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Protocol Title: Phase II Trial of Metronomic Eribulin (Halaven) In Pretreated Metastatic Breast Cancer (MBC)

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1. Background

1.1 Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women in the United States. In 2012, the National Cancer Institute estimates that 226,870 new cases of breast cancer will be diagnosed making it the most common non-skin cancer. Despite optimal treatment, approximately 30% of breast cancer patients develop disease recurrence requiring additional treatment. Despite an increase in the active agents available to treat metastatic disease, overall survival has changed little over the past few decades.

1.2 Eribulin

Eribulin mesylate is a non-taxane microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*.

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

In 2010, the Food and Drug Administration approved eribulin mesylate under the trade name HALAVEN for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

2. Rationale

Anti-tubulin therapy is an established cornerstone of chemotherapeutics for MBC. Work at our center and others has shown a favorable therapeutic index for weekly metronomic vinorelbine (1-4). Given the efficacy and tolerability, including lack of alopecia and nausea, many clinicians use vinorelbine early in therapy for metastatic breast cancer. Eribulin (Halaven®) is the first new therapeutic in breast cancer to show a survival advantage in salvage therapy. However, the tolerability of the FDA approved dose and schedule may limit its use in clinical practice, the number of patients offered the therapy, *and* the number of doses administered (duration of use) in metastatic breast cancer. The history of other effective and tolerable agents, including paclitaxel, capecitabine, as well as, vinorelbine, suggest that a low dose metronomic schedule of eribulin would be effective, well tolerated and result in a longer time to progression (TTP), and higher quality of life during therapy as has been seen clinically with low dose metronomic programs of capecitabine (5). In phase I studies, Eribulin showed activity at doses well below the maximally tolerated

1.4mg/m^2 given 2/3 weeks, suggesting a lower metronomic schedule would not compromise efficacy.

Eribulin has a novel mechanism of microtubule inhibition providing dynamic inhibition which is irreversible (6-7). Eribulin was studied in two phase 2 trials for patients with MBC in the salvage setting. In the first (8), patients with prior anthracyclines and taxanes exposure were given eribulin at 1.4 mg/m2 on days 1, 8 and 15 of a 28-day cycle, subsequently modified to days 1 and 8 of a q 21-day cycle due neutropenia seen on day 15; the median number of prior chemotherapy regimens was 4. A partial response (PR) rate of 11.5% was seen, with median progression free survival of 2.6 months and median survival of 9 months. Grade 3 of 4 neutropenia was appreciated in 64%, febrile neutropenia in 4%, and peripheral neuropathy in 5%. In the second trial (9) prior capecitabine, anthracycline and taxane exposure were required. The same dose was given on the q 21-day cycle. The median number of prior chemotherapy regimens was 4. The response rate was 9.3% (investigator-reported, 14%), median progression-free survival was 2.6 months, and median survival was 10.4 months. Grade 3 of 4 neutropenia was seen in 54%, febrile neutropenia in 5.5%, and grade 3 neuropathy in 6.9%.

These phase II studies set the stage for the pivotal phase III EMBRACE trial, comparing eribulin in the same dose and schedule (days 1 and 8 every 3 weeks) to physician's choice of salvage therapy among anthracycline- and taxane-pretreated MBC patients, with at least two prior regimens for advanced disease. In a major advance in metastatic breast cancer, overall survival, the primary endpoint, was improved from 9.3 months to 13.1 months in patients receiving eribulin (4). There was a longer but not significant difference in progression free survival (3.7 vs 2.2 months), and the response rate was higher for eribulin (12.2 vs. 4.7%, p=.002). Similar to the findings in phase II, the dominant grade 3 of 4 toxicity was neutropenia (45%) for eribulin, which was higher than in the control arm. Peripheral neuropathy occurred in 8.2%. The overall incidence of reported treatment-related serious adverse events was 12% for eribulin and 7% for the control treatments. Based on the outcome of EMBRACE, eribulin is now an FDA- approved therapy in the salvage setting for MBC.

