BRE 186

Phase II Trial of Eribulin in Patients Who Do Not Achieve Pathologic Complete Response (pCR) Following Neoadjuvant Chemotherapy

SCRI PROTOCOL NUMBER:	BRE 186
TRIAL DRUGS:	Eribulin
SPONSOR:	SCRI Oncology Research Consortium 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@scresearch.net
STUDY CHAIR/COORDINATING INVESTIGATOR	Denise A. Yardley, MD Sarah Cannon Research Institute (SCRI) 3322 West End Ave., Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@scresearch.net
MEDICAL MONITOR:	John D. Hainsworth, MD Sarah Cannon Research Institute (SCRI) 3322 West End Ave., Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@scresearch.net
DATE FINAL:	26 MAY 2011

Amendment Number:	1	**Amendment Date:**	25 JAN 2012
Amendment Number:	2	**Amendment Date:**	20 MAR 2013

Clinical Trial Protocol Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the <Study Chair> / <Coordinating Investigator>/ <Principal Investigator>, I understand that my signature on the protocol constitutes my agreement and understanding of Principal Investigator responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities to the CRO and the <Study Chair> / <Coordinating Investigator>/ <Principal Investigator> as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Clinical Trial Protocol Approval Page

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Denise A. Yardlev. MD

Study Chair/Coordinating Investigator (Name Printed or Typed)

Study Chair/Coordinating Investigator Signature March 25, 2013 **Date**
Denise A. Yardley, MD
Sarah Cannon Research Institute

John D. Hainsworth, MD

Medical Monitor (Name Printed or Typed)

Medical Monitor Signature **Date**
John D. Hainsworth, MD, Chief Scientific Officer
Sarah Cannon Research Institute

Sheetal Khedkar

Sponsor Representative (Name Printed or Typed)

Sponsor Representative Signature **Date**
Sheetal Khedkar, Director
Sarah Cannon Research Institute

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Denise A. Yardlev. MD		
Study Chair/Coordinating Investigator (Name Printed or Typed)	**Study Chair/Coordinating Investigator Signature** Denise A. Yardley, MD Sarah Cannon Research Institute	**Date**
John D. Hainsworth, MD	John D Hainsworth 20/MAR/2013	
Medical Monitor (Name Printed or Typed)	**Medical Monitor Signature** John D. Hainsworth, MD, Chief Scientific Officer Sarah Cannon Research Institute	**Date**
Sheetal Khedkar	20/March/2013	
Sponsor Representative (Name Printed or Typed)	**Sponsor Representative Signature** Sheetal Khedkar, Director Sarah Cannon Research Institute	**Date**

Clinical Trial Protocol Acceptance Form

Phase II Trial of Eribulin in Patients Who Do Not Achieve Pathologic Complete Response (pCR) Following Neoadjuvant Chemotherapy

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Denise A Yardley MD

Principal Investigator Name
(Name Printed or Typed)

Principal Investigator Signature **Date**
<Insert Site Name and ID info as applicable>
<Insert Site Location>

March 25, 2013

Clinical Trial Protocol Acceptance Form

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_____	_____	_____
Principal Investigator Name (Name Printed or Typed)	**Principal Investigator Signature** *<Insert Site Name and ID info as applicable>* *<Insert Site Location>*	**Date**

Phase II Trial of Eribulin in Patients Who Do Not Achieve Pathologic Complete Response (pCR) Following Neoadjuvant Chemotherapy

History of Amendments

Amendment #	Amendment Date	Revision(s) Made
1	25 JAN 2012	Inclusion Criteria were clarified as follows: 2. Histologically confirmed breast cancer prior to surgery with the following staging criteria: T1-T3, ~~N1~~***N0***-N2, and M0 (T1N0M0 patients are excluded). 4. ~~At least 3 weeks~~ ***Patients must be ≥21 days and ≤ 84 days*** from breast surgery and fully recovered. Patients may have had mastectomy or breast conservation surgery with axillary node dissection. 5. Pathologic CR (pCR) not achieved following neoadjuvant treatment (i.e., residual invasive breast cancer (>5 mm) in the breast or presence of nodal disease at surgery [***ypT0, N1-N3a, M0 or*** ypT1b-T4, ~~N1~~***N0-N3a***~~N2~~, M0]. 14. Female patients who are not of child-bearing potential (see Appendix D), and female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix D), who are not breastfeeding, and who have a negative serum pregnancy test performed within ~~48 hours~~***7 days*** prior to start of trial treatment. Exclusion Criterion #2 was clarified as follows: ***2. Radiotherapy prior to the start of study treatment.*** Section 5 Trial Design and Figure 1: Patients may undergo locoregional radiation therapy either during or following chemotherapy according to institutional guidelines (Section 7.8). ***Radiotherapy prior to the start of study treatment is not permitted.*** Patients in Cohort B (hormone-receptor-positive) ***and Cohort C (HER2-positive)*** may receive adjuvant therapy according to institutional guidelines.

History of Amendments

Amendment #	Amendment Date	Revision(s) Made
1	25 JAN 2012	7.2 Baseline Assessments Note: baseline laboratory assessments will be allowed up to 7 days outside of the 7-day specified window, provided that critical laboratory assessments ***(CBC, CMP, pregnancy test, and PT/INR and PTT [for patients receiving warfarin only])*** are repeated on Cycle 1, Day 1 prior to study treatment. • Complete blood count (CBC) including 3-part differential and platelets ***(may be done up to 72 hours prior to treatment)*** • Coagulation analysis: prothrombin time (PT)/International Normalization Ratio (INR) and partial thromboplastin time (PTT) ***(may be done up to 72 hours prior to treatment)*** • Serum pregnancy test within ~~48 hours~~ ***7 days*** of first dose of trial drug (Section 7.5.3) 7.5.4 Pregnancy Test All females of childbearing potential must complete a serum pregnancy test within ~~48 hours~~ ***7 days*** prior to the initiation of eribulin therapy. Minor typographical errors were corrected. ICF modifications were made.

History of Amendments

Amendment #	Amendment Date	Revision(s) Made
2	20 MAR 2013	Inclusion Criteria were clarified as follows: 2. Histologically confirmed breast cancer prior to surgery with the following staging criteria: T1-T3, ***T4a, T4b***, N0-N2, ***N3a*** and M0 (T1N0M0 patients are excluded). ***Inflammatory disease is excluded.*** 5. Pathologic CR (pCR) not achieved following neoadjuvant treatment (i.e., residual invasive breast cancer (>5 mm) in the breast or presence of nodal disease at surgery [ypT0***/T1a***, N1-N3a, M0 or ypT1b-T4, N0-N3a, M0]. Section 6.2 Dose Modifications for Eribulin: For patients who experience toxicities during the trial, one or more doses of eribulin may need to be reduced, delayed, or withheld. Patients can ***either have trastuzumab delayed or*** continue to receive trastuzumab on an every-3-week schedule even if administration of eribulin is delayed or withheld on Day ***11per the treating physician's discretion***. Section 6.2.1 Recommended Dose Delays of Eribulin ***For ANC <1500/µL on Day 1, delay dose of Eribulin until ANC >1500/µL, then:*** • ***Initiate treatment with prophylactic granulocyte-CSFs, with no dose reductions.*** • ***If patient is already receiving granulocyte-CSF treatment, reduce dose by 1 dose level.*** Section 7.2 Baseline Assessments and Appendix C Patients must have the following assessments performed ≤7 days before receiving their first dose of study drug. Note: baseline laboratory assessments ***(except the serum pregnancy test)*** will be allowed up to 7 days outside of the 7-day specified window, provided that critical laboratory assessments (CBC, CMP, ~~pregnancy test,~~ and PT/INR and PTT [for patients receiving warfarin only]) are repeated on Cycle 1, Day 1 prior to study treatment. Section 7.3.1 Day 1 of each cycle The following assessments will be performed at each of these visits: • CBC, including 3-part differential and platelets ***(may be done up to 72 hours prior to treatment)*** • CMP plus magnesium ***(may be done up to 72 hours prior to treatment)***

Phase II Trial of Eribulin in Patients Who Do Not Achieve Pathologic Complete Response (pCR) Following Neoadjuvant Chemotherapy

History of Amendments

Amendment #	Amendment Date	Revision(s) Made
2	20 MAR 2013	Section 7.5.1 Follow-Up After Completion of Eribulin Treatment Patients will be followed every 3 months during years 1 and 2~~, every 6 months during years 3 through 5, and annually thereafter~~ for toxicity~~,~~ ***and*** disease progression~~, and survival~~. At each visit, patients will have a physical examination, complete blood counts, chemistry profile, and evaluation of any new symptoms. ~~After disease progression is documented, patients will be followed until they initiate new treatment as specified in Section **Error! Reference source not found.**.~~ Assessments at these visits will be performed as described in Appendix C. ~~Section 7.5.2. Follow-Up After Disease Progression~~ ~~After disease progression is documented, patients will be followed to document any new anti-cancer therapies received after discontinuation of study treatment. Patients may be contacted during outpatient visits or by telephone.~~ Section 7.8 Radiation Therapy Experience with concurrent eribulin and radiation therapy is limited and hence safety will be evaluated after the first 10 patients ~~on each cohort~~ have been treated with concurrent eribulin and radiotherapy. Section 8.1.1 Eribulin, Labeling, Packaging, Storage Eribulin mesylate (HALAVEN™) is a clear, colorless, and sterile solution for injection that contains 1.0 mg eribulin drug substance in 2.0 mL of solution. Eribulin ***clinical supply*** is packaged in single-use glass vials. ~~Clinical supplies of eribulin should be stored at room temperature. Storage at temperatures between 2°C and 8°C, however, are acceptable and provide an extended provisional shelf life.~~ ***The supply for this study may be provided with one of two labeled storage requirements (see 1. and 2. below). The storage conditions are not interchangeable and the supply must be stored as detailed on the supply labels.*** ***1. Refrigerated: Store in a refrigerator, between 2°C - 8°C (36°F - 46°F). Do not freeze. Store the vials in their original cartons.*** ***2. Controlled room temperature: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). Do not freeze. Store the vials in their original cartons.***

