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**CASE COMPREHENSIVE CANCER CENTER**

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STUDY NUMBER: CASE 7113

STUDY TITLE: Treatment of Brain Metastases from Breast Cancer with Eribulin Mesylate.

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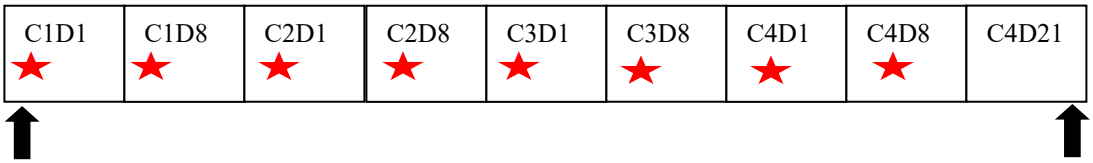
| SPONSOR: | Case Comprehensive Cancer Center<br>Eisai Incorporated |
| SUPPLIED AGENTS: | Eribulin mesylate |

# SCHEMA

**Treatment of Brain Metastases from Breast Cancer with Eribulin Mesylate**

**Primary Objectives:**
To determine the 3-month central nervous system (CNS)-progression free survival (PFS) for patients with metastatic breast cancer with brain metastases treated with eribulin mesylate.




= MRI

= Eribulin 1.4mg/m2
21 day cycles

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## 1.0 INTRODUCTION

### 1.1 Name of Study Disease/Stage: Breast cancer with brain metastases

### 1.2 Name of Investigational Agent: Eribulin Mesylate

### 1.3 Clinical Data for Eribulin:

Eribulin mesylate (Halaven®) is a microtubule inhibitor approved by FDA in metastatic breast cancer patients who have received at least two prior chemotherapy regimens for metastatic disease. Multiple phase 2 studies and one noteworthy phase 3 study have established the efficacy of eribulin mesylate (Halaven®) in patients with metastatic breast cancer (MBC) (1-4). The efficacy of eribulin mesylate has also been evaluated in other advanced solid tumors. These phase 2 studies have demonstrated that eribulin mesylate shows activity in patients with advanced non small cell lung cancer, prostate cancer, soft tissue sarcoma and platinum-susceptible ovarian, fallopian tube or peritoneal cancers. Eribulin mesylate was evaluated in a Phase 3, open label, randomized trial for patients with metastatic or locally recurrent breast cancer against the therapy of physician's choice (TPC) (4). Eribulin mesylate 1.4mg/$m^2$ was administered intravenously over 2-5 minutes on days 1 and 8 of 21 days cycles; the median duration of treatment was 3.9 months. TPC included chemotherapy (96% received single agent vinorelbine, gemcitabine, capecitabile, taxanes, or anthracyclines) or hormonal therapy. The median duration of treatment in the TPC arm was 2.1 months for chemotherapy and 1 month for hormonal therapy. Participants had either received, responded poorly or became refractory to at least 2 prior chemotherapy treatments including an anthracycline and taxane unless contraindicated either the adjuvant or metastatic setting. Overall, 16% of the patients had human epidermal growth factor receptor 2 (HER2)-positive disease and 19% were estrogen receptor (ER), progesterone receptor (PR) and HER2- negative (triple-negative). Although only 2 previous chemotherapy regimens were mandatory for enrollment, 9% of patients had received 4 or more chemotherapy regimens. For the 508 women treated with eribulin mesylate, the median overall survival (OS) was 13.1 months; the median OS was 10.6 months in 254 women in the TPC arm ($p = 0.041$). A significantly higher overall response rate (ORR) was also found with eribulin mesylate compared to TPC (12% vs. 5%) ($p = 0.002$). Further analysis of the study results suggested that survival benefit with eribulin mesylate was independent of age without resulting in additional toxicity in older patients. Hence, it was recommended that age alone should not preclude older patients from receiving the drug regimen (5**).** Overall, this study demonstrated that eribulin mesylate was an effective agent associated with survival benefit compared to other standard regimens in heavily pretreated patients with locally advanced breast cancer or MBC. This trial formed the basis for the 2010 United States Food and Drug Administration approval of eribulin mesylate for advanced breast cancer after two or more chemotherapy regimens.

### 1.3.1 Clinical Pharmacokinetics of Eribulin:

Eribulin mesylate when dosed at 1.4 mg/m2 as an intravenous bolus has been shown to be well tolerated at 2 dosing schedules: on days 1 and 8 of 21-day cycles and on days 1, 8, and 15 of 28-day cycles in patients with MBC (1-4). Eribulin is a colorless, sterile solution for injection. Each vial contains 1 mg of eribulin as a 0.5-mg/mL solution in a 5:95 ratio of ethanol to water (6). Eribulin does not require pretreatment with corticosteroids or antihistamines (6) since its water solubility negates the requirement for a lipophilic vehicle such as polysorbate 80 (docetaxel) or

