral and i.v. contrast) should be used to characterize each identified and reported lesion at Baseline/Screening and at

reassessment time points during the study. All measurements should be taken and recorded in metric notation, using calipers if clinically assessed.

Computed tomography and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Computed tomography should be performed with slices of 5 mm or less in thickness (as a general rule, lesion diameter should be no less than double the slice thickness). This applies to tumors of the chest, abdomen, and pelvis. Magnetic resonance imaging is also acceptable in certain conditions (e.g., for body scans). A CT of the chest without contrast is preferred over MRI.

Bone scans, positron emission tomography (PET) scan, or plain films are not sufficient to measure bone lesions and document objective response, but may be used to confirm the presence or disappearance of such lesions. Bone scans should be performed using 99m-technetium-labeled polyphosphonate scintigraphy.

Chest x-rays should not be used for baseline assessment of the chest or for follow-up of known lesions. Chest CT should be used.

Ultrasound should not be used to measure tumor lesions.

Endoscopy and laparoscopy should not be used to measure tumor lesions. However, such techniques can be useful in confirming complete pathological response or determine relapse.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

**Documentation of "Target" and "Nontarget" Lesions**

Lesions are evaluated and classified at Baseline as either target or nontarget and all are then followed throughout the study.

*Target Lesions:*

Target lesions are all measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The short axis (≥15 mm) of any lymph nodes selected as target lesions at Baseline will be measured and recorded at each evaluation time point, even if the nodes become nonpathological (short axis <10 mm).

The sum of the diameters of all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated at Baseline and reported as the baseline sum diameter. This baseline sum diameter will be used as the reference by which to characterize objective tumor response. For lesions measurable in two or three dimensions, the LD must be reported at the time of each assessment.

*Target Lesions Too Small To Measure*:

Lesions that become too small to measure during treatment should be assigned a default measurement of either 0 mm (if the investigator believes the lesion has disappeared) or 5 mm (if the lesion is believed to be present and is faintly visible).

*Target Lesions That Split or Coalesce*:

If a non-nodal target lesion fragments during treatment, the longest diameters of each fragment should be added together to calculate the total sum for that lesion. When lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements for each individual lesion. If the lesions are no longer separable, the vector of the longest diameter in this instance should be

the maximal longest diameter for the coalesced lesion.

*Nontarget Lesions:*

All other lesions (or sites of disease) should be identified as **nontarget lesions** and should also be recorded at Baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout Follow-up.

*New Lesions*:

The finding of a new lesion should be unequivocal (i.e., not attributable to a change in scanning technique or imaging modality, and not thought to represent something other than a tumor). If a possible new lesion is equivocal, treatment and radiographic evaluation should continue per this protocol until confirmation of PD or until additional scans confirm the presence of a new lesion. In such a case, the date of progression will be the date of the initial scan.

A lesion identified on a Follow-up study of an anatomical location **not** studied as Baseline will be considered a new lesion.

Scanning with FDG-PET may be employed as a complement to CT scanning in the assessment of PD. A negative FDG-PET scan at Baseline with a positive scan during the study will be evidence of PD. If there is no FDG-PET scan at Baseline and a positive FDG-PET scan during the study, it will be considered evidence of PD if the positive FDG-PET corresponds to a new site of disease **confirmed by CT scan**. A positive postbaseline FDG-PET result corresponding to a pre-existing site of disease with no radiographic evidence of progression will not be considered evidence of PD.

**Evaluation of Response for an Individual Assessment Time Point**

To determine tumor response, the sum of all target lesions is calculated at Baseline and at each subsequent assessment time point (i.e., every 9 weeks). Each response parameter (target, nontarget, and new lesions) will be reported independently at each radiographic reading as shown in Table 1 for target lesions and Table 2 for nontarget lesions. The investigator will then make a determination of OR for each assessment time point based on a composite evaluation of target, nontarget, and new lesions, as shown in Table 3.