We believe that the optimal schedule of eribulin has yet to be defined and that an approach similar to that used with vinorelbine could improve the tolerability of the agent without sacrificing efficacy. A lower dose metronomic schedule would allow responding patients to remain on treatment, resulting in a longer time to progression, and greater use of the drug in practice. Based on the phase I studies of eribulin we propose a dose of 0.9 mg/m^2 on days 1, 8 and 15 every 4 weeks as a metronomic schedule in a phase II trial, with the hope of averting alopecia and significant cytopenias. Given the lack of pharmacologic interaction between the drugs and the efficacy of vinorelbine with anti-HER2 agents(2, 10), we would propose to allow inclusion of HER2 positive patients with concomitant use of trastuzumab.

3. Trial Objectives

Primary:

- Progression free survival (PFS). We hypothesize that metronomic dosing of eribulin will result in a PFS of 4-6 months.

Secondary:

- Frequency of alopecia with absence or decrease to <50%
- Incidence of grade 3 and 4 neutropenia of <30%
- Incidence of sensory neuropathy (all grades) to <25%

Exploratory:

- Assess the role of circulating endothelial cell precursors (CEPs) and apoptotic CECs, in predicting early response to treatment.

4. Trial Design

This is an open-label, multi-center, phase II study of eribulin for patients with metastatic breast cancer.

Patients will receive eribulin 0.9 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1, 8 and 15 of a 28-day cycle. Treatment will be continued until disease progression, unacceptable toxicity or withdrawal of patient consent.

5. Subject Selection

Patients with metastatic breast cancer (MBC) whose disease has progressed following at least one prior regimen of chemotherapy in the setting of metastatic breast cancer will be recruited from the Seattle Cancer Care Alliance (SCCA), University of Arizona and SCCA Network sites.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

- Ability to provide written informed consent
- Prior exposure to taxane in the adjuvant, neoadjuvant or metastatic setting.
- At least one prior regimen of chemotherapy in the setting of metastatic breast cancer; no upper limit on the number of prior endocrine regimens for metastatic breast cancer, however no more than 6 chemotherapeutic regimens may have been given in the metastatic setting.
- Age $\geq$ 18 years.
- ECOG performance status of 0, 1, or 2.

- Patients must have baseline imaging within 30 days prior to the start of therapy and satisfy one of the following:
    - Measurable disease per RECIST 1.1 criteria [Eisenhauer]. At least one non lymph node lesion of ≥ 1.0 cm or lymph node ≥ 1.5 cm in short axis by CT scan (CT scan thickness no greater than 5 mm which is serially measurable according to RECIST 1.1 using either computerized tomography (CT) or magnetic resonance imaging (MRI). Lesions that have had radiotherapy must show evidence of progressive disease (PD) based on RECIST 1.1 to be deemed a target lesion.
    - Non-measurable disease by RECIST 1.1 criteria (includes bone only disease and lesions < 10 mm or lymph nodes <15 mm in short axis) with rising serum CA15-3 or CA 27.29 or CEA documented by two consecutive measurements taken at least 14 days apart with the most recent measurement being within 42 days prior to registration. The second CA 15-3 or CA 27.29 value must have at least a 20% increase over the first and for CA 15-3 or CA27.29 be greater than or equal to 40 units/mL or for CEA be greater than or equal to 4 ng/mL.

- Patients must have normal organ and marrow function as defined below:
    - absolute neutrophil count ≥1,500/mm^3
    - hemoglobin ≥ 10 g/dL
    - platelets ≥100,000/mm^3
    - creatinine ≤ 1.5 x ULN
    - total bilirubin ≤ 1.5 x ULN
    - alkaline phosphatase ≤ 3.0 x ULN. Up to 5X ULN is acceptable if due to bone metastases in the absence of liver metastases
    - AST and ALT ≤ 3.0 x institutional upper limit of normal, unless due to liver metastases (≤ 5 X ULN)
- Women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for the duration of study participation.
- Life expectancy of > 12 weeks.