Cremophor (paclitaxel), which have the potential to cause a hypersensitivity reaction. Eribulin is freely soluble in water and various organic solvents including ethanol, benzyl alcohol, and dimethyl- sulfoxide (7). Eribulin vials should be stored at 25 degree Centigrade and should not be frozen (6). The pharmacokinetic profile of eribulin is linear and dose proportional. When administered intravenously, eribulin has a rapid and extensive volume of distribution, slow elimination phase, and biexponential plasma disposition (8-13).The mean plasma half-life of eribulin is approximately 37.8hours, which allows for prolonged drug exposure to exert the antimitotic action (11). Eribulin is eliminated primarily via theliver, where it is metabolized to 4 monooxygenated metabolites by CYP3A4. The CYP3A4-mediated biotransformation of eribulin is slow, which results in delayed hepatic clearance (14). A minor amount of eribulin (~7%) is renally excreted as the parent compound (10). Dose adjustments for patients with moderate renal impairment, with creatinine clearance between 30 and 50 mL/min, are recommended (17). In a clinical setting, eribulin presents an insignificant risk for drug-drug interactions with CYP3A4 inhibitors and inducers (17). Hepatic impairment decreases clearance and prolongs the elimination half-life of eribulin (15). Because of a significant risk of grade3/4 neutropenia, it is recommended to reduce the eribulin dose by half in patients with moderate hepatic impairment (16).

### 1.4 Study Rationale

Brain metastases occur in 20-40% of all cancer patients (18) and account for more than half of all intra-cranial tumors in adults with approximately 170,000 new cases diagnosed annually in the United States alone (19). Breast cancer represents the primary tumor in 15-20% of patients with brain metastases (19). The risk of developing brain metastases from breast cancer varies with the underlying biology of the disease (20), stage of the disease and effectiveness of systemic therapy. Among women with advanced breast cancer, the long term cumulative risk for developing brain metastases from breast cancer is estimated at 10- 15% (21). The 5 year cumulative incidence of brain metastases in triple negative breast cancer has been reported as 10% (22) but has been reported to be 46 % following the diagnosis of metastatic breast cancer (23). In HER-2 positive disease, the incidence may be up to 36% following the diagnosis of metastatic breast cancer (24, 25) and has been recently estimated as almost 50% based on data in long term follow up patients with both early and advanced HER-2 positive disease (26).

Brain metastases are associated with considerable morbidity and mortality. The most common presenting symptoms of brain metastases are headache, cognitive impairment and focal weakness, seizures and ataxia. Treatment of brain metastases are mainly palliative and typically include whole brain radiation therapy (WBRT), stereotactic surgery (SRS) or surgical resection. In patients with brain metastases from breast cancer the median survival depending on the subtype is 4-7.5 months (27) and median survival with SRS is 7-18 months (28, 29).

Currently there is no approved drug therapy for brain metastases from metastatic breast cancer. Conventional cytotoxic drugs penetrate the brain poorly and intracranial response rates are low and of short duration. Paclitaxel which has become a standard of care for breast cancer has very little penetration across the blood-brain barrier (20) and has not demonstrated efficacy against breast metastases to brain. Targeted therapies such as lapatinib have been tested in HER 2 positive metastatic breast cancer with a response rate of 3-6% (31). Furthermore, the use of cytotoxic drugs is limited by systemic toxicity; restrictions imposed by blood brain barrier and the chemo sensitivity of the primary tumor. Patient outcomes with brain metastases are poor. Median survival following development of

brain metastases from triple negative breast cancer is approximately 4 months with combine modality of WBRT with chemotherapy (22). Outcomes are generally better for patients with HER 2 positive brain metastases (32) but when progression after cranial irradiation occurs, outcomes are similarly poor even after administration of a combination of capecitabine plus lapatinib. Given the poor prognosis of patients with brain metastases and the lack of effective drug treatment options, there is a need for development of new therapeutic agents and technology to evaluate early response to these therapeutic agents.

Despite being approved in metastatic breast cancer treatment, eribulin mesylate's therapeutic effectiveness on brain metastases from breast cancer has not been studied in a prospective clinical study. Matsuoka and colleagues described a case of a woman with brain metastases from breast cancer who had a significant response in brain that persisted for 4 months when treated with eribulin mesylate (33).

Additionally two patients with brain metastases from breast cancer treated at University Hospitals Seidman Cancer Center showed marked response to eribulin. Based on these observations, we hypothesize that eribulin may have activity in patients with brain metastases from breast cancer.

We propose to study a clinically meaningful endpoint, the 3-month CNS-progression free survival (PFS), of eribulin mesylate in breast cancer patients with brain metastases.

## 2.0 OBJECTIVES

### 2.1 Primary Objectives:

To determine the 3-month central nervous system (CNS)-progression free survival (PFS) for patients with metastatic breast cancer with brain metastases treated with eribulin mesylate.

### 2.2 Secondary Objective(s):

2.2.1 Estimate CNS complete and partial response rates (CR and PR) and duration of CNS response in this patient population.