History of Amendments

Amendment #	Amendment Date	Revision(s) Made
2	20 MAR 2013	Section 8.1.3 Precautions and Risks with Eribulin For a complete discussion of risk information including precautions and adverse reactions for Eribulin, please refer to the current Eribulin Investigator's Brochure. ~~The most common adverse reactions (≥25%) reported in patients receiving eribulin were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving eribulin were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of eribulin was peripheral neuropathy (5%).~~ ~~8.1.3.1 Neutropenia~~ ~~If patients develop severe neutropenia lasting longer than five days or neutropenia with a fever, their next dose of erlibulin should be delayed and reduced. Severe neutropenia (ANC <500/mm^3) lasting more than one week occurred in 12% (62/503) of patients in the recently completed Phase 3 trial, leading to discontinuation in <1% of patients. Patients with ALT or AST >3 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin >1.5 × ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia. Monitor complete blood counts prior to each dose; increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Delay administration of eribulin and reduce subsequent doses in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than five days.~~ ~~8.1.3.2 Peripheral Neuropathy~~ ~~In the Phase 3 trial with eribulin, Grade 3 peripheral neuropathy occurred in 8% (40/503) of patients, and Grade 4 in 0.4% (2/503) of patients. Peripheral neuropathy was the most common toxicity leading to discontinuation of erlibulin (5% of patients; 24/503). Neuropathy lasting more than one year occurred in 5% (26/503) of patients. Twenty-two percent (109/503) of patients developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25 to 662 days). Monitor patients closely for signs of peripheral motor and sensory neuropathy. Withhold erlibulin in patients who experience Grade 3 or 4 peripheral neuropathy until resolution to Grade 2 or less.~~

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History of Amendments

Amendment #	Amendment Date	Revision(s) Made
2	20 MAR 2013	~~8.1.3.3 QTc Interval Prolongation~~ ~~In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. Electrocardiogram monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics, (Appendix E) and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating eribulin and monitor these electrolytes periodically during therapy. Avoid eribulin in patients with congenital long QT syndrome.~~ Appendix C Schedule of Assessments Footnote g: ***Complete staging work-up to confirm localized disease should include computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or a bone scan. (Note: a PET/CT is acceptable for baseline imaging in lieu of CT examinations or bone scan)***. Negative scans performed prior to the initiation of neoadjuvant therapy, or at any subsequent time, are acceptable and do not need to be repeated. Footnote l: After completion of eribulin treatment, patients will be followed every 3 months during years 1 and 2~~, every 6 months during years 3-5, and annually thereafter~~ for toxicity and ***disease progresson*** ~~survival~~. Footnote m: ***CBC, including 3 part differential and platelets and CMP plus magnesium may be done up to 72 hours prior to treatment.*** ~~After disease progression is documented, patients will be followed every 3 months until they initiate new treatment.~~

CLINICAL PROTOCOL BRE 186 SYNOPSIS

Title of Trial:	Phase II Trial of Eribulin in Patients Who Do Not Achieve Pathologic Complete Response (pCR) Following Neoadjuvant Chemotherapy (BRE 186)	
SCRI Protocol Number:	BRE 186	
Sponsor:	Sarah Cannon Research Institute (SCRI) Oncology Research Consortium	
Trial Duration:	The duration of the trial from first enrollment to last patient last visit (LPLV) is 18 to 24 months.	**Phase of Trial:** II
Trial Centers:	This is a multicenter trial to be conducted in the United States at approximately 20 sites.	
Objectives:	Primary objective The primary objective of this trial is to: • Assess the efficacy of eribulin when administered to patients who do not achieve pCR following standard neoadjuvant chemotherapy (+/- trastuzumab). The primary endpoint will be 2-year disease-free survival (DFS) rate. Secondary objective The secondary objectives of this trial are to: • Assess the feasibility of administering 6 cycles of eribulin following standard neoadjuvant chemotherapy and primary surgical therapy. • Assess the toxicity of eribulin in this patient population.	
Trial Design:	This is a nonrandomized, open-label trial that will evaluate 6 cycles of eribulin administered postoperatively in patients who do not achieve pCR following a standard neoadjuvant chemotherapy regimen. There will be three cohorts of patients based on tumor type: triple-negative (A), hormone-receptor-positive/HER2-negative (B), and HER2-positive (C). Patients who are HER2-positive will receive trastuzumab as part of neoadjuvant treatment and concurrently with postoperative eribulin treatment.	
Trial Population:	The trial population will consist of consenting female patients who do not achieve pCR (i.e., have residual invasive disease in breast or lymph node tissue) after treatment with a standard neoadjuvant chemotherapy regimen and surgery.	
Number of Patients:	One-hundred forty-eight patients will be enrolled in this trial (54 in Cohort A, 42 in Cohort B, and 52 in Cohort C).	
Drug Supply	The pharmaceutical company, Eisai, will provide eribulin (HALAVEN™) for this trial. Trastuzumab (Herceptin®) is commercially available and will be obtained from commercial sources. Eribulin will be dispensed to the sites by the SCRI Oncology Research Consortium.	

Trial Drugs, Dose, and Mode of Administration:

All patients will receive eribulin 1.4 mg/m^2 IV Days 1 and 8 every 21 days for 6 cycles. Patients with HER2-positive tumors will also receive trastuzumab 6 mg/kg IV Day 1 every 21 days to complete a total of 1 year (52 weeks) of treatment from the start of neoadjuvant administration. If the last dose of trastuzumab was given >28 days from trial treatment start, the loading dose should be 8 mg/kg.

Patients will receive either eribulin alone (Cohorts A & B) or eribulin + trastuzumab (Cohort C) based on their HER2 status and/or hormone receptor status.

Cohort	Trial Drugs & Mode of Administration
Cohort A: Triple-negative	Eribulin 1.4 mg/m^2 IV (Days 1 & 8 every 21 days)
Cohort B: Hormone-receptor-positive/HER2-negative	Eribulin 1.4 mg/m^2 IV (Days 1 & 8 every 21 days)
Cohort C: HER2-positive	Eribulin: 1.4 mg/m^2 IV (Days 1 & 8 every 21 days) Trastuzumab: 6 mg/kg IV (Day 1 every 21 days)

Inclusion Criteria:

Patients must meet the following criteria in order to be included in this clinical trial:

1. Female patients ≥18 years-of-age.
2. Histologically confirmed breast cancer prior to surgery with the following staging criteria: T1-T3, T4a, T4b, N0-N2, N3a and M0 (T1N0M0 patients are excluded). Inflammatory disease is excluded.
3. Previous treatment with a minimum of 4 cycles of neoadjuvant anthracycline and/or taxane containing chemotherapy (+trastuzumab in HER2-positive patients).
4. Patients must be ≥21 days and ≤ 84 days from breast surgery and fully recovered. Patients may have had mastectomy or breast conservation surgery with axillary node dissection.
5. Pathologic CR (pCR) not achieved following neoadjuvant treatment (i.e., residual invasive breast cancer (>5 mm) in the breast or presence of nodal disease at surgery [ypT0/T1a, N1-N3a, M0 or ypT1b-T4, N0-N3a, M0].
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 (see Appendix A).
7. Recovery from any toxic effects of prior therapy to ≤ Grade 1 per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0) except fatigue or alopecia.
8. Peripheral neuropathy Grade ≤2 per NCI CTCAE v4.0 at trial entry.
9. Normal left ventricular ejection fraction (LVEF), within the institutional limits of normal, as measured by echocardiography (ECHO) or multi-gated (MUGA) scan in patients to receive trastuzumab with eribulin (Cohort C).
10. Adequate hematologic function defined as:
    - Absolute neutrophil count (ANC) ≥1500/μL
    - Hemoglobin (Hgb) ≥9 g/dL
    - Platelets ≥100,000/uL

Inclusion Criteria (continued):	11. Adequate liver function defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN) • Total bilirubin ≤1.5 x ULN (unless the patient has grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin). 12. Adequate renal function defined as: • Serum creatinine ≤1.5 mg/dL (133 μmol/L) **OR** calculated 24-hour creatinine clearance ≥45 mL/min. 13. Complete staging work-up to confirm localized disease should include computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or a bone scan. (Note: a PET/CT is acceptable for baseline imaging in lieu of CT examinations or bone scan). Negative scans performed prior to the initiation of neoadjuvant therapy, or at any subsequent time, are acceptable and do not need to be repeated. 14. Female patients who are not of child-bearing potential (see Appendix D), and female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix D), who are not breastfeeding, and who have a negative serum pregnancy test performed within 7 days prior to start of trial treatment. 15. Willingness and ability to comply with trial and follow-up procedures. 16. Ability to understand the investigative nature of this trial and give written informed consent. 17. Agree to delay in reconstruction in terms of implants placed in setting of expanders until chemotherapy is completed and the patient has recovered. Expansion of expanders may continue during trial treatment.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from entry into this trial: 1. Presence of other active cancers, or history of treatment for invasive cancer <3 years prior to trial entry (except thyroid, cervical cancer). Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer. 2. Radiotherapy prior to the start of study treatment. 3. History or clinical evidence of central nervous system metastases or other metastatic disease. 4. Non-healed surgical wound. 5. Known or suspected allergy/hypersensitivity to eribulin. 6. Cardiac disease, including: congestive heart failure Class II-IV per New York Heart Association classification (Appendix B); cardiac ventricular arrhythmias requiring anti-arrhythmic therapy; unstable angina (anginal symptoms at rest) or new-onset angina (i.e., began within the last 3 months), or myocardial infarction within the past 6 months. 7. Chronic use of drugs that cause QTc prolongation (see Appendix E). Patients must discontinue use of these drugs 7 days prior to the start of study treatment. 8. Women who are pregnant or lactating. All females of child-bearing potential must have negative serum or urine pregnancy tests within 48 hours prior to trial treatment (see Appendix D).

Exclusion Criteria (continued):	9. Patients with known diagnosis of human immunodeficiency virus (HIV), hepatitis C virus, or acute or chronic hepatitis B infection. 10. Prolongation of heart rate-corrected QT interval (QTc) >480 msecs (using Bazett's formula). 11. Minor surgical procedures (with the exception of the placement of port-a-cath or other central venous access) performed less than 7 days prior to beginning protocol treatment. 12. History of cerebrovascular accident including transient ischemic attack (TIA), or untreated deep venous thrombosis (DVT)/ pulmonary embolism (PE) within the past 6 months. Note: Patients with recent DVT/PE receiving treatment with a stable dose of therapeutic anti-coagulating agents are eligible. 13. Patients may not receive any other investigational or anti-cancer treatments while participating in this trial. 14. History of any medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risks associated with the trial participation or investigational product(s) administration or may interfere with the interpretation of the results. 15. Inability or unwillingness to comply with trial and/or follow-up procedures outlined in the protocol.
Statistical Methodology:	The efficacy and safety analysis populations will consist of all patients who received at least 1 dose of protocol treatment. Three cohorts of patients with residual disease following neoadjuvant therapy (triple-negative [A], hormone-receptor-positive (ER+ and/or PR+)/HER2-negative [B], and HER2-positive [C]) will be evaluated separately to obtain preliminary efficacy information. With standard neoadjuvant therapy, the approximate 2-year DFS of patients who do not achieve pCR are as follows: triple-negative, 40%; hormone-receptor-positive/HER2-negative, 80%; and HER2-positive, 60%. Treatment capable of providing relative improvement in these results by 40% in the triple-negative cohort, 15% in the hormone-receptor-positive/HER2-negative cohort, or 25% in the HER2-positive cohort would be worthy of further development. For a one-sided test of hypothesis at alpha = 0.10 and power = 0.80, the required sample sizes are 49, 38 and 47, respectively. In order to adjust for potential non-evaluable patients, this preliminary study will treat 54, 42, and 52 patients, respectively, in the three cohorts. This will allow determination of a 2-year DFS within 95% confidence intervals for each subgroup, as follows: Cohort A Triple-negative: 42.0% - 67.9% Cohort B Hormone-receptor-positive (and HER2-negative) cohort: 78.7% - 96.9% Cohort C HER2-positive cohort: 61.0% - 84.5% Evaluation of safety among patients in each cohort will also provide sufficient experience to determine the tolerability and toxicity of this regimen. Safety data will be tabulated for patients who receive any amount of trial medication. Adverse events (AEs) will be tabulated by body system, preferred term, severity, and relation to treatment. Worst toxicity grades per patient will be tabulated for selected AE and laboratory measurements by using NCI CTCAE criteria V4.0.