5.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial:

- Prior treatment with Eribulin
- Plan to administer any other systemic antitumor including endocrine therapy except for following standard of care treatment:
    1. Trastuzumab at standard dosing HER2 positive tumors;
    2. Denosumab or bisphosphonates to treat metastatic bone disease.
- Plan to administer concurrent radiation therapy now or for progressive symptoms during treatment
- Patients with known CNS metastases must have stable disease off steroids after treatment with surgery or radiation therapy
- Second primary malignancy that is clinically detectable or clinically significant at the time of consideration for study enrollment

- Patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic and/or moderate (CrCl 30-50 mL/min) renal impairment
- Radiotherapy within 14 days of study treatment
- Major surgery within 21 days of study treatment. Minor surgery within 2 weeks of study treatment. Placement of vascular access device and biopsies allowed and is not considered major or minor surgery.
- Treatment with any systemic chemotherapy or investigational agents within 3 weeks of the start of study treatment. Endocrine treatment must be stopped prior to initiating study treatment. Subjects must have recovered from toxicities of prior therapy.
- Patients with peripheral neuropathy > grade 2 regardless of etiology
- Significant cardiovascular impairment: congestive heart failure >Class II according to the New York Heart Association (NYHA), unstable angina or myocardial infarction within 6 months of enrollment, or serious cardiac arrhythmia (> grade 2).
- Concomitant severe or uncontrolled medical disease
- Significant psychiatric or neurologic disorder which would compromise participation in the study
- Pregnant or breast-feeding females

6. Trial Treatments

All patients enrolled will receive treatment with eribulin.

6.1 Drug Supplies

6.1.1 Formulation and Packaging

Eribulin mesylate will be supplied by Eisai in single-use vials at a concentration of 1 mg/2 mL (0.5 mg/mL) solution in ethanol: water (5:95). Eribulin is a clear, colorless, sterile solution for intravenous administration.

6.1.2 Preparation and Dispensing

Aseptically withdraw the required amount of eribulin mesylate from the single-use vial and administer undiluted.

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.

Store undiluted eribulin mesylate in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or/ 4°C).

Discard unused portions of the vial.

6.2 Treating the Patient

6.2.1 Conditions patients must meet prior to administering any treatment on any week.

Prior to receiving any study treatment on Day 1, 8 or 15 of each cycle, the patient must meet all of the following criteria:

- Neutrophils are $\geq$ 1,000/mm^3
- Hemoglobin $\geq$ 8.0 g/dL
- Platelets $\geq$ 50,000/mm^3
- No grade 3 or 4 non-hematological toxicities.

If any of these criteria are not met the dose for that treatment day should be omitted.

Blood tests must be performed prior to resuming treatment with toxicities resolved or improved to $\leq$ grade 2 severity. Treatment should resume according to these criteria at the appropriate dose reduction outlined in Table 6-1.

There should always be a two week treatment free interval between cycles when the patient criteria is not met (as above) and the dose is omitted.

Non toxicity related treatment delays/omissions will be considered on a case by case basis in consultation with the P.I.

If a delay of > 3 weeks is required, the patient should be removed from study treatment and continue to be treated in accordance with the Investigator's standard clinical practice.

6.2.2 Eribulin administration

Eribulin will be administered at 0.9 mg/m^2 on days 1, 8 and 15 every 4 weeks. Treatment will continue until patient develops disease progression, unacceptable toxicity or chooses to stop study treatment.

Guidelines for dose modification and dose interruption of study drug are described in Table 6-1.

6.2.3 Dose Modifications

Any dose reduction or dose delay of study drug is based upon the severity of toxicity as graded by NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycles.

All toxicity-related causes for dose reductions or dose delays must be recorded as adverse events. Please refer to Table 6-1 for recommended study drug dose adjustments. Patients requiring a delay in study treatment of greater than 3 weeks or greater than 3 dose reductions will be discontinued from study treatment.

Table 6-1 Recommended Dose Reductions of Eribulin

Event Description	Recommended Dose
Hold treatment and reduce to recommended dose for subsequent treatments for any of the following: • Grade 3 neutropenia (ANC <1,000/mm^3) • Grade 3 anemia (Hgb < 8.0 g/dL) • Grade 3 thrombocytopenia (platelets <50,000/mm^3) • Non-hematologic Grade 3 or 4 toxicities • Omission or delay of Day 8 or 15 dose in previous cycle for toxicity	0.7 mg/m^2
Occurrence of any of the above events while receiving 0.7 mg/m^2 dose	0.6 mg/m^2
Occurrence of any of the above events while receiving 0.6 mg/m^2 dose	0.5 mg/m^2
Occurrence of any of the above events while receiving 0.5 mg/m^2 dose	Discontinue eribulin

GCS-F may be used according to NCCN Guidelines (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf) and the treating physician's clinical judgment. When G-CSF is given, it should begin the day after administration of eribulin and stop at least 24 hours prior to the next dose of eribulin. G-CSF dates of administration and doses must be documented in source documents.

