Academic and Community Cancer Research United (ACCRU)

A Randomized Phase III Trial of Eribulin Compared to Standard Weekly Paclitaxel as First- or Second-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

ACCRU protocol # RU011201I

[redacted]

For any communications regarding this protocol, please contact the protocol resource person on the following page.

ACCRU Study Chair: Minetta C. Liu, M.D

[redacted]

Statisticians: David Hillman, M.S. √

[redacted]

Drug Availability
Commercial Agents: Paclitaxel
Drug Company Supplied: Eribulin mesylate (IND #126070)
√ Study contributor(s) not responsible for patient care.

Study Participants	**Date Activated**
ACCRU Membership	January 17, 2014

Research Coordinating Center
Academic and Community Cancer Research United

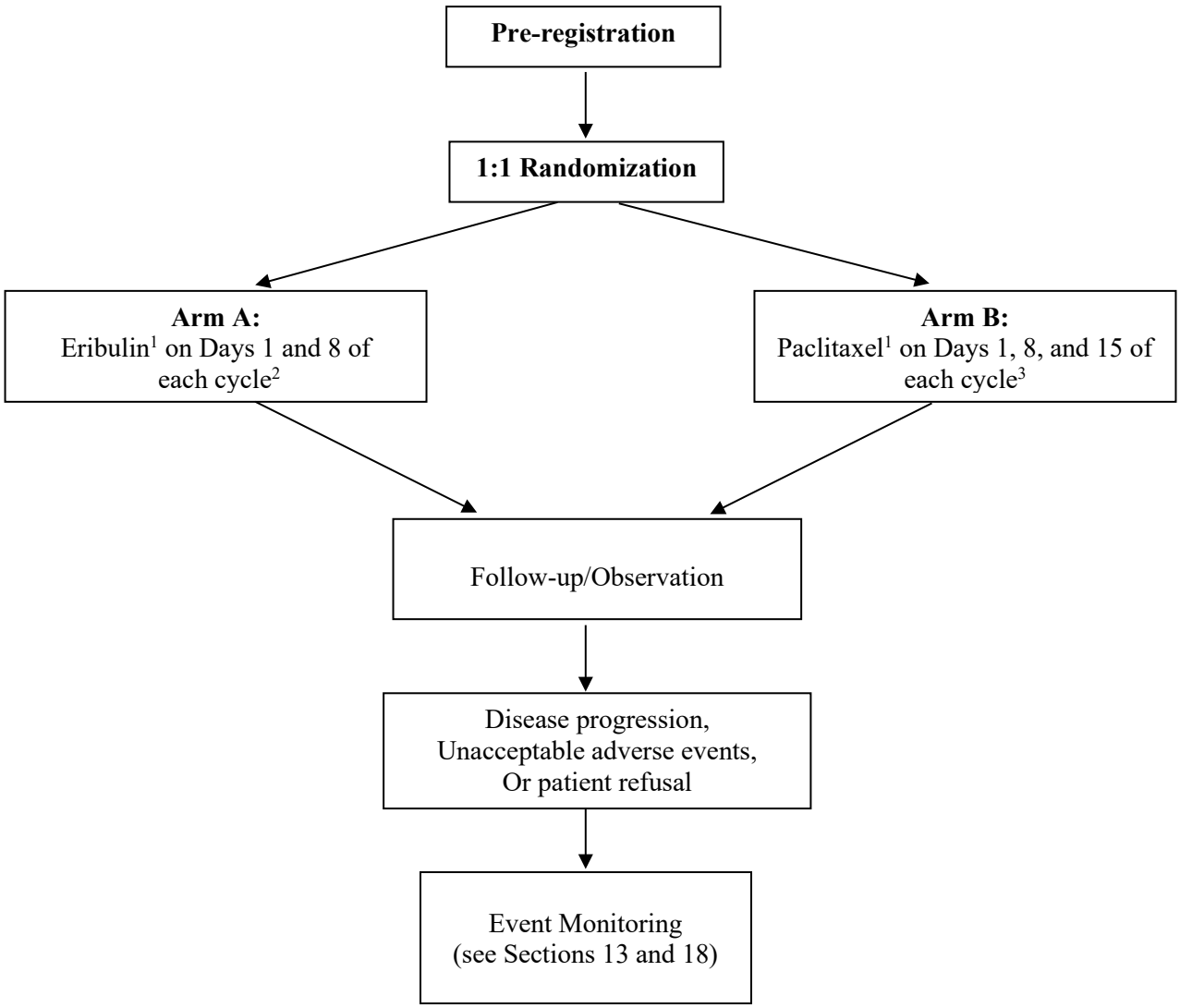
[redacted]