CLINICAL TRIAL BRE 186 CONTACT INFORMATION:

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Enrollment Phone # / Fax #:	(877) MY-1-SCRI / (866) 699-0258

List of Abbreviations

AE	adverse event
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
AST (SGOT)	aspartate aminotransferase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CMP	comprehensive metabolic profile
CRF	Case Report Form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	estrogen receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HalB	halichondrin B
HER2	human epidermal growth factor receptor 2
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous(ly)
MUGA	multigated (radionuclide) angiogram
NCI	National Cancer Institute
OS	overall survival
pCR	pathologic complete response
PET	positron emission tomography
PR	progesterone receptor
PT	prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
SAE	serious adverse event
SCRI	Sarah Cannon Research Institute
TNBC	triple-negative breast cancer
ULN	upper limit of normal
VACP	vincristine, doxorubicin, cyclophosphamide, and prednisone
VbMP	vinblastine, methotrexate, and prednisone

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1. INTRODUCTION

1.1. Background

Neoadjuvant chemotherapy has become the standard of care for patients with locally advanced breast cancer. Patients achieving a pathologic complete response (pCR) to their neoadjuvant therapy have experienced better disease-free survival (DFS) and overall survival (OS). Unfortunately, the approximately 20% to 25% rate of pathologic complete response reported with standard non trastuzumab containing regimens leaves the majority of patients at increased risk of recurrence with inferior DFS and OS.

In a review of neoadjuvant patients treated at MD Anderson, recurrence and death rates were higher in the first 3 years for triple-negative breast cancer (TNBC) compared with non-TNBC (1). In another study examining breast cancer subtypes and outcome to neoadjuvant chemotherapy, patients with basal-like and human epidermal growth factor receptor 2 (HER2)-positive /estrogen-receptor-(ER)-negative subtypes with residual disease experienced more frequent early relapses and death. While it was easier to achieve a pathologic complete response in patients with basal-like or HER2-positive /ER-negative subtypes, the patients who did not achieve a pCR had a relatively poor prognosis, with most relapses occurring during the first 2 years following surgery (2).

Currently, there is little evidence to support the use of further adjuvant chemotherapy for patients who do not achieve pCR after treatment with a neoadjuvant chemotherapy regimen. Since residual disease reflects resistance to neoadjuvant chemotherapy, pilot trials have attempted to offer further non-cross-resistant chemotherapy. In a trial from MD Anderson, 110 patients who had received neoadjuvant VACP (vincristine, doxorubicin, cyclophosphamide, and prednisone) and had residual disease were randomized to receive further treatment with VACP or vinblastine, methotrexate, and prednisone (VbMP) (3). Results demonstrated that adjuvant treatment was tolerable, with a suggestion of improved outcomes with VbMP (OS 65% versus 47%, p=0.06). Additional data from small pilot trials administering various postoperative chemotherapies have also supported this approach, as have pilots with novel biological therapies such as bevacizumab. Treatments were generally well tolerated and extended follow-up continues.

1.2. Eribulin

Eribulin mesylate (Halaven™) is a synthetic analog of halichondrin B (HalB), a natural product isolated from the marine sponge, *Halichondria okadai* (4). HalB is a large polyether macrolide that exerts potent anticancer effects in cell-based and animal models of cancer (4, 5, 6). The structurally simplified synthetic analog, eribulin, encompasses the biologically active macrocyclic portion of HalB, and shows similar or identical anticancer properties in preclinical models (7).

Following discovery of the potent anticancer activity of HalB in 1986 (4) it was tested in the US National Cancer Institute (NCI) 60-cell line screen using known antimitotic agents and other anticancer drugs as comparators (5). While antiproliferative patterns of HalB in the NCI cell line screen were similar to those of other antitubulin drugs, the biochemical mechanism of HalB's interaction with tubulin was distinct (5, 8, 9). HalB noncompetitively inhibited vinblastine binding to tubulin, enhanced bis-5,5'-[8-(N-phenyl)-amino-naphthalene-1-sulfonic acid] binding

to tubulin, and had no effect on iodoacetamide alkylation of tubulin sulfhydryl groups; yet HalB did not stabilize or inhibit colchicine binding to tubulin. Therefore, it was concluded that HalB's tubulin-based mechanism is distinct from all other known classes of antitubulin agents (5, 8, 9).

Eribulin exerts its antiproliferative effects via a tubulin-based antimitotic mechanism. Currently-available data indicate that its mechanism of action is similar or identical to that of HalB (7, 8). Like HalB, eribulin was shown to be a potent inhibitor of tubulin polymerization into microtubules as well as microtubule dynamics in vitro and in whole cells (7, 10). Nonclinical data show that sub- to low-nmol/L levels of eribulin inhibit cancer cell proliferation via induction of irreversible cell cycle blocks at G2/M, disruption of mitotic spindles, and initiation of apoptosis (7, 11).

Human tumor xenograft studies in mice (ovary, lung, breast, colon, melanoma, pancreatic, and fibrosarcoma) demonstrate tumor regressions, remissions, and an increased lifespan at dose levels below the maximum tolerated dose (7, 12). In vivo animal model data predict that eribulin will have greater efficacy than the taxanes and that increased antitumor activity can be achieved with fewer adverse effects. In addition, the potential for common side effects and drug-drug interactions with eribulin are less than or equal to existing therapies. Currently, there is no evidence for taxol-like hypersensitivity with eribulin. Although eribulin is a PgP drug efflux pump substrate (13), it retains full in vitro activity against cancer cells that are taxane-resistant due to β-tubulin mutations (14), suggesting that eribulin may show clinical effectiveness in subjects with refractory tumors that are taxane resistant based on β-tubulin mutations.

In summary, eribulin kills cancer cells via apoptosis secondary to inhibition of cellular microtubule dynamics, disruption of mitotic spindle formation and induction of irreversible cell cycle arrest at G2/M. When tested in a variety of animal models of human cancer, these molecular- and cell-based anticancer activities of eribulin result in significant antitumor effects including tumor growth inhibition, regressions, remissions and increased life span. Current nonclinical data predict anticancer efficacy greater than the taxanes, achieved with fewer adverse effects.

Eribulin was approved by the U.S. Food and Drug Administration (FDA) on 15 November 2010 to treat patients with metastatic breast cancer who had received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based chemotherapies.

1.2.1. Clinical experience with eribulin

Eleven Phase 1 and 5 Phase 2 trials of eribulin have been conducted worldwide (USA, Europe, and Japan). In addition, one Phase 3 study in patients with advanced breast cancer has been completed.

The pharmacokinetic profile of eribulin was established in the early phase studies. In general, the pharmakokinetics of eribulin are characterized by a rapid distribution phase, with a prolonged elimination phase after intravenous infusion. The disposition of E7389 follows linear kinetics over the dose range studied, as shown by consistent dose-independent pharmacokinetic parameters and similar dose-normalized parameters.

Eribulin's safety and effectiveness were established in the single Phase 3 study in 762 women with metastatic breast cancer who had received at least two prior chemotherapy regimens for late-stage disease (15, 16). Patients were randomly assigned to receive treatment with either eribulin or a different single-agent therapy chosen by their oncologist in a 2:1 ratio.

The study was designed with OS as the primary endpoint. The median OS for patients receiving eribulin was 13.1 months compared with 10.6 months for those who received a different single-agent therapy and was considered to demonstrate a clear survival benefit.

The most common side effects reported by women treated with eribulin include neutropenia/ leukopenia, asthenia/fatigue, nausea, constipation, alopecia, arthralgia/myalgia, pyrexia, and peripheral neuropathy.

1.3. Rationale for the Trial

Eribulin, a novel chemotherapeutic agent with efficacy in patients with refractory metastatic breast cancer, may be effective in the treatment of patients with locally advanced breast cancer who do not achieve pCR following neoadjuvant therapy. We propose to evaluate eribulin as adjuvant therapy in patients who do not achieve pCR following standard neoadjuvant chemotherapy. Three cohorts of patients will be evaluated separately: triple-negative, hormone-receptor-positive/HER2-negative, and HER2-positive. Hormone-receptor-positive patients may be ER and /or PR positive.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Primary objective

The primary objective of this trial is to:

- Assess the efficacy of eribulin when administered to patients who do not achieve pCR following standard neoadjuvant chemotherapy (+/-trastuzumab). The primary endpoint will be 2-year DFS rate.

2.2. Secondary objectives

The secondary objectives of the trial are to:

- Assess the feasibility of administering 6 cycles of eribulin following standard neoadjuvant chemotherapy and primary surgical therapy.
- Assess the toxicity of eribulin in this patient population.

3. TRIAL POPULATION

Patients must have baseline evaluations performed prior to the first dose of trial drug and must meet all inclusion and exclusion criteria. The Principal Investigator or his/her designee must review the results of all baseline evaluations that assure that all inclusion and exclusion criteria have been satisfied prior to enrollment of that patient.