**Table 1 Evaluation of Target Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. All pathological lymph nodes (whether target or nontarget) must have a reduction in their short axis to <10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of the LD of target lesions, taking as reference the Baseline sum diameters |
| Progressive Disease (PD) | At least a 20% increase in the sum of the LD of target lesions, taking as reference the *smallest* sum LD recorded at Baseline or during treatment. The sum must also have an absolute increase of ≥5 mm. The appearance of one or more new lesions is also considered PD. |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the *smallest* sum LD since the treatment started |
| Not Evaluable (NE) or Unevaluable | No imaging/measurement done at all or only on a subset of lesions at a particular time point; a target lesion at Baseline which is subsequently not measured or which is unable to be evaluatedIncludes scans that are not performed at a specified time |

| | |
|---|---|
| | point to evaluate the target lesion(s). |

**Table 2 Evaluation of Nontarget Lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all nontarget lesions; normalization of tumor marker level. All lymph nodes <10 mm (short axis) |
| Non-CR/Non-PD | Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits |
| Progressive Disease (PD) | Unequivocal progression (substantial worsening in nontarget disease such that overall tumor burden has increased sufficiently to warrant discontinuation of therapy); appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions[a] |
| Not Evaluable (NE) | A nontarget lesion at Baseline which is subsequently not measured or which is unable to be evaluated |

a. Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the site radiologist should prevail.

**Table 3 Overall Response at Each Assessment Time Point for Subjects with Target (+/- Nontarget) Disease**

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response; NE = not evaluable; PD = disease progression; PR = partial response; SD = stable disease

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time point assessment should be classified as having "symptomatic deterioration." Every effort should be made to document objective progression after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR.

**Evaluation of Best Overall Response and Confirmation of Response**

The best OR is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria as shown in Table 4.

Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In this study, bone scan and brain CT/MRI are performed at treating physician discretion. Scans can also occur as clinically indicated for new symptoms or to confirm disease response. Radiological scans that were negative at baseline do not have to be repeated unless clinically indicated.

- The main goal of confirmation of the PR or CR objective response is to avoid overestimating the response rate. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome that the response(s) are not confirmed.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 5 weeks for this protocol.

**Table 4 Best Overall Response with Confirmation**

| **Unconfirmed Response (First Time Point)** | **Confirmatory Response (Subsequent Time Point)** | **Best Overall Response of:** |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD or PD[b] |
| CR | PD | SD or PD[b] |
| CR | NE | SD or NE[c] |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD[b] |
| PR | NE | SD[c] |
| NE | NE | NE |

BL = baseline; CR = complete response; NE = not evaluable; PD = disease progression; PR = partial response; SD = stable disease

a: If a CR is truly met at first time point, then any reappearance of disease seen at a subsequent time point (including disease meeting PR criteria relative to BL) makes the disease PD at that time point

b: Classify response as SD, provided that confirmatory scan a minimum of 5 weeks later is still “SD.” Otherwise, response classified as PD.

c: Classify response as SD, provided that confirmatory scan a minimum of 5 weeks later is still “SD.” Otherwise, response classified as NE.

**Duration of Overall Response**

The duration of OR is measured from the date that measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest sum LD recorded since the treatment started.

**Duration of Stable Disease**

Stable disease is measured from the start of the treatment until the criteria for PD are met, taking as reference the smallest sum LD recorded since the treatment started.
The clinical relevance of the duration of SD varies for different tumor types and grades. For this protocol, duration of stable disease is not being measured.

**Response Review**

For this Phase 2 study, response review will be performed at the site by appropriately qualified personnel (radiologist in conjunction with clinical investigator).

**Reporting of Results**

All subjects included in the study should be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

## 17.2. Appendix 2 - ECOG Performance Status Scale

| Score | Status |
|---|---|
| 0 | Fully active, able to carry on all predisease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work) |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

ECOG =Eastern Cooperative Oncology Group.
Adapted from Oken MM et al. Am J Clin Oncol. 1982;5:649-5.

## 17.3. Appendix 3 - Cockcroft and Gault Formula

Male $\frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$

Female $\frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min} \times 0.85$

.