2.2.2 Evaluate toxicity in patients with breast cancer with brain metastases treated with eribulin mesylate.

2.2.3 Estimate clinical benefit rate (CBR) at 3 months in breast cancer patients with brain metastases treated with eribulin mesylate. (CBR is the sum of CR, PR and stable disease at 3 months).

2.2.4 To estimate systemic disease (extra cranial) response rate and duration of systemic response in this patient population.

2.2.5 Overall survival in this patient population.

## 3.0 STUDY DESIGN

### 3.1 Design:
This is a phase II study that will require 20 patients to evaluate the primary objective (CNS PFS at 3 months). Study patients will have a baseline brain MRI and a second MRI at 12 weeks to evaluate disease.

**3.2 Number of Subjects:** A total of 20 evaluable patients will be required for the study:

**3.3 Expected Duration of Subject Participation:** Death or disease progression or toxicity.

### 3.4. Duration of Therapy
In the absence of treatment delays due to adverse events, treatment may continue on study until one of the following criteria applies:

- Systemic or CNS disease progression,
- Intercurrent illness that prevents further administration of treatment,
- The investigator considers it, for safety reasons, to be in the best interest of the patient.
- Unacceptable treatment related toxicity, NCI CTC AE version 4.0. Grade 3 or 4 that fails to recover to baseline or < Grade 2 in the absence of treatment within 4 weeks
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent),
- Pregnancy during the course of the study
- Death

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

### 3.5 Duration of Follow Up:

**30-Day Follow-Up**: Patients will be followed *for toxicity* for 30 days after treatment has been discontinued or until death, whichever occurs first.

**Long term Follow-Up**: Patients will be followed *for survival* every 3 months until death after discontinuation of study medications.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

### 3.6 Replacement of Subjects

Subjects who do not obtain the two MRI scans (baseline and 12 weeks) will be considered not evaluable for response and will be replaced.

## 4.0 PATIENT SELECTION

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. The checklist must be completed for each patient and must be signed and dated by the treating physician.

Patient's Name _____

Medical Record # _____

Research Nurse /
Study Coordinator Signature: _____ Date _____

Treating Physician [Print] _____

Treating Physician Signature: _____ Date _____

### 4.1 Inclusion Criteria

_____ 4.1.1 Female with histologically confirmed breast cancer.

_____ 4.1.2 Patients must have evidence of metastatic disease (non measurable disease is eligible).

_____ 4.1.3 Radiologically confirmed metastatic brain lesion by MRI.

_____ 4.1.4 Brain metastases from breast cancer with or without previous treatment. WBRT, STS or surgical resection permitted through progression. Progression must be documented in an at least one lesion untreated by SRS or in any site after surgery or WBRT.

_____ 4.1.5 Patients must be neurologically stable and with stable dose steroids and anticonvulsants for at least 1 week prior to obtaining the baseline MRI of the brain, and/or at least 1 week prior to beginning study treatment.

_____ 4.1.6 No presence of uncontrolled systemic disease or tumor related complication which, in opinion of the investigator, might restrict life expectancy to less than 3 months.

_____ 4.1.7 Patients may not be on any cytotoxic chemotherapy or hormonal treatment for breast cancer during protocol treatment. Trastuzumab is allowed in HER2 positive patients).

_____ 4.1.8 Subject age ≥ 18 years

_____ 4.1.9 Able to comprehend and willing to sign an Informed Consent Form (ICF)

_____ 4.1.10 Karnofsky performance status ≥ 60

_____ 4.1.11 No brain radiation therapy > 4 weeks before planned start of protocol treatment.

_____ 4.1.12_ No chemotherapy for > 3 weeks before planned start of protocol treatment.

_____ 4.1.13 Adequate bone marrow, renal, and hepatic function, per local reference laboratory ranges as follows:

_____ 4.1.13.1 Absolute neutrophil count (ANC) ≥ 1,500/$mm^3$
ANC= _____ Date: _____

_____ 4.1.13.2 Platelet count ≥ 100,000/$mm^3$
Platelets= _____ Date: _____

_____ 4.1.13.3 Hemoglobin ≥ 9 g/dL
Hemoglobin= _____ Date: _____

_____ 4.1.13.4 Calculated creatinine clearance (CrCl) ≥ 30mL/min (Cockcroft-Gault method)
Creatinine= _____ Date: _____
Crcl = _____ Date: _____

_____ 4.1.13.5 Patients with normal, mild or moderate hepatic dysfunction are eligible.
Pugh-Child class= _____ Date:_____

_____4.1.13.6 Calcium <10.1 mg/dL (corrected to serum albumin as follows:
Corrected Calcium = (0.8 x (4 - patient albumin)) + serum Ca
Corrected calcium=_____ Date: _____

_____4.1.14 Females of child-bearing potential must have a negative pregnancy test at screening and agree to take appropriate precautions to avoid pregnancy (double barrier method of birth control or abstinence) from screening through 3 months after the last dose of treatment

____ 4.1.15 Able to undergo MRI evaluation with and without gadolinium contrast

**4.2 Exclusion Criteria**

_____ 4.2.1 Patients with the presence of an active infection, abscess or fistula

_____ 4.2.2 Known leptomeningeal disease or CNS midline shifts.

_____ 4.2.3 Any evidence of severe or uncontrolled systemic disease such as clinically significant cardiovascular, pulmonary, hepatic, renal or metabolic disease.