3.1. Inclusion Criteria

Patients must meet the following criteria in order to be included in this clinical trial:

1. Female patients ≥18 years-of-age.
2. Histologically confirmed breast cancer prior to surgery with the following staging criteria: T1-T3, T4a, T4b N0-N2, N3a and M0 (T1N0M0 patients are excluded). Inflammatory disease is excluded.
3. Previous treatment with a minimum of 4 cycles of neoadjuvant anthracycline and/or taxane containing chemotherapy regimen (+trastuzumab in HER2-positive patients).
4. Patients must be ≥21days and ≤ 84 days from breast surgery and fully recovered. Patients may have had mastectomy or breast conservation surgery with axillary node dissection.
5. Pathologic CR (pCR) not achieved following neoadjuvant treatment (i.e., residual invasive breast cancer (>5 mm) in the breast or presence of nodal disease at surgery [ypT0/T1a, N1-N3a, M0 or ypT1b-T4, N0-N3a, M0].
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 (see Appendix A).
7. Recovery from any toxic effects of prior therapy to ≤ Grade 1 per the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) except fatigue or alopecia.
8. Peripheral neuropathy Grade ≤2 per NCI CTCAE v4.0 at trial entry.
9. Normal left ventricular ejection fraction (LVEF), within the institutional limits of normal, as measured by an echocardiogram (ECHO) or multi-gated angiogram (MUGA) in patients to receive trastuzumab with eribulin (HER2-positive).
10. Adequate hematologic function defined as:
    - Absolute neutrophil count (ANC) ≥1500/μL
    - Hemoglobin (Hgb) ≥9 g/dL
    - Platelets ≥100,000/uL
11. Adequate liver function defined as:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN)
    - Total bilirubin ≤1.5 x ULN (unless the patient has grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin).
12. Adequate renal function defined as:
    - Serum creatinine ≤1.5 mg/dL (133 μmol/L) OR calculated 24-hour creatinine clearance ≥45 mL/min.
13. Complete staging work-up to confirm localized disease should include computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or a bone scan. (Note: a PET/CT is acceptable for baseline imaging in lieu of CT examinations or bone scan). Negative scans performed prior to the initiation of

neoadjuvant therapy, or at any subsequent time, are acceptable and do not need to be repeated.

14. Female patients who are not of child-bearing potential (see Appendix D), and female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix D), who are not breastfeeding, and who have a negative serum pregnancy test performed within 7 days prior to start of trial treatment.
15. Willingness and ability to comply with trial and follow-up procedures.
16. Ability to understand the investigative nature of this trial and give written informed consent.
17. Agree to delay in reconstruction in terms of implants placed in setting of expanders until chemotherapy is completed and the patient has recovered. Expansion of expanders may continue during trial treatment.

3.2. Exclusion Criteria

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

1. Presence of other active cancers, or history of treatment for invasive cancer <3 years prior to trial entry (except thyroid, cervical cancer). Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.
2. Radiotherapy prior to the start of study treatment.
3. History or clinical evidence of central nervous system metastases or other metastatic disease.
4. Non-healed surgical wound.
5. Known or suspected allergy/hypersensitivity to eribulin.
6. Cardiac disease, including: congestive heart failure Class II-IV per New York Heart Association classification (Appendix B); cardiac ventricular arrhythmias requiring anti-arrhythmic therapy; unstable angina (anginal symptoms at rest) or new-onset angina (i.e., began within the last 3 months), or myocardial infarction within the past 6 months.
7. Chronic use of drugs that cause QTc prolongation (see Appendix E). Patients must discontinue use of these drugs 7 days prior to the start of study treatment.
8. Women who are pregnant or lactating. All females of child-bearing potential must have negative serum pregnancy test within 48 hours prior to trial treatment (see Appendix D).
9. Patients with known diagnosis of human immunodeficiency virus (HIV), hepatitis C virus, or acute or chronic hepatitis B infection.
10. Prolongation of heart rate-corrected QT interval (QTc) >480 msecs (using Bazett's formula).

11. Minor surgical procedures (with the exception of the placement of port-a-cath or other central venous access) performed less than 7 days prior to beginning protocol treatment.
12. History of cerebrovascular accident including transient ischemic attack (TIA), or untreated deep venous thrombosis (DVT)/ pulmonary embolism (PE) within the past 6 months. Note: Patients with recent DVT/PE receiving treatment with a stable dose of therapeutic anti-coagulating agents are eligible.
13. Patients may not receive any other investigational or anti-cancer treatments while participating in this trial.
14. History of any medical or psychiatric condition or laboratory abnormality that in the opinion of the investigator may increase the risks associated with the trial participation or investigational product(s) administration or may interfere with the interpretation of the results.
15. Inability or unwillingness to comply with trial and/or follow-up procedures outlined in the protocol.

3.3. Discontinuation from Trial Treatment

Patients will be discontinued from trial treatment for any of the following reasons:

- Disease progression
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Patient requests to withdraw from the trial and discontinue treatment
- Patient requests to discontinue treatment
- Pregnancy (see Section 3.3.1)
- Inability of the patient to comply with trial requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Non-compliance/lost to follow-up

Patients who have been discontinued from trial treatment will not be replaced. After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of trial drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the Case Report Form (CRF).

All patients who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

3.3.1. Pregnancy

During the course of the trial, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix D) must contact the treating Investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating Investigator).

If an Investigator suspects that a patient may be pregnant prior to administration of trial drugs, the trial drugs must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any trial drugs, and must be discontinued from the trial.

If an Investigator suspects that a patient may be pregnant after the patient has been receiving trial drugs, the trial drugs must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the trial drugs must be permanently stopped, the patient must be discontinued from the trial, and the Investigator must notify the SCRI Study Chair as soon as possible. If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and faxed to the SCRI Safety Department. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 10.5.1.

4. TRIAL REGISTRATION

Each patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, and risks and discomforts. Human protection committee (Institutional Review Board [IRB]) approvals of this protocol and consent form are required prior to patient enrollment. Registration must occur prior to the initiation of protocol therapy.

Patients eligible to participate in the trial may enroll through the Sarah Cannon Research Institute (SCRI) Oncology Research Consortium (ORC) Central Enrollment Desk at 1-877-MY-1-SCRI. Registration may be done via fax (866) 699-0258 Monday through Friday, 8:30 a.m. to 4:30 p.m., Central Standard Time. Patient registration will be confirmed via fax within 24 hours, or by the next business day.

5. TRIAL DESIGN

All patients will receive eribulin 1.4 mg/m^2 on Days 1 and 8 every 21 days for 6 cycles via the intravenous (IV) route. Patients with HER2-positive tumors will also receive trastuzumab 6 mg/kg IV Day 1 every 21 days to complete a total of 1 year (52 weeks) of treatment from the start of neoadjuvant administration. If the last dose of trastuzumab was given >28 days from trial treatment start, the loading dose should be 8 mg/kg.

Patients will receive either eribulin alone (Cohorts A & B) or eribulin + trastuzumab (Cohort C) based on their HER2 status and/or hormone-receptor status (Table 1).

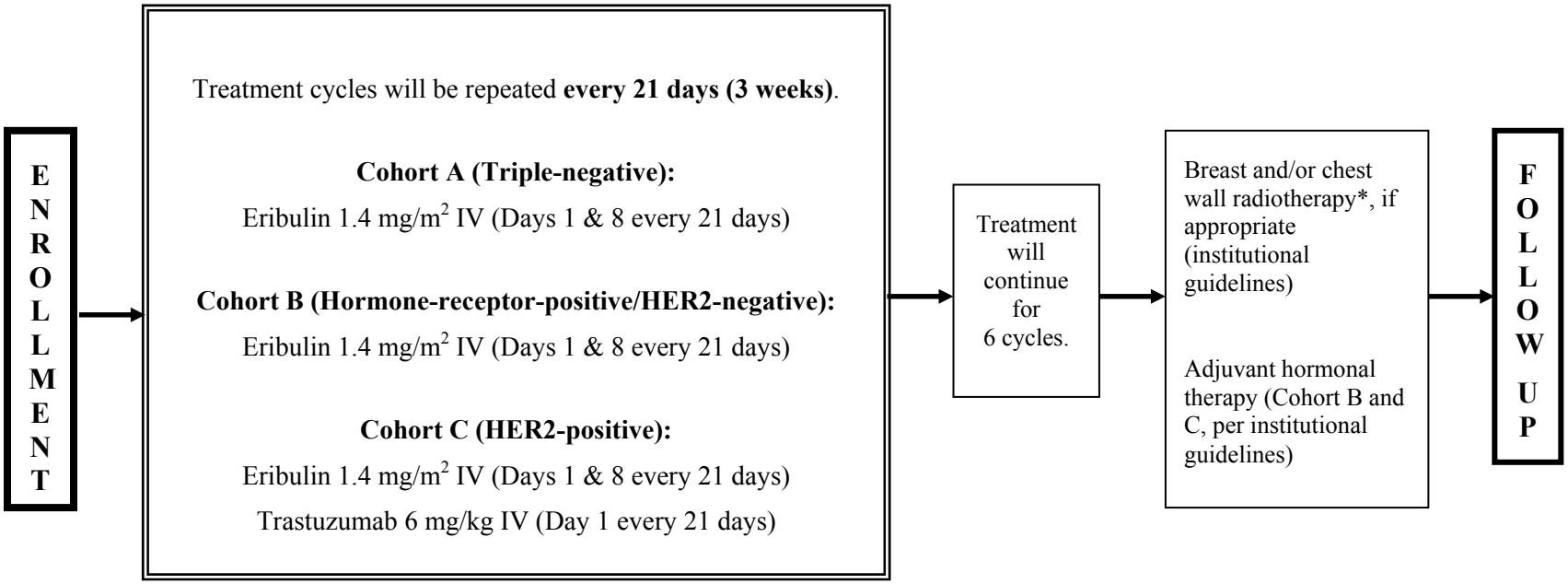
Table 1: Description of Dosing by Cohort

Cohort	Trial Drugs & Mode of Administration
Cohort A: Triple-negative	Eribulin 1.4 mg/m^2 IV (Days 1 & 8 every 21 days)
Cohort B: Hormone-receptor-positive/HER2-negative	Eribulin 1.4 mg/m^2 IV (Days 1 & 8 every 21 days)
Cohort C: HER2-positive	Eribulin: 1.4 mg/m^2 IV (Days 1 & 8 every 21 days) Trastuzumab: 6 mg/kg IV (Day 1 every 21 days)

Patients may undergo locoregional radiation therapy either during or following chemotherapy according to institutional guidelines (Section 7.8). Radiotherapy prior to the start of study treatment is not permitted. Patients in Cohort B (hormone-receptor-positive) and Cohort C (HER2-positive) may receive adjuvant hormonal therapy according to institutional guidelines.

The treatment schema is presented in Figure 1.

Figure 1: Treatment Schema for BRE 186



* Patients may receive radiation therapy either during or following chemotherapy per institutional guidelines.

5.1. End of Trial

The primary endpoint of this trial is 2-year DFS. Therefore, patients will be followed for at least 2 years after last treatment.

5.2. Method of Treatment Assignment and Blinding

This is a non-randomized trial in which patients will be assigned to treatment based on their tumor type.

This is an open-label trial and so blinding is not necessary.

5.3. Concomitant Medications

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the trial without prior consultation with the Investigator. At each visit, the Investigator will ask the patient about any new medications he/she has taken after the start of the trial drug.