Adapted from Cockcroft DW et al. Nephron. 1976;16(1):31-41.**Error! Bookmark not defined.**

## 17.4. Appendix 4 - New York Heart Association Cardiac Disease Classification

The New York Heart Association (NYHA) Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. Based on NYHA definitions, subjects are to be classified as follows:

| Class | Definition |
|---|---|
| Class I | Subjects with no limitation of activities; they suffer no symptoms from ordinary activities. |
| Class II | Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion. |
| Class III | Subjects with marked limitation of activity; they are comfortable only at rest. |
| Class IV | Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest. |

## 17.5. Appendix 5 - Common Terminology Criteria for Adverse Events (version 4.0)

The National Cancer Institute's CTCAE v 4.0 published 28 May 2009 provides descriptive terminology to be used for AE reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE version 4.0 have be correlated with single-concept, MedDRA® terms.

Grades in CTCAEs v 4.0 refer to the severity of the AE. Grades of 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

| Grade | Status |
|---|---|
| 1 | Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a] |
| 3 | Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b] |
| 4 | Life-threatening consequences: urgent intervention indicated. |
| 5 | Death related to adverse event. |

ADL = Activities of Daily Living

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Cancer Therapy Evaluation Program, NCI CTCAE v 4.0. Available from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev 4.pdf.

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddramsso.com. CTCAE v 4.0 is available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev 4.pdf.

## 17.6. Appendix 6 – Quality of Life Surveys


Study ID: _____

Quality of Life Assessment:

DF/HCC 13-077

A Phase 2 Study of Eribulin in Patients with HER2-negative, Metastatic Breast Cancer: Evaluation of Efficacy, Toxicity, and Patient-Reported Outcomes

Thank you for completing this survey. The first questions ask about some of your symptoms in the last 7 days.

1. In the last 7 days, what was the SEVERITY of your **constipation** at its WORST?
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

2. In the last 7 days, how OFTEN did you have **loose or watery stools (diarrhea)**?
   - ☐ Never
   - ☐ Rarely
   - ☐ Occasionally
   - ☐ Frequently
   - ☐ Almost constantly

3. In the last 7 days, what was the SEVERITY of your **dry mouth** at its WORST?
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

4. In the last 7 days, what was the SEVERITY of your **mouth or throat sores** at their WORST?
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

5. In the last 7 days, how much did **mouth or throat sores** INTERFERE with your usual or daily activities?
   - ☐ Not at all
   - ☐ A little bit
   - ☐ Somewhat
   - ☐ Quite a bit
   - ☐ Very much

6. In the last 7 days, how OFTEN did you have **nausea**?
   - ☐ Never
   - ☐ Rarely
   - ☐ Occasionally
   - ☐ Frequently
   - ☐ Almost constantly

7. In the last 7 days, what was the SEVERITY of your **nausea** at its WORST?
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

8. In the last 7 days, how OFTEN did you have **vomiting**?
   - ☐ Never
   - ☐ Rarely
   - ☐ Occasionally
   - ☐ Frequently
   - ☐ Almost constantly

9. In the last 7 days, what was the SEVERITY of your **vomiting** at its WORST?
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe
   - ☐ Very severe

10. In the last 7 days, did you have any **hair loss**?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

11. In the last 7 days, how OFTEN did you have **arm or leg swelling**?
    - ☐ Never
    - ☐ Rarely
    - ☐ Occasionally
    - ☐ Frequently
    - ☐ Almost constantly

12. In the last 7 days, what was the SEVERITY of your **arm or leg swelling** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

13. In the last 7 days, how much did **arm or leg swelling** INTERFERES with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

14. In the last 7 days, did you have any **rash**:
    - ☐ Yes
    - ☐ No

15. In the last 7 days, what was the SEVERITY of your **fatigue, tiredness, or lack of energy** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

16. In the last 7 days, how much did **fatigue, tiredness, or lack of energy** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

17. In the last 7 days, how OFTEN did you have **pain**?
    - ☐ Never
    - ☐ Rarely
    - ☐ Occasionally
    - ☐ Frequently
    - ☐ Almost constantly

18. In the last 7 days, what was the SEVERITY of your **pain** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

19. In the last 7 days, how much did **pain** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

20. In the last 7 days, what was the SEVERITY of your **decreased appetite** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

21. In the last 7 days, how much did **decreased appetite** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

22. In the last 7 days, what was the SEVERITY of your **problems with concentration** at their WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