Document History	**(effective date)**
Pre-activation ACCRU	December 20, 2013
Activation ACCRU	January 17, 2014
Addendum 1	May 26, 2015
Addendum 2	November 13, 2015
Addendum 3	June 22, 2018
Addendum 4	April 28, 2021

This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s). (ICH E6 section 6.2.5)

Index

Schema



Treatment will continue until disease progression, unacceptable toxicity, or patient withdrawal.

If a patient is deemed ineligible or a cancel, please refer to Section 16.0 for follow-up information.

[1]See Section 7.0 for dose and administration.
[2]Cycle length for Arm A = 21 days
[3]Cycle length for Arm B = 28 days

Generic name: Eribulin mesylate Brand name(s): Halaven ACCRU Abbreviation: E7389 Availability: Eisai Co, Ltd	Generic name: Paclitaxel Brand name(s): Taxol ACCRU Abbreviation: TAXOL Availability: Commercially available

1.0 Background

1.1 Rationale for selected approach and trial design.

Metastatic breast cancer is generally incurable with few patients achieving long-term survival with standard chemotherapy.[1] Despite a marked increase in the choice of active agents for the treatment of metastatic disease, overall survival has changed little during the last half century. Most recently, the introduction of new cytotoxic agents, new formulations of existing drugs and modifications of dose and/or schedule have resulted in improvements in outcome with generally well tolerated toxicity profiles. These advances have not only resulted in improved treatment options for patients with metastatic disease, but also in clinical trials investigating the most promising treatment approaches in the adjuvant setting.

Paclitaxel is a taxane derivative and is among the most active agents in the treatment of breast cancer. A major limitation of paclitaxel is poor water solubility, requiring Cremophor® EL as a water soluble solvent. Cremophor® EL requires specialized intravenous tubing and has been associated with significant toxicities, including the risk of anaphylaxis (for which premedication with corticosteroids and antihistamines is required); bone marrow suppression; and peripheral neurotoxicity. Its poor solubility also requires paclitaxel to be dissolved in a relatively large volume of fluid administered over a longer period of time than many other chemotherapy agents. Given these toxicities and inconvenience, there has been interest in new microtubule stabilizing agents that modify the toxicity profile with the potential for similar or even superior efficacy. Two of the more effective agents currently in use are nanoparticle albumin bound paclitaxel (nab-paclitaxel) and ixabepilone.

In October 2008, the CALGB/Alliance Breast Committee activated Protocol 40502, a phase III clinical trial comparing the current standard of weekly paclitaxel at 90 mg/m^2 to weekly nab-paclitaxel at 150 mg/m^2 and weekly ixabepilone at 16 mg/m^2 as first-line therapy in patients with taxane naïve metastatic breast cancer. Planned interim analyses of the primary endpoint of PFS were performed by the Alliance Data and Safety Monitoring Board on June 24, 2011 and then again on November 18, 2011. The first review led to the conclusion that it is very unlikely that ixabepilone (with or without bevacizumab) will be better than standard weekly paclitaxel (with or without bevacizumab). The second review led to the conclusion that it is very unlikely that nab-paclitaxel (with or without bevacizumab) will be better than standard weekly paclitaxel (with or without bevacizumab). Both ixabepilone and nab-paclitaxel were shown to have a higher toxicity profile than paclitaxel as well. Therefore, accrual to the ixabepilone arm closed on July 8, 2011, and accrual to the nab-paclitaxel arm (and thus the trial as whole) closed on November 30, 2011 with 799 of 900 planned subjects.[2]

Eribulin is a novel, non-taxane, tubulin-targeted agent whose activity in patients with heavily pretreated advanced breast cancer was established in three phase II clinical trials.[3,4] The established dose and schedule of administration for eribulin mesylate is 1.4 mg/m^2 on days 1 and 8 of each 21-day cycle, with a break on day 15. Results from a randomized, open-label, phase III clinical trial (EMBRACE) demonstrated a statistically significant OS improvement with eribulin *versus* the treatment physician's choice (TPC) of standard single agent therapy in patients who had received 2-5 prior chemotherapy regimens for metastatic breast cancer and had prior exposure to an anthracycline and taxane.[5] 97% of subjects on the control arm received single agent chemotherapy, and the remaining 3% received single agent endocrine therapy; no patients received best

supportive care alone, although that was included as an option. Reported toxicities were acceptable and not unexpected.