_____ 4.2.4 Severe conduction abnormality including significant QTc prolongation >450ms.

_____ 4.2.5 Patients with grade 3/4 peripheral neuropathy.

_____ 4.2.6 Patients with pacemaker or an ICD devices.

_____ 4.2.7 Previous treatment with eribulin mesylate.

### 4.3 **Inclusion of *Women and* Minorities**

Women of all races and ethnic groups are eligible for this trial.

## 5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore Database. All subjects will be registered through Seidman Cancer Center CTU and will be assigned a study number by the study coordinator at 216-286-1086.

## 6.0 TREATMENT PLAN

### 6.1 **Agent Administration:** Eribulin

**TABLE 1:TREATMENT REGIMEN DESCRIPTION**

| Agent | Pre-medicate at the Treating Physician's Discretion | Dose | Route | Schedule | Cycle Length |
|---|---|---|---|---|---|
| Eribulin mesylate | Zofran 8mg oral<br>Decadron 8mg oral | 1.4 mg/m$^2$ (see section 7.1 for details) | IV over 2-5 Min | Days 1 & 8 of each 21 day cycle | 21 days |

### 6.2 General Concomitant Medications and Supportive Care Guidelines:

Patient may receive trastuzumab if tumor is HER2 positive. No other cytotoxic or hormonal treatment is allowed while patient is on eribulin mesylate. Three weeks must elapse before beginning eribulin treatment (not protocol entry) after previous cytotoxic chemotherapy.

## 7.0 DOSING DELAYS / DOSE MODIFICATIONS:

### 7.1. Dosing

The recommended starting dose of eribulin mesylate is 1.4 mg/m$^2$ administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. No calculation of Child-Pugh score is necessary for those without known hepatic impairment from hepatitis, cirrhosis or liver metastases.

**7.1.1** The recommended dose of eribulin mesylate in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m$^2$ administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

**7.1.2** The recommended dose of eribulin mesylate in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m$^2$ administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

**7.1.3** The recommended dose of eribulin mesylate in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) is 1.1 mg/m$^2$ administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

## 7.2 Dose Modification

**Assess for peripheral neuropathy and obtain complete blood cell counts prior to each dose.**

It is not necessary to recalculate the BSA (Body Surface Area) for each treatment if the patient's weight has not changed by more than 10% from baseline. Prior to each administration of study drug, the nurse recalculates the BSA, the daily dose and the total dose of all chemotherapy treatment drug(s). A 5% variance rule is utilized between the ordered dose and the recalculated dose. As long as the recalculated dose is within 5%, it is acceptable to proceed.

**Recommended dose delays**
**Do not administer eribulin mesylate on Day 1 or Day 8 for any of the following:**
ANC < 1,000/mm$^3$
Platelets < 75,000/mm$^3$
Grade 3 or 4 non-hematological toxicities.

**The Day 8 dose may be delayed for a maximum of 1 week.**
If toxicities do not resolve or improve to ≤ Grade 2 severity by Day 15, omit the dose.
If toxicities resolve or improve to ≤ Grade 2 severity by Day 15, administer eribulin mesylate at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions: If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume eribulin mesylate at a reduced dose as set out in Table 1. Do not re-escalate Eribulin dose after it has been reduced.

| **Table 2: Recommended Dose Reductions Event Description** | **Recommended Eribulin Dose** |
|---|---|
| **Permanently reduce the 1.4 mg/m$^2$ eribulin mesylate dose for any of the following:** | 1.1 mg/m2 |
| ANC <500/mm$^3$ for >7 days | |
| ANC <1,000 /mm$^3$ with fever or infection | |
| Platelets <25,000/mm$^3$ | |
| Platelets <50,000/mm$^3$ requiring transfusion | |
| Non-hematologic Grade 3 or 4 toxicities | |
| Omission or delay of Day 8 Eribulin dose in previous cycle for toxicity | |
| **Occurrence** of any event requiring permanent dose reduction while receiving 1.1 mg/m$^2$ | 0.7 mg/m2 |
| **Occurrence** of any event requiring permanent dose reduction while receiving 0.7 mg/m2 | Discontinue eribulin mesylate |

## 8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.
Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

### 8.1 Adverse Events and Potential Risks

### 8.1.1 Adverse Effects related to eribulin mesylate

### 8.1.2 Neutropenia

- Monitor complete blood counts prior to each dose, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days.
- Severe neutropenia (ANC <500/mm$^3$) lasting more than 1 week occurred in 12% (62/503) of patients. Patients with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels.
- Grade 3 and Grade 4 neutropenia occurred in 28% and 29%, respectively, of patients who received eribulin. Febrile neutropenia occurred in 5% of patients and two patients (0.4%) died from complications.