23. In the last 7 days, how much did **problems with concentration** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

24. In the last 7 days, what was the SEVERITY of your **problems with memory** at their WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

25. In the last 7 days, how much did **problems with memory** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

26. In the last 7 days, what was the SEVERITY of your **problems with tasting food or drink** at their WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

27. In the last 7 days, how OFTEN did you have a **headache**?
    - ☐ Never
    - ☐ Rarely
    - ☐ Occasionally
    - ☐ Frequently
    - ☐ Almost constantly

28. In the last 7 days, what was the SEVERITY of your **headache** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

29. In the last 7 days, how much did your **headache** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

30. In the last 7 days, what was the SEVERITY of your **numbness or tingling in your hands or feet** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

31. In the last 7 days, how much did **numbness or tingling in your hands or feet** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

32. In the last 7 days, how OFTEN did you feel **anxiety**?
    - ☐ Never
    - ☐ Rarely
    - ☐ Occasionally
    - ☐ Frequently
    - ☐ Almost constantly

33. In the last 7 days, what was the SEVERITY of your **anxiety** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

34. In the last 7 days, how much did **anxiety** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

35. In the last 7 days, how OFTEN did you have **sad or unhappy feelings**?
    - ☐ Never
    - ☐ Rarely
    - ☐ Occasionally
    - ☐ Frequently
    - ☐ Almost constantly

36. In the last 7 days, what was the SEVERITY of your **sad or unhappy feelings** at their WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

37. In the last 7 days, how much did **sad or unhappy feelings** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

38. In the last 7 days, what was the SEVERITY of your **insomnia including difficulty falling asleep, staying asleep, or waking up early** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

39. In the last 7 days, how much did **insomnia including difficulty falling asleep, staying asleep, or waking up early** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

40. In the last 7 days, what was the SEVERITY of your **shortness of breath** at its WORST?
    - ☐ None
    - ☐ Mild
    - ☐ Moderate
    - ☐ Severe
    - ☐ Very severe

41. In the last 7 days, how much did **shortness of breath** INTERFERE with your usual or daily activities?
    - ☐ Not at all
    - ☐ A little bit
    - ☐ Somewhat
    - ☐ Quite a bit
    - ☐ Very much

Below is a list of statements that other people with your illness have said are important. **Please check one box per line to indicate your response as it applies to the <u>past 7 days</u>.**

| **<u>PHYSICAL WELL-BEING</u>** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| I have a lack of energy | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have nausea | ☐ | ☐ | ☐ | ☐ | ☐ |
| Because of my physical condition, I have trouble meeting the needs of my family | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have pain | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am bothered by side effects of treatment | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel ill | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am forced to spend time in bed | ☐ | ☐ | ☐ | ☐ | ☐ |

| **<u>SOCIAL/FAMILY WELL-BEING</u>** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| I feel close to my friends | ☐ | ☐ | ☐ | ☐ | ☐ |
| I get emotional support from my family | ☐ | ☐ | ☐ | ☐ | ☐ |
| I get support from my friends | ☐ | ☐ | ☐ | ☐ | ☐ |
| My family has accepted my illness | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am satisfied with family communication about my illness | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel close to my partner (or the person who is my main support) | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am satisfied with my sex life | ☐ | ☐ | ☐ | ☐ | ☐ |

**Please check one box per line to indicate your response as it applies to the <u>past 7 days</u>.**

| **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| I feel sad | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am satisfied with how I am coping with my illness | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am losing hope in the fight against my illness | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel nervous | ☐ | ☐ | ☐ | ☐ | ☐ |
| I worry about dying | ☐ | ☐ | ☐ | ☐ | ☐ |
| I worry that my condition will get worse | ☐ | ☐ | ☐ | ☐ | ☐ |

| **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| I am able to work (include work at home) | ☐ | ☐ | ☐ | ☐ | ☐ |
| My work (include work at home) is fulfilling | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am able to enjoy life | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have accepted my illness | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am sleeping well | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am enjoying the things I usually do for fun | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am content with the quality of my life right now | ☐ | ☐ | ☐ | ☐ | ☐ |