Growth factor support: Routine prophylactic use of colony-stimulating factor (CSF) is not recommended during this study. Myeloid or granulocyte-specific colony-stimulating factor (G-CSF) may be used, according to standard guidelines (e.g., American Society of Clinical Oncology [ASCO] guidelines) or at the discretion of the treating investigator, after discussion with the Study Chair. Colony-stimulating agents must be held at least the day before chemotherapy, and initiated at least 1 day after chemotherapy is administered. Use of colony-stimulating agents should not substitute for protocol-mandated dose reductions due to neutropenia and/or neutropenic fever (Section **Error! Reference source not found.**). Use of erythropoietin is allowed. Use of stimulators of thrombopoiesis is not allowed.

Anti-emetics: Prophylactic anti-emetic therapy should follow standard guidelines for moderately emetogenic chemotherapy.

Drugs that cause QTc prolongation: Drugs that cause QTc prolongation are prohibited. Please see Appendix E for a list of prohibited drugs.

The use of any herbal/natural products or other "folk remedies" should be discouraged, but use of those products, as well as the use of vitamins, nutritional supplements, and all other concomitant medications, is not cause for discontinuation but must be recorded in the CRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the trial or up to 30 days after the last dose of protocol treatment must be documented.

6. DOSE MODIFICATIONS

Treatment-related toxicities will be evaluated utilizing the NCI CTCAE v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of

toxicity. If trial medication is held for over 3 weeks due to toxicity, that medication will be discontinued.

6.1. Dose Reductions

Patients who have toxicity related to treatment may have their dose(s) reduced.

All dose reductions will be made from the planned dosages. Patients who require dose reductions must be evaluated at least weekly until the toxicity stabilizes or improves. Once stable, patients can resume evaluations according to the protocol-specified visit schedule. If toxicity remains unresolved for 3 weeks, the patient will discontinue treatment with that drug. Patients in Cohort C who discontinue chemotherapy prior to completing 6 cycles can remain on study and continue to receive trastuzumab. Patients should be evaluated weekly (at a minimum), if therapy is on hold.

There is clinical evidence of QTc prolongation with both eribulin and trastuzumab. During the treatment period, if an ECG indicates a QTc interval ≥500 msec, then two additional ECGs should be obtained within 5 minutes to confirm the abnormality. The average QTc will be determined from the three ECG tracings by manual evaluation, and will be used to determine continued eligibility. If the average QTc is <500 msec, the patient may continue therapy. If the average QTc is ≥500 msec, the study treatment should be discontinued immediately. The patient should be treated appropriately for QTc interval prolongation, and monitored until resolution is documented by a repeat ECG, with QTc intervals returning to <480 msec.

6.2. Dose Modifications for Eribulin

For patients who experience toxicities during the trial, one or more doses of eribulin may need to be reduced, delayed, or withheld. Patients can either have trastuzumab delayed or continue to receive trastuzumab on an every-3-week schedule even if administration of eribulin is delayed or withheld on Day 1 per the treating physician's discretion.

6.2.1. Recommended Dose Delays of Eribulin

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

Do not administer eribulin on Day 1 or Day 8 if any of the following are present:

- 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 at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

For ANC <1500/µL on Day 1, delay dose of Eribulin until ANC >1500/µL, then:

- Initiate treatment with prophylactic granulocyte-CSFs, with no dose reductions.
- If patient is already receiving granulocyte-CSF treatment, reduce dose by 1 dose level.

6.2.2. Recommended Dose Reductions of Eribulin

If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume eribulin at a reduced dose as presented in Table 2.

Do not re-escalate the dosage of eribulin after it has been reduced.

Table 2: Recommended Eribulin Dose Reductions - Applies to Day 1 and Day 8

Event Description	Recommended Eribulin Dose
Permanently reduce the 1.4 mg/m^2 dose for any of the following: - ANC <500/mm^3 for >5 days - ANC <1,000 /mm^3 with fever or infection - Platelets <25,000/mm^3 - Platelets <50,000/mm^3 requiring transfusion or associated with bleeding - Grade 2 neuropathy - Non-hematologic Grade 3 or 4 toxicities - Omission or delay of Day 8 eribulin dose in previous cycle for toxicity	1.1 mg/m^2 (Days 1 & 8 every 21 days)
Occurrence of any event requiring permanent dose reduction while receiving 1.1 mg/m^2	0.7 mg/m^2 (Days 1 & 8 every 21 days)
Occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue eribulin

ANC = absolute neutrophil count

Toxicities graded in accordance with NCI CTCAE, Version 4.0.

6.2.3. Interruption of Eribulin Infusion

Clinical experience to date does not indicate adverse reactions to infusion with eribulin. Patients who experience any serious infusion reaction during eribulin administration will have the infusion stopped. Continuation of dosing will be based on the severity and resolution of the event and will be at the discretion of the Investigator. Suspected infusion reactions should be reported as an adverse event. All patients who experience such an event will be followed for safety.

6.3. Dose Modifications for Trastuzumab

6.3.1. Interruption of Trastuzumab Infusion

Patients with pulmonary disease or pre-existing respiratory compromise may be at increased risk from serious infusion symptoms, therefore careful consideration must be made before enrolling patients with chronic lung disease into this clinical trial. Patients who experience a life-threatening infusion reaction (eg, tachypnea, bronchospasm, hypotension, hypoxia) should be withdrawn from trastuzumab.

Patients who experience severe or moderate infusion symptoms may be managed by:

- Slowing or stopping the trastuzumab infusion
- Supportive care may include supplemental oxygen, beta agonists, antihistamines, or corticosteroids. Patients who experience mild or moderate infusion symptoms may be treated with antipyretics and antihistamines.

Patients who experience mild, moderate, or severe infusion reactions on the first dose may be retreated with trastuzumab. Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent trastuzumab infusions.

6.3.2. Trastuzumab Dosage Adjustments

The dose of trastuzumab is 6 mg/kg every 3 weeks. If the dosing of trastuzumab is interrupted for >28 days, however, the loading dose upon resumption should be 8 mg/kg. There is no planned dose modification schedule for trastuzumab. In case of any need of dose or schedule modification this should be discussed with the Sponsor.

6.3.3. Criteria for Withholding a Dose of Trastuzumab

Cardiac toxicities:

Use of trastuzumab is contraindicated in patients with a LVEF of less than 45% and those with symptomatic heart failure. In an asymptomatic patient, if LVEF drops 10 percentage points from baseline (and to below 50% in patients with a normal baseline measurement) trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Non-Cardiac related toxicities:

In any trastuzumab-related case of Grade 3/4 non-cardiac toxicity, the drug should be withheld until resolution to Grade 1 toxicity.

6.3.4. Trastuzumab Delayed- or Missed-Doses

Trastuzumab should be given on Day 1 of each 21-day cycle. Missed trastuzumab doses will not be made up. Patients who miss more than 4 consecutive weeks of trastuzumab due to toxicity will be considered unable to tolerate trastuzumab and will not be retreated with trastuzumab.

If trastuzumab treatment cannot be continued due to unresolved trastuzumab-related toxicities, eribulin can be continued at the Investigator's discretion.

6.3.5. Criteria for Re-treatment with Trastuzumab

Patients should be assessed for toxicity before each dose.

Patients who develop a toxicity that does not meet the criteria for withholding a dose of trastuzumab should continue to receive trastuzumab and their symptoms should be treated. Trastuzumab-related toxicity will be considered resolved if it improves to a degree that allows for re-treatment with trastuzumab.

7. TRIAL ASSESSMENTS AND TREATMENT

7.1. Overview

All patients should visit the study center on the days specified within this protocol. The complete schedule of assessments is presented in Appendix C.

7.2. Baseline Assessments

Patients must have the following assessments performed ≤7 days before receiving their first dose of study drug. Note: baseline laboratory assessments (except the serum pregnancy test) will be allowed up to 7 days outside of the 7-day specified window, provided that critical laboratory assessments (CBC, CMP, and PT/INR and PTT [for patients receiving warfarin only]) are repeated on Cycle 1, Day 1 prior to study treatment. Negative scans performed prior to the initiation of neoadjuvant therapy, or at any subsequent time prior to trial entry, do not need to be repeated. If not performed previously, scans should be performed <4 weeks prior to trial entry (±7 days).

- Informed consent form prior to any other trial-related procedures
- Medical history (including assessment of baseline signs and symptoms)
- Physical examination including measurements of height (body surface area), weight, vital signs (resting heart rate, blood pressure, respiratory rate, and oral temperature), and assessment of peripheral neuropathy
- Complete blood count (CBC) including 3-part differential and platelets (may be done up to 72 hours prior to treatment)
- Comprehensive metabolic profile (CMP) plus magnesium (Section 7.5.2) (may be done up to 72 hours prior to treatment)
- Coagulation analysis: prothrombin time (PT)/International Normalization Ratio (INR) and partial thromboplastin time (PTT) (may be done up to 72 hours prior to treatment)
- Serum pregnancy test within 48 hours of first dose of trial drug (Section 7.5.3)
- ECOG performance status (Appendix A)
- 12-lead electrocardiogram (ECG)

- Baseline LVEF measurement by MUGA/ECHO (Cohort C patients only)
- Concomitant medication review

7.3. Trial Treatment Assessments

The treatment regimens for all treatment arms in this study will be given in 3-week (21-day) cycles (±5 days). Patients without evidence of undue toxicity will complete 6 cycles of therapy.

All patients will visit the trial center on Days 1 and 8 of each 3-week (21-day) treatment cycle (±5 days) during trial treatment. For specific information about the administration of each drug, see Sections 8.1.2 and 8.2.2, respectively.

7.3.1. Day 1 of each cycle

The following assessments will be performed at each of these visits:

- Update of medical history
- Physical examination including measurements of weight, vital signs (resting heart rate, blood pressure, respiratory rate, and oral temperature), and assessment of peripheral neuropathy
- CBC, including 3-part differential and platelets (may be done up to 72 hours prior to treatment)
- CMP plus magnesium (may be done up to 72 hours prior to treatment)
- ECOG performance status
- ECG (this test is required on Day 1 of each cycle; however, ECGs may be performed at any time during the study, at the discretion of the treating physician, if clinically indicated [see Section 7.7])
- ECHO or MUGA for LVEF (**after Cycle 3, before start of Cycle 4** for Cohort C patients only)
- PT/INR and PTT will be checked for patients who are receiving warfarin.
- Adverse event assessment
- Concomitant medication review
- Administration of eribulin (Cohorts A & B) or eribulin and trastuzumab (Cohort C)

7.3.2. Day 8 of each cycle

The following assessments will be performed at each of these visits:

- CBC, including 3-part differential and platelets
- Adverse event assessment
- Administration of eribulin (all cohorts)

7.4. Post-Treatment and End of Study Treatment

Patients will return to the study center ≤30 days after treatment ends either due to completion of eribulin treatment, or discontinuation from treatment due to unacceptable toxicity or a decision to discontinue treatment by the patient or the trial physician.