Demonstration of an OS benefit with single agent chemotherapy and a manageable toxicity profile in a heavily pretreated breast cancer population led eribulin to receive approval by the US Food and Drug Administration in November 2010. The approved indication is for the treatment of metastatic breast cancer patients with prior exposure to an anthracycline and taxane and who have received at least two chemotherapeutic regimens for metastatic disease. The next logical investigation is to compare eribulin to other microtubule stabilizing agents earlier in the treatment of advanced disease. The proposed phase III clinical trial is designed as the successor to CALGB 40502 and will compare eribulin mesylate (1.4 mg/m^2 on days 1 and 8 of each 21-day cycle) to paclitaxel (90 mg/m^2 on days 1, 8, and 15 of each 28-day cycle) as first- or second-line chemotherapy in patients with locally recurrent or metastatic breast cancer.

1.2 Primary translational objectives

The format of this clinical trial provides the framework for a number important correlative studies focused on toxicity and efficacy related to the microtubule stabilizing agents. The primary aim of these translational efforts is to develop tools that will allow physicians to promptly and accurately identify patients with the highest likelihood of treatment benefit and the lowest probability of toxicity. Specifically, this trial will investigate the following relative to eribulin and standard weekly paclitaxel:

1.2.1 Use of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) to collect relevant patient-reported symptom toxicity information.

The PRO-CTCAE is an item bank consisting of individual questions to assess symptom toxicity events from the patient perspective (*e.g.*, nausea, fatigue). The PRO-CTCAE was developed to complement the CTCAE, under an ongoing contract with the NCI (PI: Dr. Ethan Basch). To date, 78 symptoms in the CTCAE have been developed for patient self-reporting via the PRO-CTCAE, have undergone cognitive testing in patients, and are undergoing validation in a separate national study.[6] In this study, the feasibility of assessing administration of 11 PRO-CTCAE symptoms (fatigue, nausea, vomiting, diarrhea, constipation, insomnia, sensory neuropathy, mucositis, pain, anorexia, alopecia) to patients on a weekly basis via an automated telephone system (*i.e.*, interactive voice response system [IVRS]) will be assessed. The PRO-CTCAE system is hosted and maintained on servers at the NCI and has undergone rigorous security and privacy assessment per NCI requirements.

1.2.2 The rs7349683 polymorphism in *EPHA5* as a predictor of peripheral neuropathy.

Chemotherapy-associated toxicity is highly variable. This may be largely due to host factors such as differences in absorption, distribution, and particularly metabolism and clearance. These sources of variability may be compounded by the presence of vomiting and diarrhea, poor nutritional status, concomitant medications, prior therapies, and liver metastases or effusions.[7] Variability in hepatic metabolism and membrane transport was the focus of many initial studies addressing the sources of interindividual differences in CIPN.[8-13] More recently, genome-wide approaches have been used to identify single nucleotide polymorphisms (SNPs) and genes important in this dose-limiting toxicity.[14-17]