**Please check one box per line to indicate your response as it applies to the past 7 days.**

| **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| I have been short of breath | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am self-conscious about the way I dress | ☐ | ☐ | ☐ | ☐ | ☐ |
| One or both of my arms are swollen or tender | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel sexually attractive | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am bothered by hair loss | ☐ | ☐ | ☐ | ☐ | ☐ |
| I worry that other members of my family might someday get the same illness I have | ☐ | ☐ | ☐ | ☐ | ☐ |
| I worry about the effect of stress on my illness | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am bothered by a change in weight | ☐ | ☐ | ☐ | ☐ | ☐ |
| I am able to feel like a woman | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have certain parts of my body where I experience pain | ☐ | ☐ | ☐ | ☐ | ☐ |

**Please check one box per line to indicate your response as it applies to the past 7 days.**

| **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Some-what** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|
| I have numbness or tingling in my hands | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have numbness or tingling in my feet | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel discomfort in my hands | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel discomfort in my feet | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have joint pain or muscle cramps | ☐ | ☐ | ☐ | ☐ | ☐ |
| I feel weak all over | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have trouble hearing | ☐ | ☐ | ☐ | ☐ | ☐ |
| I get a ringing or buzzing in my ears | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have trouble buttoning buttons | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have trouble feeling the shape of small objects when they are in my hand | ☐ | ☐ | ☐ | ☐ | ☐ |
| I have trouble walking | ☐ | ☐ | ☐ | ☐ | ☐ |

## Thank you for completing the survey!

## 17.7. Appendix 7 - Blood Sampling for Pharmacogenomics Analysis

Subjects enrolled in this clinical study will have blood samples collected for pharmacogenomic analysis.

#### SAMPLE COLLECTION AND HANDLING

Blood samples will be collected according to the Study Calendar. The DNA blood plasma/serum samples will be collected at the same time blood samples are collected for the main study; therefore, there is no additional risk to the study participant. The site staff will add the study center ID-subject number and collection time (hh:mm) to the tube. In addition, a sample sheet will be completed indicating the study ID, site number, subject number, visit number, and date and time of collection. Collection of the blood sample and informed consent will also be recorded in the subject's eCRF. Frozen samples will be transferred from the central lab to a specialty laboratory for processing, analysis, and storage.

Collection and Processing
1 10ml EDTA tube will be collected at baseline for all participating patients.

- Freeze the whole tube at -80°C shortly after collection.
- Ship on dry ice.

Samples will be shipped from sites in batches to the Laboratory of Bryan P. Schneider, MD for analysis.

**Laboratory of Bryan P. Schneider, M.D.**
Indiana Cancer Pavilion
Walter Hall
980 W. Walnut Street
Indianapolis, IN 46202
Phone: 317-274-6473
Fax: 317-274-3646
bpschnei@iupui.edu

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#### SECURITY OF THE SAMPLES, USE OF THE SAMPLES, RETENTION OF THE SAMPLES

Sample processing, including DNA/RNA extraction and genotyping, sequencing or other analysis will be performed by a local laboratory. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.
Samples will be stored for up to 15 years after the completion of the study (defined as submission of the CSR to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single- or double-coded (according to the ICH15 guidelines) to maintain subject privacy.

### RIGHT TO WITHDRAW

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, the sponsor (DFCI) will destroy the samples, if they can still be identified (not anonymized). Once samples are anonymously labeled, it will not be possible to identify which samples have come from a particular individual. Therefore, it will not be possible to destroy those subject's samples at that time. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

### SUBJECT PRIVACY AND RETURN OF DATA

No information that identifies the subject (e.g., initials, date of birth, government identifying number) will be associated with the sample. Samples that are processed for analysis (DNA/RNA extracted) may be double-coded. Double-coding involves removing the initial code and replacing with another code such that the subject can be re-identified by use of two code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded (the first code being the subject number) as long as the initial tube does not contain any personal identifiers or the random code assigned by the central laboratory or biorepository. Laboratory personnel performing the genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."
Sample anonymization may occur by destruction of the "key." Once the "key" is destroyed, it will not be possible to trace the pharmacogenomics assay results back to an individual. The Principal Investigator will take steps to ensure that data are protected accordingly and confidentiality is maintained to the extent possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.
The sponsor (DFCI) and its representatives and agents may share anonymous data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor;
- Independent ethics committees or institutional review boards that have responsibility for this research study;
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the anonymous data, in listing or summary format. Other publications (e.g., in peer-reviewed scientific journals) or public presentations of the study results will only include summaries of the study population, and no identified individual results will be disclosed.