### 8.1.3 Peripheral Neuropathy

- Grade 3 peripheral neuropathy occurred in 8% of patients, and Grade 4 in 0.4% of patients who received eribulin. Delay administration of eribulin until resolution to Grade 2 or less.
- Neuropathy lasting more than 1 year occurred in 5% of patients. Twenty-two percent of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days)
- Peripheral neuropathy (5%) was the most common adverse reaction resulting in discontinuation

### 8.1.4 Pregnancy Category D

- Eribulin is expected to cause fetal harm when administered to a pregnant woman and patients should be advised of these risks

### 8.1.5 QT Prolongation

- In an uncontrolled ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no prolongation on Day 1. ECG monitoring is recommended for patients with congestive heart failure; bradyarrhythmias; concomitant use of drugs that prolong QT interval, including Class Ia and III antiarrhythmics; and electrolyte abnormalities.
- Correct hypokalemia or hypomagnesaemia prior to initiating eribulin mesylate and monitor electrolytes periodically during therapy. Avoid in patients with congenital long QT syndrome.

### 8.1.6 Hepatic and Renal Impairment

For patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic and/or moderate (CrCl 30-50 mL/min) renal impairment, a reduction in starting dose is recommended.

## 8.2 MRI

### 8.2.1 Adverse Events related to Magnetic Resonance Imaging (MRI)

A known risk related to MRI examinations is that the MRI magnet could attract certain kinds of metal that may cause injury to the patient. In order to avoid that, patients will be screened for any hazardous metal object that they may have or is implanted inside their body which includes pacemakers, intracranial aneurysm clips, heart valve prostheses and other implanted devices that are not compatible with MRI. Although there is no risk from ionizing radiation with MRI, subjects will be exposed to strong magnetic fields and radio waves, neither of which are associated with any known detrimental health effects.

For MR perfusion imaging we will use a contrast agent, gadolinium. This agent is approved by the FDA and commercially available. There is a risk of an allergic or nephrogenic systemic fibrosis (NSF) reaction. Allergic (anaphylactic) reactions to gadolinium contrast medium have occurred but are

extremely rare. These severe reactions occur in about 1 in every 10,000 people who have gadolinium.NSF has not been reported in patients with normal kidney function. Patients at greatest risk for developing NSF after receiving gadolinium are those with impaired elimination of the drug, including patients with acute kidney injury (AKI) or chronic, severe kidney disease (with a glomerular filtration rate or GFR < 30 mL/min/1.73m$^2$). Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF.

Generally, an injection of 10-20 ml IV of gadolinium contrast agent will be used, provided that the subject has no known reaction to contrast agents used in previous MRI scans. As with all such injections, bleeding, bruising, dizziness, fainting or infection may occur. Also, the injection may be painful but the discomfort should be brief and efforts will be made to minimize the pain.

The MRI scanner makes a loud buzzing sound during the exam that could affect a patient's hearing. In order to protect patient from this sound, they will be provided earplugs during the exam. There might also be some claustrophobia-related discomfort involved with being required to lie still in a small space. If this occurs, patients can signal the technologist attending the MRI who will terminate imaging. The subject will be removed from the MRI machine and regarded as being withdrawn from the study, with the exception of following the patient for any sign of adverse event to the injected study drug.

### 8.3 Reporting Procedures for All Adverse Events (AEs)

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

### 8.4 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

### 8.5 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur from day of registration through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

#### 8.5.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

**Institutional Review Board Reporting Requirements:**

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

### 8.6 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

### 8.7 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

### 8.8 Data and Safety Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

## 9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

**9.1 Name of Agent:** Halaven®

**Chemical Name:** Eribulin mesylate

**Other Names:** None

**Classification:** Antineoplastic drug

**Molecular Formula**: C40H59NO11•CH4O3S

**Mode of Action:** Microtubule Inhibitor

**Metabolism:** Unchanged eribulin mesylate was the major circulating species in plasma following administration of 14C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites

**Product description:** Eribulin mesylate is a microtubule inhibitor which is FDA approved for metastatic breast cancer in patients previously exposed to taxane and anthracycline

**Solution preparation:** Each vial contains 1 mg of eribulin as a 0.5-mg/mL solution in a 5:95 ratio of ethanol to water

**Storage requirements:** Room temperature

**Stability:** Soluble in water

**Route of administration:** IV

**The cost of this agent will be covered by a grant from Eisai, Incorporated.**

**Drug Accountability:** The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the

investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

**Drug Destruction*:*** At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

## 10.0 STUDY PARAMETERS AND CALENDAR

### 10.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion.

Baseline imaging evaluations must be completed within 30 days prior to administration of protocol therapy. All other evaluations must be completed ≤ 7 days prior to administration of protocol therapy.