6.3 Concomitant Medications

Other systemic antitumor therapy is not allowed except for:

a. Trastuzumab, at standard doses, as this is standard of care for HER2 positive tumors.
b. Denosumab or bisphosphonates to treat metastatic bone disease, as these are also standard of care.

Radiation therapy may have been administered previously. However, concurrent radiation therapy or its institution to treat progressive symptoms during treatment is not permitted. Patients who require palliative radiation must discontinue eribulin for 7-14 days and wait 7-14 days after completing radiation before resuming eribulin therapy.

Endocrine therapy is not permitted during the study. However, good clinical practice would imply that for ER+ patients, endocrine therapy will previously have been given unless contraindicated in the judgment of the treating physician (e.g., for significant visceral involvement).

Patients should also be screened for concomitant use of drugs that prolong QT interval. If identified, these drugs should be discontinued. A list of drugs that prolong QT interval is available at http://www.azcert.org/medical-pros/drug-lists/printable-drug-list.cfm. Please note that low dose Zofran is allowed because QT safety issues are associated with high dose Zofran. The expectation is that sites will use the list together with the same good medical practice procedures used for patients who are not on a study. This may involve consultation with the site's pharmacist.

7. Trial Procedures

Prior to undergoing any study-specific procedure, patients must read and sign the current Institutional Review Board (IRB)-approved informed consent form. The schedule of assessments is presented in Appendix 1 (Visit Schedule).

Assessments outlined in the visit schedule include the following components:

7.1 Screening Visit

The screening visit will occur within 30 days prior to initiating study treatment. Laboratory tests must be done within 14 days prior to cycle 1 day 1.

- Medical History - metastatic breast cancer diagnosis, prior treatment history, and demographics.
- Physical Examination - examination of major body systems, ECOG performance status, body weight and vital signs (i.e., blood pressure, heart rate).
- Laboratory Evaluations must be obtained up to 14 days prior the first dose of eribulin
    - Hematology (CBC with platelets and absolute neutrophil count)
    - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)
    - Pregnancy test - serum or urine pregnancy test performed for all women of childbearing potential
    - Tumor markers - CEA and either CA 27.29 or CA 15-3
    - Research blood sample
- CT scan or PET with diagnostic CT of chest, abdomen and pelvis to determine areas of involvement. With principal investigator approval, ultrasound or MRI may be substituted for CT or PET with diagnostic CT.

7.2 Prior to Each Cycle

Evaluations and procedures required for screening may be used for cycle 1 day 1 and do not need to be repeated.

In the absence of adverse events requiring dose delays, day 1 will occur approximately every 28 days (+/- 4 days or as determined by consultation with principal investigator). Procedures to be completed after recovery from the previous cycle and prior to the start of each subsequent cycle include:

- Physical examination - monthly clinical evaluation of major body systems, assessment of toxicity and clinical assessment of disease response, ECOG performance status, body weight and vital signs (i.e. blood pressure, heart rate).
- Laboratory Evaluations
    - Hematology (CBC with platelets and absolute neutrophil count)
    - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)
    - Tumor markers if elevated at baseline
    - Research blood sample- prior to day 1 of cycles 2, 4 and 6
- Adverse Event Assessment
- Disease reassessment of known sites of disease by same method used at baseline should be repeated approximately every 12 weeks (i.e. after completing cycles 3, 6, 9, etc. and before beginning the next cycle.)

7.3 Day 8 (+/- 1 Day) and Day 15 (+/- 1 Day) of Each Cycle.

- CBC with differential and platelet count - to be done prior to each dose of chemotherapy
- Adverse event assessment.

7.4 End of Treatment Visit

Patients should undergo the following assessments when all study treatment is discontinued. If it is not feasible for a patient to come to the clinic for an end of treatment visit the patient may be contacted by phone to assure any serious and ongoing adverse events are managed and reported appropriately.