- Update of medical history
- Physical examination including measurement of weight, vital signs, and assessment of peripheral neuropathy
- CBC, including 3-part differentials and platelets
- CMP plus magnesium
- ECG
- ECOG performance status
- ECHO or MUGA for LVEF (Cohort C patients only)
- Adverse event assessment
- Concomitant medication review

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no trial treatment is administered, that visit may fulfill the End of Treatment Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for adverse events for 30 calendar days after the last dose of trial drug.

7.5. Follow-Up

7.5.1. Follow-Up After Completion of Eribulin Treatment

Patients will be followed every 3 months during years 1 and 2 for toxicity and disease progression. At each visit, patients will have a physical examination, complete blood counts, chemistry profile, and evaluation of any new symptoms. Assessments at these visits will be performed as described in Appendix C.

7.5.2. Comprehensive Metabolic Profile

The following laboratory tests should be performed for each patient for assessment of CMP:

- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide (CO_2)
- alkaline phosphatase
- AST (SGOT)
- ALT (SGPT)
- total bilirubin
- total protein
- albumin, and

and

- magnesium

7.5.3. Pregnancy test

All females of childbearing potential must complete a serum pregnancy test within 7 days prior to the initiation of eribulin therapy. Women of childbearing potential must use effective birth control measures during treatment and during the 6 months following completion of trial treatment. Postmenopausal women must have been amenorrheic for ≥12 months in order to be considered "of non-childbearing potential" (Appendix D).

7.6. Echocardiograms and Multi-gated Angiograms

Patients in Cohort C (eribulin + trastuzumab) will have an ECHO or MUGA for LVEF at baseline and after Cycle 3 (prior to receiving Cycle 4 treatment). In addition, an end-of-treatment ECHO/MUGA is required.

7.7. 12-Lead Electrocardiograms

There is clinical evidence of QTc prolongation with both eribulin and trastuzumab. Therefore, a 12-lead ECG will be taken at the pre-treatment visit, and will be repeated on Day 1 of each cycle. Electrocardiograms may also be performed at any time during the study, at the discretion of the treating physician, if clinically indicated. Patients should rest at least 10 minutes before ECG testing. Patients should be in the semi-recumbent or supine position when tested; the same position must be used for all subsequent ECGs.

All ECGs must include QTc measurements, either manually or machine-calculated using Bazett's formula, and recorded in the CRF.

Bazett's formula: $QTcB = QT/RR^{1/2}$

At screening, if there is significant QTc interval prolongation (defined as a QTc interval ≥480 msec), the patient will **NOT** be eligible for the study.

During the treatment period, if an ECG indicates a QTc interval ≥500 msec, then two additional ECGs should be obtained within 5 minutes to confirm the abnormality. The average QTc will be determined from the three ECG tracings by manual evaluation, and will be used to determine continued eligibility. If the average QTc is <500 msec, the patient may continue therapy. If the average QTc is ≥500 msec, the study treatment should be discontinued immediately. The patient should be treated appropriately for QTc interval prolongation, and monitored until resolution is documented by a repeat ECG, with QTc intervals returning to <480 msec.

7.8. Radiation Therapy

Patients may be treated with breast and or chest wall radiation therapy either during or following chemotherapy on this study, according to the institutional or practice standards. Experience with concurrent eribulin and radiation therapy is limited and hence safety will be evaluated after the first 10 patients have been treated with concurrent eribulin and radiotherapy. In MBC patients who have received concurrent eribulin with radiation, no adverse safety signals or skin toxicity has been noted (personal communication).

8. INVESTIGATIONAL PRODUCTS

All trial drugs must be kept in a secure place under appropriate storage conditions.

The Sponsor or its representatives must be granted assess on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1. Eribulin

8.1.1. Labeling, Packaging, and Storage

Eribulin mesylate (HALAVEN™) is a clear, colorless, and sterile solution for injection that contains 1.0 mg eribulin drug substance in 2.0 mL of solution. Eribulin clinical supply is packaged in single-use glass vials.

Eribulin clinical supply must be stored only as detailed on the clinical supply labeling (carton and vial labels).

The supply for this study may be provided with one of two labeled storage requirements (see 1. and 2. below). The storage conditions are not interchangeable and the supply must be stored as detailed on the supply labels.

1. Refrigerated: Store in a refrigerator, between 2°C - 8°C (36°F - 46°F). Do not freeze. Store the vials in their original cartons.

2. Controlled room temperature: Store at controlled room temperature of 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). Do not freeze. Store the vials in their original cartons.

Photostability studies have demonstrated that protection from light is not necessary.

The Sponsor, SCRI Oncology Research Consortium, will provide eribulin to the sites participating in the trial.

8.1.2. Preparation and Administration of Eribulin

Aseptically withdraw the required amount of eribulin from the single-use vial and administer undiluted or diluted in 0.9% Sodium Chloride Injection, USP, to concentrations between 0.005 and 0.2 mg/mL mL over 2 to 5 minutes. Alternatively, the drug may be administered undiluted by slow IV push.

Do not dilute in or administer through an IV line containing solutions with dextrose. Do not administer in the same IV line concurrent with the other medicinal products.

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

Discard unused portions of the vial.

8.1.3. Precautions and Risks Associated with Eribulin

For a complete discussion of risk information including precautions and adverse reactions for Eribulin, please refer to the current Eribulin Investigator's Brochure.

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8.2. Trastuzumab

Trastuzumab (Herceptin®) is a recombinant humanized IgG1 monoclonal antibody that binds to domain four of the extracellular segment of the HER2 receptor. Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle so there is reduced proliferation. It has been suggested that trastuzumab induces some of its effect by down regulation of HER2 leading to disruption of receptor dimerization and signaling through the downstream PI3K cascade. P27Kip1 is then not phosphorylated and is able to enter the nucleus and inhibit cdk2 activity, causing cell cycle arrest. Also, trastuzumab suppresses angiogenesis by both induction of antiangiogenic factors and repression of pro-angiogenic factors. It is thought that a contribution to the unregulated growth observed in cancer could be due to proteolytic cleavage of HER2 that results in the release of the extracellular domain. Trastuzumab has been shown to inhibit HER2 ectodomain cleavage in breast cancer cells. In addition, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity. In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2-overexpressing cancer cells compared with cancer cells that do not over express HER2 (15).

Trastuzumab will be administered IV at 6 mg/kg on Day 1 of each 21-day cycle.

8.2.1. Labeling, Packaging, Supply, and Storage

Labeling

Herceptin® is the brand name for trastuzumab.

Packaging and Formulation

Trastuzumab is a sterile, white to pale yellow, preservative free lyophilized powder for IV administration. Each vial of trastuzumab contains 400 mg of trastuzumab, 9.9 mg of L histidine HCl, 6.4 mg of L histadine, 400 mg of α,α trehalose dihydrate, and 1.8 mg of polysorbate 20, USP. Reconstitution with 20 mL of the supplied Bacteriostatic Water for Injection USP, containing 1.1% benzyl alcohol as a preservative, yields 21 mL of a multidose solution containing 21 mg/mL trastuzumab, at a pH of ~6.

Supply

Trastuzumab will be obtained from commercial sources.

Storage

From a microbiological point of view, the trastuzumab infusion solution should be used immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 to 8°C.

8.2.2. Preparation and Administration

Trastuzumab will be administered as an IV infusion in accordance with the Herceptin package insert.

8.2.3. Precautions and Risks Associated with Trastuzumab

For a complete discussion of risk information including precautions and adverse reactions for trastuzumab, please refer to the Herceptin package insert and the Investigator Brochure.

8.2.3.1. Cardiac Dysfunction

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, cardiac failure, hypertension, cardiomyopathy, and cardiac death.

Signs and symptoms of cardiac dysfunction were observed in a number of women who received trastuzumab alone or in combination with chemotherapy, most often anthracycline-based treatment. Cardiac dysfunction was observed most frequently among patients who received trastuzumab plus anthracycline (doxorubicin/cyclophosphamide) chemotherapy (28%), compared with those who received anthracycline alone (7%), trastuzumab plus paclitaxel (11%), paclitaxel alone (1%), or trastuzumab alone (7%). Severe disability or fatal outcome due to cardiac dysfunction was observed in ~1% of all patients.

The nature of the observed cardiac dysfunction was similar to the syndrome of anthracycline-induced cardiomyopathy. The signs and symptoms of cardiac dysfunction usually responded to treatment. Complete and partial responses were observed among patients with cardiac dysfunction. The risk appears to be independent of tumor response to therapy. Analysis of the clinical database for predictors of cardiac dysfunction revealed only advanced age and exposure

to an anthracycline as possible risk factors. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy, often including discontinuation of trastuzumab. In many cases, patients were able to resume treatment with trastuzumab. In a subsequent study using weekly paclitaxel and trastuzumab as first-line treatment for MBC, the observed incidence of serious cardiac dysfunction was 3% (N=95) (18). Since the occurrence of cardiac dysfunction in the trastuzumab plus chemotherapy trial was an unexpected observation, no information is available regarding the most appropriate method for monitoring cardiac function in patients receiving trastuzumab. Significant advances in the understanding and treatment of congestive heart failure have been made in the past several years, with many of the new drugs demonstrating the ability to normalize cardiac function. Patients who develop symptoms of congestive heart failure while on trastuzumab should be treated according to standard guidelines.

Management of Cardiac Safety

All patients must have an ECHO or MUGA scan at baseline, and on a regular schedule throughout the course of the study. Investigators are strongly urged to schedule MUGA scans or ECHOs at the same radiology facility where the patient's baseline was done, whenever possible. MUGA scans or ECHO are required at protocol-specified time points and after any patient has any develops symptoms of congestive heart failure or discontinues protocol treatment.

8.2.3.2. Infusion Associated Symptoms

During the first infusion with trastuzumab, a symptom complex consisting of chills and/or fever is observed in approximately 40% of patients. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. These symptoms are usually mild to moderate in severity, and occur infrequently with subsequent trastuzumab infusions. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine.

8.2.3.3. Serious Infusion Associated Events

Serious adverse reactions to trastuzumab infusion including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress have been reported infrequently. In rare cases (4 per 10,000), these events were associated with a clinical course culminating in a fatal outcome. Serious reactions have been treated with supportive therapy such as oxygen, beta-agonists, corticosteroids and withdrawal of trastuzumab as indicated.

8.2.3.4. Hematologic Toxicity and Neutropenic Infections

In the clinical trials, an increased incidence of anemia was observed in patients receiving trastuzumab plus chemotherapy compared with patients receiving chemotherapy alone. The majority of these anemia events were mild or moderate in intensity and reversible; none resulted in discontinuation of trastuzumab therapy.