The Kroetz laboratory performed the first genome-wide association study (GWAS) of paclitaxel-induced peripheral neuropathy using samples from CALGB 40101 ("Cyclophosphamide and doxorubicin [CA x 4 cycles] versus paclitaxel [4 cycles] as adjuvant therapy for breast cancer in women with 0-3 positive axillary lymph nodes: A phase III randomized study").[14] A single nucleotide polymorphism in *FGD4* was associated with the onset of sensory peripheral neuropathy in the discovery cohort of 858 genetic Europeans (rs10771973; HR, 1.57; 95% CI, 1.30-1.91; $P = 2.6 \times 10^{-6}$) and in a European (HR, 1.72; 95% CI, 1.06-2.80; $P = 0.013$) and African American (HR, 1.93; 95% CI, 1.13-3.28; $P = 6.7 \times 10^{-3}$) replication cohort. *FGD4* encodes a Rho GTPase that is critical for proper myelination of peripheral nerves. Rare mutations in *FGD4* are associated with the congenital peripheral neuropathy Charcot-Marie-Tooth disease.[18] The more common *FGD4* polymorphism identified in CALGB 40101 may be associated with Schwann and nerve cell communication in peripheral nerves following paclitaxel treatment. There was also evidence that markers in *EPHA5* (rs7349683; $p=9.6 \times 10^{-7}$; HR=1.63) and *FZD3* (rs10771973; $p=3.1 \times 10^{-9}$; OR=0.57) were associated with the onset or severity of paclitaxel-induced sensory peripheral neuropathy.[14] Similar analyses in other taxane-treated cohorts have led to the discovery of additional SNPs and genes. To date, members of the ephrin receptor gene family have been most consistently implicated in CIPN. rs7349683 in *EPHA5*, reported in CALGB 40101,[14] has been replicated in a smaller paclitaxel-treated breast cancer population[19] and variants in related ephrin receptor genes (rs301927 in *EPHA6* and rs209709 in *EPHA8*) have also been associated with CIPN.[19,20] *EPHA5* encodes an ephrin receptor involved in axon guidance. In mice, EPHA5 is important for neuronal regeneration following injury.[21] We hypothesize that patients carrying a reduced function *EPHA5* allele may have an attenuated repair response following paclitaxel-induced injury. The current study provides a unique population to test the general relevance of this EPHA5 SNP for the prediction of CIPN associated with treatment with microtubule targeting agents.

1.3 Secondary translational objectives

The format of this clinical trial provides the framework for a number important correlative studies focused on toxicity and efficacy related to the microtubule stabilizing agents. The primary aim of these translational efforts is to develop tools that will allow physicians to promptly and accurately identify patients with the highest likelihood of treatment benefit and the lowest probability of toxicity. Specifically, this trial will investigate the following relative to eribulin and standard weekly paclitaxel:

1.3.1 Common single nucleotide polymorphisms in *FGD4, FZD3,* and *VAC14* as predictors of peripheral neuropathy.

1.3.2 Circulating markers of cell death as predictors of clinical benefit.

1.3.3 Tubulin isotype expression, mutations, and signaling pathway modifications as predictors of clinical benefit.

Detailed information related to these secondary translational objectives is provided in Sections 14.0 and 17.0.

1.4 Importance of the trial

The primary goal for the treatment of metastatic breast cancer is to palliate symptoms and control disease progression in the setting of maintaining quality of life. Despite the known efficacy of the standard taxanes, there are a number of toxicities and inconveniences that impact negatively on patient quality of life and the ability to deliver more effective therapy.[22] For paclitaxel, which is among the most active agents in the treatment of breast cancer, these toxicities and inconveniences are compounded by the Cremophor® EL solvent required for solubility and include the risk of hypersensitivity reactions, bone marrow suppression, peripheral neuropathy, the need for steroid premedications (with the potential for added toxicity), prolonged infusion times, and the need for specialized intravenous tubing.

Although two combination chemotherapy regimens, namely gemcitabine/paclitaxel[23] and capecitabine/docetaxel,[24] have been associated with improved survival over taxane monotherapy for the treatment of anthracycline exposed advanced disease, evaluation of the data is difficult given the fact that subjects received limited additional therapy following participation in these clinical trials; it is likely that at least similar survival benefits would be seen with sequential single agent therapy (*i.e.,* paclitaxel followed by gemcitabine *versus* gemcitabine/paclitaxel; docetaxel followed by capecitabine *versus* capecitabine/docetaxel). Combination regimens are also complicated by increased toxicity over sequential single agent therapy, limiting the value of symptom control on the quality of life endpoints. Sequential single agent chemotherapy therefore remains an important treatment approach in metastatic breast cancer, and optimizing the agent, formulation, dose, and schedule is necessary to our efforts to maximize treatment benefit and significantly improve clinical outcomes.

Eribulin is a new chemotherapeutic agent with OS benefits in heavily pretreated patients with advanced breast cancer. Direct comparison of this agent to standard weekly paclitaxel will provide clinicians with important information on the relative clinical benefits and toxicity profiles associated with each of these potentially effective microtubule stabilizing agents. It also provides an important opportunity to investigate putative biomarkers that may function either as surrogate measures for the selection of those patients who are most likely to respond to specific therapies, or as early determinates of response or resistance during therapy. Data from the proposed clinical trial will be critical in making future decisions regarding systemic therapy in patients with metastatic disease, and in designing the next generation of adjuvant trials.