- Physical Examination - examination of major body systems, ECOG performance status, body weight and vital signs (i.e., blood pressure, heart rate).
- Laboratory Evaluations
    - Hematology (CBC with platelets and absolute neutrophil count)
    - Blood chemistry (sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium)
    - Tumor markers if elevated previously
    - Research blood sample (unless patient has started a new treatment regimen).
- Adverse Event Assessment
- Disease reassessment of known sites of disease by the same method used at baseline if not done within the last 12 weeks (+/-1 week).

7.5 Subject Withdrawal

Patients will be removed from study treatment if they present with disease progression, as defined by RECIST version 1.1 criteria. Subjects will also be removed from study treatment if they require more than three dose level reductions or more than three weeks to recover from treatment related adverse events. Patients may withdraw consent at any time.

Patients will be followed for survival until one year after the last patient is registered to the study. Follow up testing will be performed according to standard of care.

8. Assessments

The schedule of assessments is presented in Appendix 1. The description of assessments is provided in Section 7.

8.1 Efficacy Assessments

Patients will have their disease assessed for response by conventional imaging methods. This will most often include a CT scan of the chest, abdomen and pelvis for baseline tumor burden. Bone scan or other appropriate imaging may also be used as clinically indicated. All baseline imaging must be obtained no more than 30 days prior to the first study drug dose and after all previous treatment has been discontinued. Imaging will be repeated every 12 weeks + / - 1 week (i.e. after completing treatment on cycles 3, 6, 9, etc. and before beginning the next treatment cycle) by the same methods used at baseline unless clinically indicated sooner as part of standard of care.

8.1.1 Definition of Measurable and Non-Measurable Disease

Measurable disease: The presence of at least one lesion (non-lymph node) that is $\geq$10mm in longest diameter on an axial image on CT or MRI with $\leq$ 5 mm reconstruction interval (if slice thickness is > 5mm, the longest diameter must be at least two times the thickness) or a lymph node that is $\geq$ 15 mm in short axis. Skin lesions $\geq$ 10 mm in longest diameter on clinical exam (photo) are considered measurable. The photo should include a ruler.

Non-measureable disease by RECIST 1.1 criteria (includes bone only disease and lesions < 10 mm or lymph nodes < 15 mm in short axis) with rising serum CA15-3 or CA 27.29 or CEA documented by two consecutive measurements taken at least 14 days apart with the most recent measurement being within 42 days prior to registration. The second CA 15-3 or CA 27.29 or CEA value must have at least a 20% increase over the first and for CA 15-3 or CA 27.29 be greater than or equal to 40 units/mL or for CEA be greater than or equal to 4 ng/mL.

8.1.2 Baseline Documentation of Tumor Burden

- Target lesions: A maximum of five target lesions in total (up to two per organ) will be identified. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter (SLD). The baseline SLD will be used as the reference by which to characterize the objective tumor response.

- 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.

8.1.3 Response Criteria

Radiological response will be defined as per the RECIST 1.1 criteria. Treatment outcomes will be defined as:

- Complete response (CR): complete disappearance of all extranodal target and non-target lesions. All pathological lymph nodes must have decreased to <1mm in short axis.
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions taking as a reference the baseline sum of diameters.
- Stable disease (SD): neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify for PD.
- Progressive disease (PD): Sum of diameters increased by at least 20% from the smallest value on study (including baseline if that is the smallest). The sum of diameters must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2mm to 3mm, for example, does not qualify). Unequivocal progression of existing non-target lesions also constitutes disease progression as does the appearance of one or more new lesions.

FDG-PET can be used to complement CT scanning. A positive FDG-PET scan is one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected images. Progressive disease by FDG-PET: Negative FDG-PET at baseline, with a positive FDG-PET at follow-up based on a new lesion, or No FDG-PET at baseline and a positive FDG-PET at follow-up. Either of these findings should be correlated with CT scan imaging as described in RECIST 1.1 but date of progression is assigned to the date of the initial abnormal FDG-PET scan.

Tumor Marker (CEA and either CA 27.29 or CA 15-3) Response:

- Tumor Marker Complete Response: Reduction in CEA and CA 15-3 or CA 27.29 to ≤ ULN.
  Tumor Marker Partial Response: Greater than or equal to a 50% reduction in CEA and CA 15-3 or CA 27.29 from baseline, but not qualifying as CR.