- Informed Consent
- Demographics
- Medical History
- Complete physical examination
- Height
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- Karnofsky Performance status
- Baseline Symptoms Assessment
- MRI of the brain with and without contrast
- CT, chest abdomen and pelvis with IV contrast, or total body FDG PET scan
- EKG
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - Prothrombin time/INR for calculation of Pugh-Child classification of hepatic dysfunction
    - ß-HCG for women of childbearing potential
    - Prothrombin time/INR

### 10.1.1 Treatment Period

Treatment cycles are 21 days long.

A visit window of up to 3 days before treatment is allowed for chemistry, coagulation and hematology labs.

A visit window of ± 7 days is allowed for 3 month MRI/CT scans and follow-up visits.

**Cycles 1-4**

**Laboratory Studies: to be completed 0-3 days prior to Day 1 eribulin administration**

- Complete Blood Count (CBC) with differential and platelets.
- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, Mg
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.

**Day 1**

Cycle 1, Day 1 evaluations do not need to be repeated if screening evaluations were conducted within 3 days prior to administration of protocol therapy.

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- Karnofsky Performance status
- Eribulin administration – 1.4mg/$m^2$ (or adjusted dose for renal or hepatic insufficiency)
- Baseline symptoms and adverse events assessment

**Cycles 1-4**

**Laboratory Studies: to be completed 0-3 days prior to Day 8 eribulin administration**

- Complete Blood Count (CBC) with differential and platelets.
- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, Mg
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.

**Day 8**

- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Karnofsky Performance status
- Eribulin administration – 1.4mg/$m^2$ (or adjusted dose for renal or hepatic insufficiency)
- Adverse events assessment

**Cycles 4+**

**Laboratory Studies: to be completed 0-3 days prior to Days 1 and 8 eribulin administration**

- Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, Mg
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- MRI of the brain with and without contrast every 12 weeks
- CT, chest abdomen and pelvis with IV contrast, or total body FDG PET scan

**Days 1 and 8**

- Physical Exam (only day 1)
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- Adverse events assessment
- Karnofksy Performance status
- Eribulin administration – 1.4mg/$m^2$ (or adjusted dose for renal or hepatic insufficiency)

**30-day follow-up**

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- Adverse events assessment
- Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, Mg
- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- Karnofksy Performance status

**Long term follow-up** (Every 3 months)

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, temperature, and respiratory rate
- Concomitant Medications Assessment including prescription medications, OTC, and nutritional/herbal supplements.
- Adverse events assessment
- Complete Blood Count (CBC) with differential and platelets. ALC will be calculated from CBC and differential
- Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, Mg

- Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.
- Karnofksy Performance status

**10.2 Calendar**

| Study Days | Pre-Study | Cycles 1-4 Day 1 | Cycles 1-4 Day 8 | Cycles 4+ Days 1 and 8 | 30 Day Follow Up | Long term Follow-Up |
|---|---|---|---|---|---|---|
| **REQUIRED ASSESSMENTS** | | | | | | |
| Informed Consent | X | | | | | |
| Demographics | X | | | | | |
| Medical History | X | | | | | |
| Height | X | | | | | |
| Weight | X | X | | X[c] | X | X |
| Vitals (blood pressure, pulse, temperature, and respiratory rate) | X | X | X | X | X | X |
| Physical Examination | X | X | | X[c] | X | X |
| Concomitant Medication Assessment | X | X | X | X[c] | X | X |
| Karnofksy PS | X | X | X | X | X | X |
| Baseline Symptoms | X | X[f] | | | | |
| Adverse Event Assessment | | X | X | X | X | X |
| CBC / diff / platelets/[b] | X | X[b] | X[b] | X[b] | X | X |
| Serum Chemistry [a,b] | X | X[b] | X[b] | X[b] | X | X |
| PT/INR | X | | | | | |
| ß-HCG, women of childbearing potential | X | | | | | |
| EKG | X | | | | | |
| **DISEASE ASSESSMENT** | | | | | | |
| MRI brain with and without contrast | X | | | X[d] | | |
| CT chest, abdomen and pelvis with IV contrast or total body FDG PET | X | | | X[e] | | |
| **TREATMENT** | | | | | | |
| Eribulin mesylate | | X | X | X | | |

**a:** Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, Mg. Calculated creatinine clearance will be done if creatinine and/or BUN are abnormal.

**b:** Laboratory Studies: to be completed 0-3 days prior to eribulin administration

**c:** Day 1 only

**d:** MRI brain to be completed every 12 weeks while on study eribulin mesylate

**e:** CT chest/abd/pelvis or total body PET every 12 weeks in patients with systemic disease while on study eribulin mesylate.

f:: cycle 1 day 1 only

## 11.0 MEASUREMENT OF EFFECT

CNS and non-CNS disease will be followed during the course of the trial. The primary endpoint will be response in brain.