1.5 Use of control and experimental arms

1.5.1 Paclitaxel

Paclitaxel is among the most active agents in the treatment of breast cancer. The mechanism of action is related to disruption of microtubule disassembly due to the binding of paclitaxel to dimeric tubulin; this results the cessation of mitosis and eventual cell death. Response rates in taxane naïve metastatic breast cancer have ranged from 20-60% with activity noted in anthracycline pretreated disease. Randomized phase III trials of paclitaxel have highlighted the significance of dose and schedule on efficacy and tolerability. Studies evaluating a dose relationship for paclitaxel documented improved response rates at 175 mg/m^2 compared to 135 mg/m^2,[25] and doses above 175 mg/m^2 yielded more toxicity in the absence of further improvements in response rates or survival [26]. Duration of exposure of cycling cells to paclitaxel may be an important determinant of anti-

tumor efficacy;[27,28] however, long duration infusions have been associated with increased hematologic toxicity with an increase in efficacy at 24 but not 96 hours.[29]

Weekly dosing of paclitaxel in patients with metastatic breast cancer was initially evaluated on the basis of mathematical models that predicted superiority for more frequent dosing.[30] In a phase II trial, thirty patients with metastatic breast cancer received weekly paclitaxel therapy at an initial dose of 100 mg/m^2 until disease progression.[31] The overall response rate (ORR) was 53% (95% confidence interval [CI], 34% to 72%), with a median response duration of 7.5 months. Grade 3/4 neutropenia occurred in four patients; febrile neutropenia was not observed. Peripheral neuropathy prohibited dose escalation above 100 mg/m^2, and grade 3 neuropathy was observed in two of 21 patients at <100 mg/m^2. CALGB 9840 subsequently randomized 577 women with taxane naïve metastatic breast cancer to receive weekly paclitaxel at 100 or 80 mg/m^2 *versus* standard three-weekly paclitaxel at 175 mg/m^2 as first or second-line therapy.[32] Weekly paclitaxel was superior to standard three-weekly paclitaxel with respect to response rates (42 *versus* 29%, odds ratio [OR] 1.75, p=0.0004) and time to progression (TTP; 9 *versus* 5 months, hazard ratio [HR] 1.43, p<0.001). Toxicity was also different; weekly paclitaxel caused less grade 3/4 granulocytopenia (9 *versus* 15%, p=0.017) but more grade 3/4 sensory neuropathy despite a mid-trial dose reduction from 100 to 80 mg/m^2 per week (24 *versus* 12%, p=0.0003).

As a result of these trial results, weekly paclitaxel appears to be superior to standard three-weekly paclitaxel, and it is currently the preferred schedule of administration in the treatment of metastatic breast cancer.

1.5.2 Eribulin

Halichondrin B is a large polyether macrolide isolated from the rare marine sponge *Halichondrin okadai.* It exhibits potent anticancer effects both *in vitro* and *in vivo*[33-35] with a tubulin-based mechanism that appears to be distinct from all other antitubulin agents.[33,36,37] E7389 (eribulin) is a structurally simplified, synthetic analog of this marine natural product that exhibits similar anticancer properties in preclinical models[38] through a tubulin-based antimitotic mechanism similar to that of halichondrin B. It is a nontaxane microtubule dynamics inhibitor that suppresses microtubule growth and sequesters tubulin into nonfunctional aggregates, preventing mitotic spindle formation with subsequent G2-M arrest and apoptosis. It exhibited potent anticancer effects in preclinical models of various malignancies, including breast cancer.[33,36,38-41] This mechanism of action is distinct from that of other antitubulins, such that it may be effective in patients with disease that is resistant to these agents. In fact, eribulin demonstrated antitumor activity in preclinical studies with cell lines that are paclitaxel resistant as a result of beta tubulin mutations.[42] The *in vivo* animal model data also predicted that this agent would achieve greater efficacy than the taxanes and with fewer adverse effects.