- Tumor Marker Progression: Greater than or equal to a 50% increase in CEA and CA 15-3 or CA 27.29 from baseline.
- Tumor Marker Stable Disease: or CEA and CA 15-3 or CA 27.29 response not qualifying as CR, PR, or Progression.
- Tumor Marker Inadequate Assessment, response unknown: CEA and CA 15-3 or CA 27.29 response has not been adequately assessed.

8.2 Time-to-Event Measures

The following definitions for time-to-event measures will apply:

- Duration of Tumor Response is measured from the date of the first objective assessment of PR or CR to the first date of disease relapse or death from any cause.
- Progression-free survival is measured from the date of enrollment to the first date of radiographic progression of disease per RECIST 1.1 criteria or death.

8.3 Correlative Science

Research blood samples will be collected to explore markers that may be related to eribulin's antitumor and antiangiogenic activity. Circulating endothelial cell (CEC), circulating endothelial precursor cell (CEP) and apoptotic CEC assays are among the markers that will be assessed. Other markers may also be explored.

The role of CEPs in predicting early response will be examined by serial measurements in the laboratory of Dr. Alison Stopeck at the University of Arizona Cancer Center. CECs have been shown to decrease in response to anti-angiogenic therapies (11, 12). CEPs have also been shown to correlate with increased angiogenesis and can increase in response to growth factor use with G-CSF (13, 14). One mechanism by which metronomic therapy is hypothesized to be more effective is by specifically acting on endothelial cells resulting in increased apoptosis and antiangiogenic effects as well as decreasing or eliminating G-CSF use to prevent increases in CEPs, a precursor for tumor induced angiogenesis. In advanced breast cancer patients receiving metronomic chemotherapy, an increase in apoptoic CECs after 2 months of therapy was associated with prolonged progression-free and overall survival with follow up of greater than 2 years (15). In this trial we propose to measure levels of CEPs, and apoptotic CECs, at baseline and in response to eribulin therapy in an effort to validate metronomic dosing as having both antitumor as well as antiangiogenic effects.

Instructions for collecting, processing and shipping research specimens are included in the Laboratory Section of the Study Manual.

9. Adverse Event Reporting

9.1 Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study. Any unanticipated problem (incident, experience or outcome) that

involves risk to a study patient must be reported to the Coordinating Center in an expedited manner within 24 hours of awareness of the event and to the IRB of record in accordance with the IRB policy. Examples of unanticipated events are (1) adverse events, (2) breach of confidentiality, (3) accidental or unintentional change to the IRB approved protocol that harmed participants, (4) incarceration of a study patient, (5) study patient complaint.

The investigator is responsible for the appropriate medical care of patients during the study. The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue study treatment. The patient should be followed until the event resolves or stabilizes.

Safety measurements that will be used in the study include physical examinations and clinical laboratory tests. Clinical exam by the provider with CBC, absolute neutrophil count, platelet count and serum chemistry to include sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase and magnesium will be performed after recovery from the previous cycle and prior to the start of each subsequent treatment cycle. CBC, absolute neutrophil count and platelet count will be done prior to each dose of planned chemotherapy (days 1, 8, 15 of each cycle).

Adverse events will be graded for toxicity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Toxicity assessments will be performed based on procedures outlined in the Schedule of Assessments. Any adverse events leading to a treatment interruption or dose reduction along with all adverse events that are grade 3 and higher will be recorded in the CRF.

9.2 Definition of an Adverse Event

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below.

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be a symptom (e.g., nausea, chest pain), or a sign (e.g., tachycardia, enlarged liver).

9.3 Serious Adverse Events

An event that fulfills at least one of the following criteria will be designated a serious adverse event (SAE). SAEs will be reported to the Coordinating Center, Eisai and the IRB of record according to the IRB's policy/procedure.

- Results in death
- Requires initial inpatient hospitalization or prolongation of existing hospitalization
- Is immediately life-threatening
- Results in severe or permanent disability or incapacity
- Is a congenital abnormality or birth defect

- Any other important medical event that may jeopardize the subject or requires medical intervention to prevent one of the outcomes listed above.

Reportable Serious Adverse Event (SAE) - Any event that is unequivocally unrelated to study drug or is due to progression of disease should not be reported as an SAE.