In the clinical trials, the per-patient incidences of moderate to severe neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive

chemotherapy as compared to those who received chemotherapy alone. In the post marketing setting, deaths due to sepsis in patients with severe neutropenia have been reported in patients receiving trastuzumab and myelosuppressive chemotherapy, although in controlled clinical trials (pre- and post-marketing), the incidence of septic deaths was not significantly increased. The pathophysiologic basis for exacerbation of neutropenia has not been determined; the effect of trastuzumab on the pharmacokinetics of chemotherapeutic agents has not been fully evaluated.

Secondary acute leukemia or myelodysplastic syndrome has been reported in 4 of approximately 1200 patients who participated in trastuzumab clinical trials. Patients treated with chemotherapeutic agents are known to be at increased risk for secondary leukemia. The observed incidence of leukemia among trastuzumab-treated patients appears to be consistent with the expected incidence of leukemia among patients treated with chemotherapy for metastatic breast cancer. Therefore, the contribution of trastuzumab to the etiology of acute leukemia or myelodysplastic syndrome in these cases is unclear.

8.2.3.5. Pulmonary Toxicity

Trastuzumab can cause fatal pulmonary toxicity which includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency, and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Events like these may result from infusion reactions.

8.3. Accountability of Investigational Products

The Principal Investigator (or designee) is responsible for accountability of all used and unused trial drug supplies at the site. The sites should destroy any unused product at the end of the study (or expired product, if any, during the study), per the site's SOPs for doing so. A certificate of destruction that includes a description of the supplies, quantity destroyed, and method of destruction should be returned to the Sponsor.

9. STATISTICAL CONSIDERATIONS

9.1. Trial Population

The efficacy and safety analysis populations will consist of all patients who received at least one dose of protocol treatment.

9.2. Planned Interim Analyses

No interim analyses are planned.

9.3. Final Analysis Plan

Three cohorts of patients with residual disease following neoadjuvant therapy (triple-negative [A], hormone-receptor-positive (ER and/or PR+) /HER2negative [B], and HER2-positive [C]) will be evaluated separately to obtain preliminary efficacy information. With standard neoadjuvant therapy, the approximate 2-year DFS of patients who do not achieve pCR are as follows: triple-negative, 40%; hormone-receptor-positive/HER2-negative, 80%; and HER2-positive, 60%. Treatment capable of providing relative improvement in these results by 40% in

the triple-negative cohort, 15% in the hormone-receptor-positive /HER2-negative cohort, or 25% in the HER2-positive cohort would be worthy of further development. For a one-sided test of hypothesis at alpha = 0.10 and power = 0.80, the required sample sizes are 49, 38, and 47, respectively. In order to adjust for potential non-evaluable patients, this preliminary study will treat 54, 42, and 52 patients, respectively, in the three cohorts. This will allow determination of a 2-year DFS within 95% confidence intervals for each subgroup, as follows:

Cohort A Triple-negative: 42.0% - 67.9%

Cohort B Hormone-receptor-positive (and HER2-negative) cohort: 78.7% - 96.9%

Cohort C HER2-positive cohort: 61.0% - 84.5%

Evaluation of safety among patients in each cohort will also provide sufficient experience to determine the tolerability and toxicity of this regimen. Safety data will be tabulated for patients who receive any amount of trial medication. Adverse events will be tabulated by body system, preferred term, severity, and relation to treatment. Worst toxicity grades per patient will be tabulated for selected adverse event and laboratory measurements by using NCI CTCAE criteria V4.0.

9.4. Data and Safety Monitoring Board

The trial will not utilize the services of a Data and Safety Monitoring Board.

9.5. Steering Committee

The trial will not utilize the services of a Steering Committee.

10. SAFETY REPORTING AND ANALYSES

10.1. Safety Analyses

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the trial drug.

10.2. Adverse Events

The Principal Investigator is responsible for recognizing and reporting AEs and SAEs in the CRF and for notifying the SCRI Safety Department of SAEs within 1 day of initial awareness. It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory body.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

10.2.1. Definitions of Adverse Events

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 medicinal product, whether or not considered causally related to the product.

An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings).

10.2.2. Recording of Adverse Events

All AEs of any patient during the course of the trial will be reported in the case report form, and the Investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). If the adverse event is serious, it should be reported immediately (within 1 day of initial awareness) to the SCRI Safety Department.

All AEs, regardless of seriousness or relationship to the trial drugs, spanning from initiation of treatment until 30 calendar days after discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded in the CRF.

10.2.3. Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the patient to discontinue trial treatment, or the Investigator insists that the abnormality should be reported as an adverse event (AE). Any Grade 3 or 4 laboratory abnormalities or any clinically significant Grade 1 or 2 hematology or biochemistry laboratory values should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF.

10.2.4. Handling of Adverse Events

All AEs resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the CRF or EDC. After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment related are to be reported.

10.3. Serious Adverse Events

10.3.1. Definitions of Serious Adverse Events

The definitions of SAEs are presented below. The Principal Investigator is responsible for ensuring that each staff member involved in the trial is familiar with the content of this section.

An SAE or reaction is defined as any untoward medical occurrence that: results in death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method, should not be reported as a serious AE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one that was planned prior to entry in the trial), does not require reporting as a SAE to the SCRI Safety Department.

10.3.2. Serious Adverse Event Reporting by Investigators

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the CRF and SAEs on the SAE Report Form.

Adverse events classified by the treating Investigator as **serious** require expeditious handling and reporting to the SCRI Safety Department in order to comply with regulatory requirements. Serious AEs may occur at any time from the start of trial treatment through the 30-day follow-up period after the last trial treatment. The SCRI Safety Department must be notified of all SAEs, regardless of causality, within 1 day of the first knowledge of the event by the treating physician or research personnel.

To report a SAE, the SAE Report Form should be completed with the necessary information.

All SAEs and medically confirmed deaths (regardless of causality assessment) occurring on trial treatment or within 30 days of last trial treatment must be reported to the Sponsor as SAEs on the SAE Report Form and followed until resolution (with autopsy report, if applicable).

Deaths occurring within 30 days after last trial treatment that are deemed 'possibly' or 'probably' related to trial drug must be reported as SAEs on the SAE Report Form within 1 day of first knowledge of the event by the treating physician or research personnel (with an autopsy report, if available).

Deaths occurring 30 days after last trial treatment and not attributed to trial treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

The SAE report should be sent to the SCRI Safety Department via fax or e-mail using the contact information listed below:

SCRI Safety Department

Fax #: 866-807-4325

Safety Dept. Email: CANN.SAE@scresearch.net

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the SCRI Safety Department as soon as it is available; these reports should be submitted using the SCRI SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of the responsible IRB.

10.3.3. Sponsor Serious Adverse Event Reporting Requirements

Sarah Cannon Research Institute will forward all serious adverse event information, where eribulin is the suspected product, to Eisai (Fax # 732-791-1111) within 1 business day of SCRI Safety Department personnel becoming aware of the SAE.

The Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the trial drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. The Sponsor will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs associated with the use of the trial medications to the appropriate competent authorities (according to local guidelines), Investigators, and central IRBs/IECs (except in the United States where Investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

10.4. Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SCRI SAE Report Forms and AE CRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF. Adverse events that meet the definition of an SAE should additionally be reported following the procedures noted in Section 10.3.2.

10.4.1. Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Coordinating Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SCRI SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

10.4.2. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE CRF.

10.4.3. Abnormal Laboratory Values

Any Grade 3 or 4 laboratory abnormalities or any clinically significant Grade 1 or 2 hematology or biochemistry laboratory values should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered

additional information that must be collected on the relevant CRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE CRF.

10.4.4. Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Trial Discontinuation" CRF. All other on-trial deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and AE page of the CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF AE page. During post-trial survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" CRF.

10.4.5. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of preexisting hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE when there is no occurrence of an AE (refer to Section 10.3.1).

10.4.6. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the General Medical History CRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

10.4.7. Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 10.5 for specific instructions.

10.5. Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 10.2.1).

10.5.1. Pregnancy, Abortion, Birth Defects/Congenital Abnormalities

If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and faxed to the SCRI Safety Department expeditiously, irrespective of whether or not it meets

the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the SCRI Safety Department.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

10.5.2. Trial Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Safety Department within one day using the corresponding screens in the CRF, and following the same process described for SAE reporting (Section 10.3.2), if the overdose is symptomatic.

An overdose is defined as a dose of eribulin or trastuzumab administered to a patient that is greater than the protocol-defined dose for the patient. For information on how to manage an overdose, see the respective Investigator Brochures.

11. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

11.1. Institutional Review Board Approval

The trial protocol, ICF, IB, available safety information, patient documents (e.g., trial diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the trial start.

The Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and ongoing, IRB trial review. The Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

11.2. Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the Sponsor will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.

11.3. Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the Principal Investigator or site and the Sponsor.

11.4. Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The informed consent form (ICF) will be submitted for approval to the IRB that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient's consent to continue participation in the trial should be obtained.

11.5. Confidentiality

11.5.1. Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPPA) and national data protection laws, as applicable. HIPPA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH Good Clinical Practice (GCP) guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorised representatives of Sponsor, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify patients on the CRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the CRF or database. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

11.5.2. Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the SCRI database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, SCRI shall take all appropriate measures to safeguard and prevent assess to this data by any unauthorized party.

11.6. Financial Information

SCRI Oncology Research Consortium is sponsoring this trial. Eisai will provide funding to SCRI Oncology Research Consortium for this trial and will also provide the trial drug, eribulin, for all trial participants for the duration of the trial. The physicians participating in this trial will receive compensation from SCRI Oncology Research Consortium.

12. RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

12.1. Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the trial. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to trial design, risk to patient, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB at the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor after IRB approval and specifically when an increase to dosing or patient exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and/or FDA approval include, but are not limited to, the following:

- Change to trial design
- Risk to patient
- Increase to dose or patient exposure to drug
- Subject number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, their consent to continue participation in the trial should be obtained.

12.2. Documentation Required to Initiate the Trial

Before the trial may begin, certain documentation required by FDA regulations must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Research Institute
SCRI Oncology Research Consortium
Network Regulatory Affairs
3322 West End Avenue, Suite 900
Nashville, Tennessee 37203
Tel. #: (615) 329-7274
Fax #: (615) 297-2793

Documents at a minimum required to begin a trial in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the trial and the IRB members list
- Current Curricula Vita for the principal Investigator and any associate Investigator(s) who will be involved in the trial
- Indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form containing permission for audit by representatives of the Sponsor, SCRI Oncology Research Consortium, the IRB, and the FDA
- Financial disclosure forms for all Investigators listed on Form FDA 1572
- GCP Certificate for trial training
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment lists

12.3. Trial Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation, where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and trial staff are responsible for maintaining a comprehensive and centralised filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB approval documents, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain

information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., CRFs and medical records), all original, signed informed consent forms, and copies of all CRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Sponsor will notify the Investigators/institutions when the trial-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the trial, both the Sponsor and/or its representative should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

12.4. Data Collection

The trial CRF is the primary data collection instrument for the trial. CRFs will be completed using the English language and should be kept current to enable the monitor to review the patients' status throughout the course of the trial.