Three phase I clinical trials were conducted and demonstrated a manageable toxicity profile – two studies with a weekly schedule on days 1, 8, and 15 in 28-day cycles[43,44] and one study with a three-weekly schedule.[45] Neutropenia was the DLT at a maximum tolerated dose of 1.4 mg/m^2 as a bolus injection on days 1, 8, and 15 in 28-day cycles. This was selected as the initial dose and schedule for further development.

Subsequent phase II studies in patients with heavily pretreated advanced breast cancer demonstrated that eribulin is therapeutically active with a manageable toxicity profile that includes a low incidence of clinically significant peripheral neuropathy. The first study included 103 subjects who had received prior anthracyclines and taxanes with a median of four prior chemotherapy regimens.[4] The ORR was 11.5% by independent review with a clinic benefit rate of 17.2% (defined as responses in addition to stable disease of at least six months duration). Median PFS was 2.6 months, and median OS was 9.0 months. The most common grade 3/4 study drug-related adverse event was neutropenia (64%) with a low incidence of grade 3/4 fatigue (5%) and febrile neutropenia (4%). The incidence of peripheral neuropathy was also low (26% grade 1/2; 5% grade 3). Of note, the schedule was modified to days 1 and 8 in 21-day cycles for the last 33 subjects because cycle 1 dose delays, reductions, or omissions were needed as a result of neutropenia in 44 of the initial 70 treated patients.

The second related phase II study continued the 21-day schedule and treated 291 subjects who had received prior anthracycline, taxane, and capecitabine therapy for locally advanced or metastatic breast cancer – again with a median of four prior chemotherapy regimens.[3] The findings were very similar to the other study. The ORR was 9.3% by independent review and 14.1% by investigator assessment with a clinic benefit rate of 17.1% (defined as responses in addition to stable disease of at least six months duration). Median PFS was 2.6 months, and median OS was 10.4 months. The most common grade 3/4 study drug-related adverse event was neutropenia (54%) with a low incidence of grade 3/4 asthenia/fatigue (10%) and febrile neutropenia (5.5%). Eribulin was associated with a 24.1% incidence of peripheral neuropathy overall (5.5% grade 3; 0% grade 4); of the 56 subjects who had pre-existing neuropathy, the majority (79%) did not experience worsening symptoms with the administration of eribulin. No grade 4 non-hematologic events were reported in either heavily pretreated patient population.

EMBRACE (Study 305) was an open label, phase III clinical trial with a 2:1 randomization to eribulin *versus* the physician's choice of standard single agent therapy.[5] Eligible subjects were patients with progressive, locally recurrent or metastatic breast cancer who had received 2-5 prior chemotherapy regimens, including exposure to an anthracycline and taxane (actual median of 4 prior regimens). Eribulin mesylate was administered as a 1.4 mg/m^2 IV bolus injection over 2-5 minutes on days 1 and 8 in 21-day cycles. The physician's choice of therapy included any monotherapy (chemotherapy, endocrine therapy, or biologic therapy) or supportive care alone. 97% of subjects on the control arm received single agent chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other), and the remaining 3% received single agent endocrine therapy; no patients received best supportive care alone. 762 patients were treated on protocol with improved median OS of 13.1 months *versus* 10.6 months in favor of eribulin (HR 0.81, 95% CI 0.66-0.99, p=0.041). Median PFS was not statistically significant at 3.7 months *versus* 2.2 months (HR 0.87, 95% CI 0.71-1.05, p=0.14), but ORR favored eribulin at 12.2 *versus* 4.7% (p=0.002) by independent review. Grade 3 and grade 4 neutropenia occurred in 21% and 24% of subjects treated with eribulin, respectively, leading to the discontinuation of therapy in only <1% of patients. The rate of grade 3/4 febrile neutropenia with eribulin was 4%. Grade 3 and grade 4 peripheral neuropathy occurred in 8% and 0.4% of subjects treated with eribulin, respectively, despite the history of prior taxane exposure.