Given the exploratory nature of the planned analysis, it will not be possible to return individual data to subjects participating in the pharmacogenomics research

## 17.8. Appendix 8: Provider-Reported CTCAE Form

INSTRUCTIONS: Provide the worst grade the patient has experienced in the last 7 days for each adverse event listed below. If the patient has not experienced the adverse event in the last 7 days, mark "None".

Pt ID#_____ Pt Init:_____ Visit#_____ MRN#_____

| System Organ Class (SOC) | Adverse event | None | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| **Gastrointestinal Disorders** | Constipation | | | | | |
| | Diarrhea | | | | | |
| | Dry mouth | | | | | |
| | Mucositis | | | | | |
| | Nausea | | | | | |
| | Vomiting | | | | | |
| **General disorders and administration site conditions** | Hair Loss | | | | NA | NA |
| | Edema limbs | | | | | |
| | Fatigue | | | | | |
| | Pain | | | | | |
| **Metabolism and nutrition disorders** | Anorexia | | | | | |
| **Nervous system disorders** | Concentration impairment | | | | | |
| | Dysgeusia | | | | | |
| | Headache | | | | | |
| | Peripheral sensory neuropathy | | | | | |
| **Psychiatric disorders** | Anxiety | | | | | |
| | Depression | | | | | |
| | Insomnia | | | | | |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnea | | | | | |
| | Abbreviations: Not applicable | | | | | |

Provider Signature:_____Date:_____

DF/HCC Sites: Please send this completed form to Danielle Gore: dgore@partners.org

External sites: Please send this completed form to the DFCI Coordinating Center: CTOPM@dfci.harvard.edu

APPENDIX **9:** DF/HCC **Multi-Center Data and Safety Monitoring Plan**

# DFCI IRB Protocol #: 13-077

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# 1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

## 1.1. Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures, and Cancer Therapy Evaluation Program (CTEP) Multi-Center Guidelines.

## 1.2. Multi-Center Data and Safety Monitoring Plan Definitions

**DF/HCC Multi-center Protocol**: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

**Lead Institution:** One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Children's Hospital Boston (CHB), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines. The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Sponsor:** The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Principal Investigator; however, both roles can be filled by two different people.

**Participating Institution:** An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

**Coordinating Center:** The entity (i.e. Lead Institution) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

**DF/HCC Quality Assurance Office for Clinical Trials:** A unit within DF/HCC developed to computerize and manage data, and to provide a Quality Control and Quality Assurance function for DF/HCC trials.

## 2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

### 2.1. DF/HCC Sponsor

The DF/HCC Sponsor, Dr. Erica Mayer, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

## 2.2. Coordinating Center

The Coordinating Center will assume the following general responsibilities:

- Assist in protocol development
- Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
- Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc).
- Maintain documentation of all communications.
- Ensure that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP).

## 2.3. DF/HCC Quality Assurance Office for Clinical Trials (QACT)

In addition to the Coordinating Center, the DF/HCC QACT provides the following support services to assist the DF/HCC Sponsor:

- Develop protocol specific case report forms (eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide a central participant registration, which includes review of consent and eligibility.
- Provide auditing services (funding and QACT approval required).

## 2.4. Participating Institution

Each Participating Institution is expected to comply with all applicable Federal Regulations and DF/HCC requirements, the protocol and HIPAA requirements. All Participating Institutions will provide a list of personnel assigned to the role for oversight of data management at their site to the Coordinating Center.

The general responsibilities for each Participating Institution are as follows:

- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder in accordance with DF/HCC requirements.
- Provide the Coordinating Center with regulatory documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements. For CTEP trials, submit SAE reports directly to CTEP and provide copies to the Coordinating Center
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Secure and store investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.