9.4 Adverse Event Reporting Requirements

Adverse events will be collected after the patient has taken the first dose of study drug. After discontinuation from treatment, patients must be followed for all existing AEs for 30 calendar days after the last dose of study drug or until another anti-cancer therapy is initiated.

Prior to beginning study treatment, study site personnel will note the occurrence and nature of each patient's medical condition(s). During the study, site personnel will again note any change in the condition(s) and/or the occurrence and nature of any adverse events. Adverse events are to be graded according to the NCI CTCAE version 4.0.

A description of the event, including its date of onset, date of resolution and any action taken should be provided along with the investigator's assessment of causality. An event that is due to unequivocal progression of disease should not be reported as an AE. Any adverse events leading to a treatment interruption or dose reduction along with all grades 3 and higher adverse events must be recorded on a case report form (CRF).

Any SAE that is NOT unequivocally unrelated to study drug or due to progression of disease must be reported to EISAI and the appropriate IRB. Reportable SAEs experienced within 30-days after the patient has stopped study treatment must be reported. For enrollments from SCCA main campus, SCCA at Evergreen and the SCCA Network sites SAE reports should be submitted to the Consortium IRB. Reportable SAEs occurring at Arizona Cancer Center (AZCC) will be reported to their IRB.

10. Data Analysis/Statistical Methods

Patients must meet all eligible criteria and receive at least one full cycle of protocol directed therapy to be included in the efficacy analysis. All treated patients will be included in the assessment of adverse events.

10.1 Efficacy Analysis

The primary endpoint is progression free survival.
Progression free survival (PFS) will be measured as the time from study enrollment until the earliest date of disease progression or death. PFS will be censored at last radiographic assessment for patients who discontinue study therapy for reasons other than disease progression. Kaplan-Meier survival curves will be used to describe progression-free survival, overall and stratified by number of prior metastatic treatment regimens. A 95% confidence interval for the median PFS will be calculated

using the method of Brookmeyer and Crowley. The sample size of 60 eligible and evaluable patients has 99% power for the lower bound of the confidence interval to be greater than 2.2 months (the median PFS in the physician's discretion arm of the EMBRACE trial), assuming that the true median PFS is 4 months, comparable to or an incremental improvement over the median PFS for the eribulin arm of the EMBRACE trial (3.7 months).

Based on the eribulin arm of the EMBRACE trial, median progression free survival is expected to be approximately 3.7 months. Approximately 4 years of accrual and 1 year of follow up will be necessary to detect an improvement in median progression free survival from 3.7 to 4 months.

10.2 Analysis of Other Endpoints

Demographic characteristics such as patient age, gender, tumor type, and ECOG performance status will be tabulated. All continuous data will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum values). All categorical data will be summarized using frequencies and percentages.

The prevalence of key adverse events will be calculated and 95% Wilson (score) confidence intervals reported for each. With a sample size of n=60, power is approximately 88% to produce confidence intervals with an upper bound lower than the rate reported in the EMBRACE trial, assuming that the rate of the adverse event is 20 percentage points lower under the metronomic schedule of delivery.

Dose delivery, use of cytokine support and reasons for discontinuing therapy will be described for all enrolled patients.

Case report forms and an electronic database using the Redcap system from Vanderbilt University will be created during start up. Study data will be extracted from the medical record by the Coordinating Center. Response evaluations according to RECIST criteria will be provided by the University of Washington Tumor Imaging Metrics Core service.

11. Registration Guidelines

Before a subject participates in the trial, the investigator or delegate (as allowed by the IRB of record) is responsible for obtaining written informed consent after adequate explanation of the aims, methods, anticipated benefits, subject responsibilities including the use of adequate methods to prevent pregnancy, and potential hazards of the study and before any protocol-specific screening procedures or any study medications are administered.

All patients must be registered before the start of treatment. To register a patient, call the Coordinating Center at the Seattle Cancer Care Alliance (288-7232 or, toll free, (888) 201-0060) between the hours of 8:00 AM and 5:00 PM Pacific time, Monday through Friday. Materials required to complete the registration may be faxed (206 288-1310) or scanned/e-mailed (sccanetresearch@seattlecca.org) and include:

- Consent Form
- HIPAA Authorization
- Registration Form and all supporting documentation
- Eligibility Checklist
- Race and Ethnicity Form.