### 11.1 Antitumor Effect – CNS Metastases

Patients will have a baseline MRI brain scan (within 30 days before initiation of therapy) and should be re-evaluated for response by MRI scan after 12 weeks of starting the study.

Response and progression by MR will be evaluated in this study using WHO/modified McDonald's criteria.

#### 11.1.1 Definitions

Evaluable for toxicity All patients will be evaluable for toxicity from the time of registration to protocol.

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

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

#### 11.1.2 Disease Parameters

Measurable Disease Measurable lesions are defined as brain lesions that can be accurately measured in at least one dimension) as $\geq$ 10 mm by Gd-MRI. All tumor measurements must be recorded in millimeters.

Note: Tumor lesions that are previously treated with stereotactic radiosurgery are not allowed as target lesion.

Non-measurable disease All other lesions including small lesions (longest diameter < 10 mm are considered non-measurable disease.

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

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

Target lesions: All measurable brain metastases ≥ 10 mm should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance, the next largest lesion which can be measured reproducible should be selected. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum diameters.

Non-target lesions: All other lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using calipers. All baseline evaluations should be performed within 30 days of initiation of 1st cycle of Chemotherapy.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

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

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

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring

cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if is not routine or serially performed.

11.1.4 Response Criteria

Measurement of Response

Gadolinium-enhanced brain MRI will be checked at baseline, 12 weeks after after starting treatment, and every 12 weeks thereafter until progression. The slice thickness of MRI should be less than 5 mm throughout the brain (2 to 3 mm thickness is highly recommended). MR imaging will be collected electronically for ad hoc central review of responses.

Response in the brain also will be measured using dimensional measurements (WHO/modified McDonald's criteria). Systemic responses will be assessed using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009).

**Time to CNS Progression**

Patients will be followed clinically and radiographically. The date at which the tumor is documented to have first enlarged (brain or systemic progression) by 25% from best response (steroid dose stable or increased, neurologically stable or worse) will be considered the date of tumor progression. Time to progression will be the interval between the date of study entry and the date of tumor progression. In the event of a discrepancy and for the purposes of analysis, the treating physician's date of tumor progression will be deemed to be correct. Tissue confirmation of CNS tumor progression by stereotactic biopsy or other surgical procedure is encouraged to rule out treatment effect as a cause of radiographic worsening. Ancillary imaging techniques such as PET imaging, perfusion MRI, or MR spectroscopy of all "recurrent" or "progressive" lesions of CNS is recommended for patients at centers with access to these technologies.

Responses in the CNS and systemic compartments will be assessed by the same criteria in order to avoid confusion in the conduct of the trial. CNS disease will be imaged by MRI with gadolinium, and systemic disease will be imaged by CT scan with IV contrast.

**Definition of CNS response to eribulin mesylate**

Residual enhancing, non-enhancing, or minimally enhancing tumor:
PR or CR should be confirmed at least 4 weeks after scan showing response.

*Complete Response* ***(CR)***: shall be defined as the circumstance when the tumor is no longer seen by neuroimaging, with the patient off all steroids, or on adrenal maintenance only; CR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan coding a response.

*Partial Response* ***(PR)***: Decrease of >50% in the product of two diameters with the patient off all steroids, or on adrenal maintenance only; PR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan.
*Stable Disease* ***(SD)***: shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids. This will not need a confirmatory scan.

*Progression **(P)***: shall be defined as a > 25% increase in tumor area *(two diameters)* provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. This will not need a confirmatory scan. A concomitant decrease in steroid dose will rule out a progression designation during the first two months after completion of XRT. *(Note: Under exceptional circumstances disease progression may be declared in the absence of an increase in tumor size)*

11.1.4.1 Evaluation of Target lesions by MRI using McDonalds criteria

| Response | WHO/modified McDonald Criteria |
|---|---|
| CR (complete response) | Complete disappearance of all enhancing disease and off all steroids |
| PR (partial response) | **≥ 50% reduction** in the sum of products of the perpendicular diameters of up to 2 target lesions* plus no new lesion, no progression of non-measurable CNS lesion, no increasing steroid requirements, and no worsening of neurologic symptoms |
| SD (stable disease) | < 50% reduction in size or < 25% increase in size. |
| PD† (progressive disease) | • **≥ 25% increase** of up to 2 target CNS lesions relative to nadir<br>• New CNS lesions<br>• unequivocal progression (defined below‡)<br>• Tumor-related increase in steroid dose<br>• New or worsening tumor-related neurologic symptoms |

11.1.4 Duration of Response

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

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

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

**Evaluation of Best Overall Response**

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

## 11.2 Antitumor Effect – Non-CNS Metastases

Although non CNS response is not the primary endpoint of this trial, subjects with measurable disease will be assessed by standard criteria. For the purposes of this study, subjects should be re-evaluated every 4 cycles of treatment.

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

### 11.2.1 Definitions

Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with eribulin.