## 3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

### 3.1. Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

### 3.2. Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

### 3.3. Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

### 3.4. IRB Documentation

The following must be on file with the Coordinating Center:

- Approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution’s IRB
- Participating IRB’s approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the Coordinating Center their IRB approval for amendments to a protocol.

## 3.5. IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

## 3.6. Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, which covered entities (Participating Institutions) must use.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

### 3.6.1. DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number (as described below) and DF/HCC protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification

## 3.7. **DF/HCC Multi-Center Protocol Registration Policy**

### 3.7.1. Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Coordinating Center Project Manager at CTOPM@dfci.harvard.edu or by fax at 617-632-5152:

- Copy of required laboratory tests including: Hematology (CBC w/differential), Serum Chemistries, and a pregnancy test (for women of child-bearing potential only)
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed QACT Eligibility Checklist
- Radiology Report of tumor assessments
- Pathology report with documentation of ER, PR, and HER2
- Clinic note documenting history and physical examination
- ECG report

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC QACT
- Upon receiving confirmation of registration by the QACT, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and if applicable the dose treatment level.

**Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.**

Randomization can only occur during QACT's normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

### 3.7.2. Initiation of Therapy

Participants must be registered with the DF/HCC QACT before receiving study treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mail copy of the participant's registration confirmation memo from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any exceptions to this policy.

### 3.7.3. Eligibility Exceptions

The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

### 3.7.4. Verification of Registration, Dose Levels, and Arm Designation

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one business day of the registration.

Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

## 3.8. **DF/HCC Protocol Case Number**

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT eCRF completion and correspondence, and correspondence with the Coordinating Center.

## 3.9. **Protocol Deviations, Exceptions and Violations**

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe derivations from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

### 3.9.1. Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

### 3.9.2. Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations

and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

## 3.10. Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

### 3.10.1. Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 11.

Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements.

Participating Investigators will review any distributed AE reports, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

### 3.10.2. Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. The Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

## 3.11. Data Management

The DF/HCC QACT develops a set of electronic case report forms eCRFs, for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT provides a web based training for eCRF users.

### 3.11.1. Data Forms Review

When data forms arrive at the DF/HCC QACT, they are reviewed for completeness, protocol treatment compliance, adverse events (toxicities) and response. Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

<u>Incomplete or Questionable Data</u>
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC QACT Data Analyst or study monitor. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

<u>Missing Forms</u>
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of four times a year.

## 4. REQUISITIONING DRUG

Eribulin will be supplied by Eisai Inc. Participating Institutions are responsible for ordering their own supply of Eribulin. Please refer to the protocol section 7.1 for more information.

## 5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the QACT provides quality control oversight for the protocol.

### 5.1. Ongoing Monitoring of Protocol Compliance

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol deviations, pharmacy records, response assessments, and data management. Additionally, a plan will be formulated to provide regular and ongoing communication to Participating Institutions about study related information which will include participation in regular coordinating center initiated teleconferences. Teleconferences will occur approximately every other week beginning once sites are active and will continue regularly until the completion of accrual. Upon completion of accrual, teleconferences will occur quarterly thereafter (unless otherwise specified by the Protocol Chair) until study completion. Additional communication may be distributed via “Newsletters” or email as deemed appropriate by the protocol chair.

On-site and virtual monitoring will occur as specified in the study monitoring plan. Monitoring will be performed by the Coordinating Center’s Clinical Research Specialist (CRS). The Participating Institutions will be required to submit de-identified participant source documents to the Coordinating Center for virtual monitoring visits. The data will be reviewed for completeness, quality, and adherence to the protocol requirements. Sites will be asked to provide source documentation via fax, email, or mail as specified by the Clinical Research Specialist for all virtual monitoring visits. A virtual site initiation (SIV) will be conducted with each participating site prior to study activation. Participating sites may not begin enrolling until an SIV has occurred.

### 5.2. Evaluation of Participating Institution Performance

### 5.2.1. Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participating in the study. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

## 6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

### 6.1. DF/HCC Sponsored Trials

Annual on-site audits will be scheduled by the DFCI QACT assuming at least three new subjects have been treated on protocol each year. Approximately 3-4 subjects would be audited over a 2 day period. . If violations which impact subject safety or the integrity of the study are found, more subject records may be audited.Also, an audit may be triggered if deficiencies are noted related to consent practices, eligibility, missing, incomplete, or questionable data submission, non-compliance or any other issue the protocol chair deems appropriate for audit.