After eligibility has been confirmed, a patient identification number will be assigned. The patient will be considered registered, and study treatment may then begin.

12. Data Submission Schedule

Staff of the Seattle Cancer Care Alliance Network Research Office (NRO) will monitor compliance and complete data forms for all enrollments from SCCCA Network sites and the Arizona Cancer Center (AZCC). SCCA Breast Program research staff will monitor and complete the data forms for patients enrolled at the SCCA main campus and SCCA at Evergreen research staff will monitor and complete the data forms for patients enrolled at that facility.

13. Study Monitoring

Continuous Monitoring

Protocol implementation will be reviewed and summarized in an on-going manner. The principal investigator will review (1) all serious adverse events and (2) data concerning disease progression.

Teleconferences between investigators at the University of Washington and University of Arizona will occur regularly to discuss the progress of the study. The following topics will be discussed:

- Reports of serious, unexpected adverse events occurring on the study that are related to study drug
- IND safety reports of serious, unexpected adverse events that are related to study drug
- Instances of disease progression
- Pending protocol or consent form changes
- Other issues related to accrual or protocol implementation as necessary.

Written summaries of serious, unexpected adverse events occurring on the study that are related to study drug and IND safety reports received from Eisai will be distributed by the SCCA NRO to the lead investigator at each performance site as they are reported. Similarly protocol modifications and consent form changes will be distributed to each performance site as they are approved with instructions as to whether subjects must be re-consented.

Annual Monitoring

Data and safety monitoring for the study will be performed according to the Fred Hutchinson / University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan every 12 - 24 months. Enrollments from the Seattle Cancer Care Alliance main campus and SCCA at Evergreen will be monitored by the Clinical Research Support Office of the Fred Hutchinson/University of Washington Cancer Consortium which has primary oversight of the study. Enrollments from Seattle Cancer Care Alliance Network sites or the University of Arizona will be monitored by the Seattle Cancer Care Alliance NRO . Additional study monitoring may occur at each performance site according to the site's institutional policy. Copies of monitoring reports should be submitted to the Coordinating Center.

The purpose of the monitoring is to verify the accuracy of the study data, assess compliance with the protocol and with Good Clinical Practice (GCP) regulations, and assure the timely and complete reporting of safety (adverse event) data. The significant elements of the plan are summarized below.

At each monitoring visit the following documents will be reviewed in accordance with the current Consortium monitoring plan:

- Informed consent
- Eligibility -
- Data review - (safety, dosing, efficacy, etc.)
- Critical Document Review.
- Test Article Inventory.

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Appendix 1: Schedule of Assessments

Procedure	Screening evaluations & procedures may be used for C1D1		Subsequent cycle day 1 will occur approximately every 28 days +/- 4 days or as determined by consultation with principal investigator				
	within 30 days of day 1 cycle 1	within 14 days of day 1 cycle 1	Day 1	Day 8 (+/- 1 day)	Day 15 (+/- 1 day)	End of Treatment	
Medical History	X						
Physical Exam	X		X			X	
Pregnancy Test		X					
Hematology[1]		X	X	X	X	X	
Serum Chemistries[2]		X	X			X	
Tumor markers[3]		X	X			X	
Research Labs[4]		X	X			X	
Disease Assessment[5]	X		X			X[6]	
Adverse Event Assessment			X	X	X	X	
Eribulin			X	X	X		

[1] To include CBC with platelet count and absolute neutrophil count
[2] To include sodium, potassium, chloride, carbon dioxide, creatinine, BUN, glucose, calcium, LDH, albumin, bilirubin, AST, ALT, total protein, alkaline phosphatase, magnesium
[3] To include CEA and either CA 27.29 or CA 15-3 at baseline and then monthly if elevated at baseline
[4] Research blood sample at baseline (prior to the start of treatment) and before cycles 2, 4, 6 and end of treatment.
[5] Disease assessment of known sites of disease by same method used at baseline (to include chest, abdomen and pelvis) approximately every 12 weeks (i.e. after cycles 3, 6, 9, etc.)
[6] Within 1 week of end of treatment if not done within the last 12 weeks.