Evaluable for objective response: Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

***Note:*** Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

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

**11.2.2 Disease Parameters**

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

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

**11.2.3 Response Criteria**

**Response Evaluation of Target Lesions**

Complete Response (CR):

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR):
At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD):
At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
***Note****:* the appearance of one or more new lesions is also considered progression.

Stable Disease (SD)"
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

**Evaluation of Non-Target lesions**
**Response Evaluation of Non-Target Lesions**

Complete Response (CR)
Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
***Note:*** If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/ Non-PD[Incomplete response/Stable Disease (SD)]
Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)
Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of 'non-target' lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

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

## 12.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

### 12.1 Data Reporting

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

### 12.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

#### 12.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

#### 12.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

### 12.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, case report forms, source documents, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations and the institution in which the study will be conducted, or for the period specified by the sponsor, whichever is longer. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

### 12.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

### 12.2.5 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

## 13.0 STATISTICAL CONSIDERATIONS

**Overview**

This is a prospective, single arm Phase II study to determine the 3-month CNS –progression fee survival **for patients with breast cancer with brain metastases treated with eribulin mesylate**, which is the primary objective of the study. To detect treatment response of brain metastases we will enroll 20 patients and use standard imaging modality, MRI, at baseline and 12 weeks.

**Sample size and study duration**

Clinically, in this population of breast cancer with brain metastases, we expect that a therapy would induce a 35% 3-month PFS rate. A 15% rate would not be considered meaningful, and thus anything statistically significant > 15% would be considered a positive study. The 3-month CNS PFS of 35% as an indicator of efficacy was based on studies of chemotherapy in brain metastases, which demonstrated 3-month CNS PFS rates in the range of 22%–50% (34-36). If 8 or more patients (out of 20) remain progression free at three months this will be taken as evidence that eribulin may have a positive impact on PFS, as the estimate of the proportion of patients with PFS would be 40%, and the 95% CI would be 18.5-61.5%, which does not include 15%. Thus, we have determined that a total of 20 evaluable patients will be required for the study.

In terms of availability of patients to enroll in this study, the proposed institution for this trial is the Case Comprehensive Cancer Center, a collaboration that includes clinical research activities at both University Hospitals Siedman Cancer Center and the Cleveland Clinic Foundation. Approximately 9000 new cancer patients are seen at Case Comprehensive Cancer Center annually of which 30-40 patients have brain metastases from metastatic breast cancer in Seidman network

alone. The anticipated accrual rate is 20 patients per year. We have the predefined response on eribulin mesylate which will be assessed by CNS RECIST 1.1 criteria using MRI scan.

**Evaluability**
To be evaluable for inclusion in the primary objective and secondary objectives, patients must have baseline and week 12 MRI.

**13.1 Methods to address the study objectives**
**Primary Objective**: CNS PFS at 3 months
We will assess the proportion of subjects without CNS progression at 3 months. We hypothesize that this will be at least 35%. We will generate a Kaplan- Meier curve of CNS PFS and estimate the PFS and 95% CI of the PFS.

**Secondary Objective 2.2.1**: Objective RR
We will calculate the proportion (and 95% CI) of the patients with complete and partial response and duration of CNS response.

**Secondary Objective 2.2.2**: Toxicity
We will evaluate rates (and 95% CI) of toxicity in patients treated with eribulin.

**Secondary Objective 2.2.3:** CBR at 12 weeks
We will sum the proportion of the patients with complete response, partial response and stable disease at 12 weeks (CBR). We will then calculate the proportion (and 95% CI) of patients with CBR at 12 weeks.

**Secondary Objective 2.2.4:** Systemic Disease RR
For this objective, we will estimate systemic disease response rate (and 95% CI) and perform a Kaplan-Meier analysis for systemic response in this patient population

**Secondary Objective 2.2.5**: Overall Survival
We will generate a Kaplan-Meier curve of OS. Point estimates (and standard error) of OS will be calculated.

## REFERENCES


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## Appendix A

**Performance Status Criteria**

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## Appendix B

### CHILD-PUGH CLASSIFICATION OF SEVERITY OF LIVER DISEASE

| Parameter | Points Assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin (mg/dL) | ≤ 2 | 2 to 3 | > 3 |
| Albumin (g/dL) | > 3.5 | 2.8 to 3.5 | < 2.8 |
| Prothrombin Time | | | |
| Seconds over control | 1 to 3 | 4 to 6 | >6 |
| INR | < 1.7 | 1.8 to 2.3 | > 2.3 |
| Encephalopathy | None | Grade 1 to 2 | Grade 3 to 4 |

Modified Child-Pugh Classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the Prothrombin time, and the degree of encephalopathy. A total score of 5 to 6 is considered Grade A (well-compensated disease); 7-9 is Grade B (significant functional compromise); and 10 to 15 is Grade C (decompensated disease). These grades correlate with one and two year survival; Grade A – 100% and 65%; Grade B: 80% and 60%; and Grade C – 45% and 35%.