### 6.2. Participating Institution

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or external) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

### 6.3. DF/HCC Sponsor and Coordinating Center

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the

DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

## 6.4. Sub-Standard Performance

The DF/HCC Sponsor and DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

### 6.4.1. Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal regulations, will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation.

**DANA-FARBER CANCER INSTITUTE**
**Nursing Protocol Education Sheet**

| | |
|---|---|
| **Protocol Number:** | **13-077** |
| **Protocol Name:** | **A Phase 2 Study of Eribulin in Patients with Her2-Negative, Metastatic Breast Cancer: Evaluation of Efficacy, Toxicity and Patient-Reported Outcomes** |
| **DFCI Site PI:** | Erica Mayer, MD, MPH |
| **DFCI Research Nurse:** | Peg Haldoupis, RN; Liz Kasparian, RN; Mary O'Driscoll, RN; Kathy Roche, RN; Myra St. Amand, RN, Beth Tiani, RN |

***Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.***
***Please also refer to ONC 15: Oncology Nursing Protocol Education Policy***
***** Remember to check the ALERT PAGE*****

**SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL**

| | |
|---|---|
| **Study Design** | **Eribulin** is a synthetic derivative of the natural product halichondrin B, which is isolated from a marine sponge. Halichondrin B exhibits anti-cancer activity through a microtubule-destabilizing anti-mitotic mechanism of action. Eribulin exerts its effects by binding to microtubules which causes interference in the normal cell cycle. This interference leads to cell death via apoptosis. ***Study Design***: Participants will be enrolled in 2 parallel cohorts. Cohort 1 = HR+/HER2-- and Cohort 2 = HR-- and HER2-- (TNBC) – Section 1.1; ***Study Rationale*** – Section 2.5 *A cycle is 3 weeks (21 days)* – Section 5.3 |
| **Dose Calc.** | • **Eribulin** dosing is calculated in mg/m$^2$ – Section 5.4<br>• BSA is calculated on each treatment day according to institutional standard – Please review Section 5.4 |
| **Study Drug Administration** | **Eribulin** *Administration* Guidelines are found in Sections 5.4 and 7<br>• IV, administered over approximately 2 to 5 minutes on Days 1 and 8 of each 3 week cycle<br>• May be injected directly as an IV infusion over approximately 2 to 5 minutes or diluted in up to 100mL 0.9% saline for IV infusion over approximately 2 to 5 minutes. NOT compatible with solutions containing dextrose.<br>• No special tubing is required for administration<br>• Do not administer in the same IV line concurrent with other medicinal products<br>• *Criteria to treat:* See Section 5.4 |
| **Dose Modifications & Toxicity** | *Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 6<br>• This protocol uses NCI CTCAE criteria, version 4.0 – Section 13.1<br>• Expected toxicities are outlined in Section 6.1<br>• Dose modifications and delays are outlined in Section 6.2 and Table 1<br>• If Day 8 dosing is delayed, Day 1 dosing for the <u>next cycle</u> must be NO SOONER than 14 days later |
| **Concomitant Meds** | *Concomitant Therapy* Guidelines are in Section 5.6<br>• Permitted meds/therapies are in Section 5.6.2<br>• Prohibited meds/therapies are in Section 5.6.3<br>• Information on potential drug-drug interactions is in Section 5.6.4 |
| **Required Data** | *Study Calendar and Assessment Required data* are outlined in Sections 5.5, 9 and 10.5 – 10.7<br>• Please refer to Table 3 in Section 9 for the Schedule of Visits and Procedures |
| **Charting Tips** | **All study drugs require documentation of exact administration time.**<br>Please be sure to DOCUMENT study medication **<u>actual</u>** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**.<br>• If there is a discrepancy in the infusion time, delay in administration, or the infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.**<br>Please be sure to also DOCUMEN any additional vital signs, routes of administration, or injection sites |