In September 2009, accrual completed to an international, open-label, randomized, phase III clinical trial of eribulin *versus* capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.[46] The study enrolled 1102 patients for first-line, second-line, or third-line chemotherapy with co-primary endpoints of OS and PFS. Eribulin mesylate was administered as a 1.4 mg/m^2 IV bolus injection over 2-5 minutes on days 1 and 8 in 21-day cycles. Capecitabine was administered orally as 2500 mg/ m^2 in two divided doses on days 1-14 in 21-day cycles. Results of the final analysis were presented in December 2012 using the planned stratification factors of geographic region and HER2 status. An improvement in median OS was observed with 15.9 months *versus* 14.5 months in favor of eribulin, but this was not statistically significant for the entire study population (HR 0.879, 95% CI 0.770-1.003, p=0.056). Planned stratification by HER2 status, however, revealed a nominally significant benefit in median OS for patients with HER2 negative disease (15.9 months *versus* 13.5 months for eribulin *versus* capecitabine; HR 0.84, p=0.0299). Median PFS for the overall population was similar between the eribulin and capecitabine treatment groups by independent review (4.1 months *versus* 4.2 months respectively, HR 1.079, 95% CI 0.932-1.250, p=0.305). The same observation was made for ORR on the independent reviewer assessment (11.0% *versus* 11.5% for eribulin *versus* capecitabine respectively). Eribulin was generally well tolerated and had a safety profile consistent with data from EMBRACE (Study 305) and the phase II studies. Febrile neutropenia was reported in 2% of patients in Study 301 *versus* 4.6% of patients in EMBRACE (Study 305). No new safety signals were noted for eribulin.

1.6 Specific hypotheses of the current study

1.6.1 Treatment with eribulin will result in less neurotoxicity in comparison to treatment with standard weekly paclitaxel.

1.6.2 Patient-reported PRO-CTCAE data can be collected and used to detect differences in symptoms that result from exposure to eribulin and standard weekly paclitaxel.

1.6.3 Selected single nucleotide polymorphisms will predict for the risk of peripheral neuropathy associated with exposure to eribulin and standard weekly paclitaxel.

1.6.4 Serum based biologic correlates will predict for survival and/or response to therapy with eribulin specifically or the microtubule dynamics inhibitors in general.

1.6.5 Tumor based biologic correlates will predict for survival and/or response to therapy with eribulin specifically or the microtubule dynamics inhibitors in general.

2.0 Objectives

2.1 Primary

2.1.1 To demonstrate that patient-reported PRO-CTCAE data will be able to detect differences in symptoms between participants treated with eribulin and standard weekly paclitaxel at 12 weeks.

2.1.2 To validate rs7349683 in *EPHA5* as a predictor of peripheral neuropathy from treatment with a microtubule targeting agent (*i.e.*, eribulin or paclitaxel).

2.2 Secondary

2.2.1 To compare overall survival, progression free survival (PFS), objective response rate (ORR), duration of response (DOR), and time to treatment failure (TTF) in patients receiving eribulin *versus* standard weekly paclitaxel.

2.2.2 To compare the 12 month rate of disease progression in patients receiving eribulin *versus* standard weekly paclitaxel.

2.2.3 To evaluate the clinical value and feasibility of collecting patient-reported symptom toxicity information via the Patient-Report Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE); to further validate the PRO-CTCAE sensory neuropathy items; and to compare patient-reported neurotoxicity between arms using the EORTC QLQ-CIPN20 instrument.

2.2.4 To assess the toxicities in patients receiving eribulin *versus* standard weekly paclitaxel.

2.3 Exploratory

2.3.1 To compare new metastasis free survival in patients receiving eribulin *versus* standard weekly paclitaxel.

2.4 Correlative

2.4.1 To explore the relationship between common single nucleotide polymorphisms in *FGD4, FZD3,* and *VAC14* as predictors of peripheral neuropathy from treatment with a microtubule targeting agent (*i.e.,* eribulin or paclitaxel).

2.4.2 To evaluate circulating nucleosomes and the apoptosis associated M30 neo-epitope as potential biomarkers associated with clinical benefit from treatment with eribulin specifically or the microtubule dynamics inhibitors in general.

2.4.3 To evaluate tubulin isotype expression, mutations, and signaling pathway modifications in tumor tissue as potential biomarkers associated with clinical benefit from treatment with eribulin specifically or the microtubule dynamics inhibitors in general.

3.0 Patient Eligibility

3.1 Pre-registration – Inclusion criteria

3.1.1 Informed consent document signed and dated by patient.

3.2 Registration – Inclusion Criteria

3.2.1 Age ≥18 years.

3.2.2 Histologic confirmation of invasive adenocarcinoma originating in the breast.

3.2.3 Stage IV disease or Stage IIIC disease (using the 7th edition AJCC criteria) not amenable to local therapy.

3.2.4 Clinical or radiographic evidence of disease progression.

3.2.5 Documentation of HER2 negative breast cancer at the time of protocol registration. [**Note:** HER2 negativity is defined as 0 or 1+ by immunohistochemistry OR nonamplified or equivocal by FISH. Status may be defined on the basis of historic results on the breast primary or a metastatic site, whichever is most recent. Repeat biopsies are not required for participation in this protocol.]