In order to maintain confidentiality, only trial number, patient number, initials and date of birth will identify the patient in the CRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI and replaced instead with the patient number and patient's initials. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information

will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested on the CRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the CRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

12.5. Trial Monitoring, Auditing, and Inspecting

The Investigator will permit trial-related monitoring, quality audits, and inspections by the Sponsor, government regulatory authorities, the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of applicable trial-related facilities. The Investigator will ensure that the trial monitor or any other compliance or QA reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an Investigator in this trial implies the acceptance of potential inspection by government regulatory authorities, the Sponsor or its representative(s).

At the Sponsor's discretion, Source Document Verification may be performed on all data items or a percentage thereof.

12.6. Quality Assurance and Quality Control

Each trial site shall be required to have Standard Operating Procedures (SOP's) to define and ensure quality assurance/control processes for trial conduct, data generation & collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

12.7. Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

The financial disclosure information will be provided to the Sponsor prior to trial participation from all Principal Investigators and Sub-Investigators who are involved in the trial and named on the FDA 1572 form.

The SCRI Oncology Research Consortium will register the trial on *www.clinicaltrials.gov*. In addition, the SCRI Oncology Research Consortium will publish the results of the trial.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The Investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the Investigator of the results of the

trial conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within 15 months after the trial has been completed or terminated at all trial sites, and all data has been received, the Investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of SCRI Oncology Research Consortium as appropriate. Investigator shall provide SCRI Oncology Research Consortium thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If SCRI Oncology Research Consortium requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit SCRI Oncology Research Consortium to seek patent protection and to remove any SCRI Confidential Information from all publications.

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14. APPENDICES

Appendix A: ECOG 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 no 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: New York Heart Association Classifications

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

This table is an excerpt from the Oxford Textbook of Medicine, 2nd ed. Oxford; New York: Oxford University Press, 1987, p. 2228.

Appendix C Schedule of Assessments for BRE 186 (Residual Breast Cancer)

Procedures	Pre-Treatment	Trial Treatments (6 Cycles)			End of Study Treatment[k]	Follow-up
	Baseline[e]	Day 1 of Every Cycle[h]	Day 8 of Every Cycle	Post Cycle 3[j]		After Completion of Treatment[l]
TESTS & OBSERVATIONS						
Medical history (including baseline signs/symptoms)	X	X			X	X
Physical examination, vital signs, height, weight[a]	X	X			X	X
ECOG Performance Status	X	X			X	X
ECG	X	X[i]			X	
ECHO or MUGA	X[f]			X[f]	X[f]	
Adverse event evaluation		X	X		X	
Concomitant medication review	X	X			X	X
Survival status						X
LABORATORY TESTS						
CBC, including 3-part differential and platelets	X	X[m]	X		X	X
CMP plus magnesium[b]	X	X[m]			X	X
PT/INR and PTT[c]	X	X[c]				
Serum pregnancy test[d]	X					
DISEASE ASSESSMENT						
CT scans of the chest and abdomen	X[g]					
CT scan or MRI of the brain	X[g]					
PET scan or Bone scan (PET scan is preferred)	X[g]					

[a] Physical examinations will include measurements of weight, vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature), and assessment of peripheral neuropathy. At the baseline visit, height will also be recorded.

[b] CMP assessment includes the following laboratory tests: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, plus magnesium.

[c] After the baseline visit, PT/INR and PTT will be checked for any patients (in all treatment arms) who are receiving warfarin.

[d] A serum pregnancy test will be performed **only** for women of childbearing potential (see Section 3.3.1).

[e] The physical examination, ECOG performance status, CBC, CMP, PT/INR and PTT, ECG, concomitant medication review, and pregnancy test should be done ≤7 days prior to initiation of treatment. Baseline laboratory assessments will be allowed up to 7 days outside of the 7-day specified window, provided that critical laboratory assessments (CBC, CMP, pregnancy test, and PT/INR and PTT [for patients receiving warfarin only]) are repeated on Cycle 1, Day 1 prior to study treatment.

[f] ECHO or MUGA for patients in Cohort C only (eribulin plus trastuzumab)

[g] Complete staging work-up to confirm localized disease should include computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or a bone scan. (Note: a PET/CT is acceptable for baseline imaging in lieu of CT examinations or bone scan). Negative scans performed prior to the initiation of neoadjuvant therapy, or at any subsequent time, are acceptable and do not need to be repeated.

[h] For the Day 1 visits of each treatment cycle, a window for variations from the protocol-specified treatment of up to ± 7 days is allowed, provided that the laboratory value criteria for treatment and other protocol requirements are met.

[i] ECGs are required at the Pre-Treatment visit and on Day 1 of each cycle. During the treatment period, if an ECG indicates a QTc interval ≥500 msec, then two additional ECGs should be obtained within 5 minutes to confirm the abnormality. The average QTc will be determined from the three ECG tracings by manual evaluation, and will be used to determine continued eligibility. If the average QTc is <500 msec, the patient may continue therapy. If the average QTc is ≥500 msec, the study treatment should be discontinued immediately. The patient should be treated appropriately for QTc prolongation, and monitored until resolution is documented by a repeat ECG, with QTc intervals returning to <480 msec (see Section 7.7).

[j] Post Cycle 3 prior to the start of Cycle 4 treatment

[k] All patients will undergo the end-of-treatment assessments listed within 30 days after the last dose of eribulin treatment due to completion of the planned study treatment period, disease progression, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no study treatment is administered, that visit may fulfill the End-of-Treatment Visit.

[l] After completion of eribulin treatment, patients will be followed every 3 months during years 1 and 2, for toxicity and disease progression.

[m] CBC, including 3 part differential and platelets and CMP plus magnesium may be done up to 72 hours prior to treatment.

Appendix D: Guidelines Regarding Women of Childbearing Potential

Women of Child-Bearing Potential are Defined as Follows:

- Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as Follows:

- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are >45 years of age, not using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40pg/mL (140 pmol/L)
- Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy

Acceptable Contraception Methods:

Male patients with female partners of child-bearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the trial and for 3 months (women) or 6 months (men) following discontinuation of the trial drugs. Male patients must also refrain from donating sperm for 6 months following discontinuation of the trial drugs.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

The following are acceptable forms of secondary contraception, when used with a barrier method and spermicide:

- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Placement of an intrauterine device (IUD) or intrauterine system (IUS), with the exception of IUD progesterone T

Appendix D: Guidelines Regarding Women of Childbearing Potential (continued)

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Appendix E Prohibited Drugs That Prolong QT Interval and/or Induce Torsades De Pointes and Class IA and III Antiarrhythmics

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males,TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given IV or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 sibstrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	Prohibited as this drug is a sensitive 3A4 substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.		

Appendix E Prohibited Drugs That Prolong QT Interval and/or Induce Torsades De Pointes and Class IA and III Antiarrhythmics (continued)

Drug	QT risk	Comment
Alfuzosin	possible risk for Torsades de Pointes	
Amantadine	possible risk for Torsades de Pointes	
Amitriptyline	conditional risk for Torsades de Pointes	
Azithromycin	possible risk for Torsades de Pointes	
Chloral hydrate	possible risk for Torsades de Pointes	
Citalopram	conditional risk for Torsades de Pointes	
Clomipramine	conditional risk for Torsades de Pointes	
Clozapine	possible risk for Torsades de Pointes	
Desipramine	conditional risk for Torsades de Pointes	
Diphenhydramine	conditional risk for Torsades de Pointes	
Dolasetron	possible risk for Torsades de Pointes	
Doxepin	conditional risk for Torsades de Pointes	
Dronedarone	possible risk for Torsades de Pointes	
Felbamate	possible risk for Torsades de Pointes	
Flecainide	possible risk for Torsades de Pointes	
Fluoxetine	conditional risk for Torsades de Pointes	
Foscarnet	possible risk for Torsades de Pointes	
Fosphenytoin	possible risk for Torsades de Pointes	
Galantamine	conditional risk for Torsades de Pointes	
Gatifloxacin	possible risk for Torsades de Pointes	
Gemifloxacin	possible risk for Torsades de Pointes	
Granisetron	possible risk for Torsades de Pointes	
Imipramine	conditional risk for Torsades de Pointes	
Indapamide	possible risk for Torsades de Pointes	
Isradipine	possible risk for Torsades de Pointes	
Levofloxacin	possible risk for Torsades de Pointes	
Lithium	possible risk for Torsades de Pointes	
Mexiletine	conditional risk for Torsades de Pointes	
Moexipril/HCTZ	possible risk for Torsades de Pointes	
Moxifloxacin	possible risk for Torsades de Pointes	
Nicardipine	possible risk for Torsades de Pointes	
Nortriptyline	conditional risk for Torsades de Pointes	
Octreotide	possible risk for Torsades de Pointes	
Ofloxacin	possible risk for Torsades de Pointes	

Appendix E Prohibited Drugs That Prolong QT Interval and/or Induce Torsades De Pointes and Class IA and III Antiarrhythmics (continued)

Drug	QT risk	Comment
Ondansetron	possible risk for Torsades de Pointes	
Oxytocin	possible risk for Torsades de Pointes	
Paliperidone	possible risk for Torsades de Pointes	
Paroxetine	conditional risk for Torsades de Pointes	
Perflutren lipid microspheres	possible risk for Torsades de Pointes	
Protriptyline	conditional risk for Torsades de Pointes	
Ranolazine	possible risk for Torsades de Pointes	
Risperidone	possible risk for Torsades de Pointes	
Roxithromycin*	possible risk for Torsades de Pointes	*not available in the United States
Sertindole	possible risk for Torsades de Pointes	
Sertraline	conditional risk for Torsades de Pointes	
Solifenacin	conditional risk for Torsades de Pointes	
Tizanidine	possible risk for Torsades de Pointes	
Trazodone	conditional risk for Torsades de Pointes	
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes	
Trimipramine	conditional risk for Torsades de Pointes	
Venlafaxine	possible risk for Torsades de Pointes	
Ziprasidone	possible risk for Torsades de Pointes	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Class IA and III Antiarrhythmics

Class IA antiarrhythmics include:
• Disopyramide (Norpace) • Procainimide (Procainimide HCI, Procan, Procanabid, Pronestyl) • Quinidine (Quinidine sulfate, Quinaglute, Quinidex, Cardioquin)
Class III antiarrhythmics include:
• Amiodarone (Cordarone®) • Azimilide (Stedicor®) • Bepridil • Dofetilide (Tikosyn®) • Ibutilide (Corvert®) • Sotalol (Betapace®) • Tedisamil