3.2.6 Known hormone receptor status at the time of protocol registration. [**Note:** ER and/or PgR status are considered positive with a cut-off of ≥1% invasive tumor cells. Status may be defined on the basis of historic results on the breast primary or a metastatic site, whichever is most recent. Repeat biopsies are not required for participation in this protocol.]

3.2.7 Prior systemic therapy as per the following criteria:

3.2.7.1 Patients must demonstrate resolution of all toxicities related to prior chemotherapy, endocrine therapy, targeted therapy, or biologic therapy to grade ≤1, including peripheral neuropathy, with the exception of alopecia (any grade permissible).

3.2.7.2 No more than one prior chemotherapy regimen for advanced or metastatic breast cancer is allowed. Prior chemotherapy for metastatic disease must have been completed ≥14 days prior to randomization.

- Any single agent therapy, and any combination of cytotoxic, endocrine, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a preplanned treatment, given concomitantly, sequentially or both, is considered one regimen.

- Planned neoadjuvant chemotherapy and postoperative adjuvant chemotherapy is considered one regimen.

- If the dosing of one or more of the chemotherapy components of a regimen must be reduced for toxicity, the modified version of the original regimen is not considered a new regimen.

- If one or more of the chemotherapy components of a regimen must be omitted for toxicity, the modified version of the original regimen is not considered a new regimen.

- If one of the chemotherapy components of a regimen must be replaced with another similar drug of the same therapeutic class, the modified version of the original regimen is not considered a new regimen. However, if a new component, dissimilar to any of the original components, is added to the regimen, the modified version is considered a new regimen.

- If chemotherapy is interrupted for surgery or radiotherapy and then continues with an unchanged schedule and components, treatment is considered as one regimen despite the interruption.

3.2.7.3 Prior treatment may include a taxane as per the following criteria:

- Prior taxane (including paclitaxel) in the adjuvant or neoadjuvant setting is allowed, provided that the interval between the completion of (neo)adjuvant therapy and disease recurrence is >12 months.

- Prior taxane in the metastatic setting is allowed, provided that the agent administered in the metastatic setting was not standard paclitaxel.

3.2.7.4 Any number of prior endocrine therapies is allowed and must be discontinued prior to randomization.

3.2.7.5 Any number of biologic therapies (*e.g.*, bevacizumab) or immunotherapies is allowed in the absence of co-administered chemotherapy and must have been completed ≥28 days prior to randomization.

3.2.7.6 Prior treatment with an investigational agent is allowed but must have been completed ≥28 days prior to randomization with resolution of all treatment-related toxicities to grade ≤1.

3.2.8 Prior local therapy as per the following criteria:

3.2.8.1 Minor surgical procedures must be completed ≥7 days prior to randomization with documentation of adequate recovery from associated complications to grade ≤1. These include (but are not limited to) laparoscopy, thoracoscopy, bronchoscopy, mediastinoscopy, endoscopic ultrasonography, skin biopsy, percutaneous needle biopsy, and routine dental procedures. As a precautionary measure, it is recommended, but not strictly required, that placement of a central venous access device, thoracentesis, or

paracentesis be done 7 days before the initiation of protocol directed chemotherapy with documentation of adequate recovery from associated complications to grade ≤1.

3.2.8.2 Major surgical procedures and open biopsies must be completed ≥28 days prior to randomization with documentation of adequate recovery from associated complications to grade ≤1.

3.2.8.3 Prior radiotherapy must be completed ≥14 days prior to randomization with documentation of adequate recovery from associated toxicities to grade ≤1.

3.2.9 Concurrent supportive therapy as per the following criteria:

3.2.9.1 Treatment with bisphosphonates or denosumab is allowed and recommended per the standard of care.

3.2.9.2 Therapeutic anticoagulation is allowed for patients on a stable dose of warfarin or low molecular weight heparin.

3.2.10 Radiographically measurable or non-measurable disease as per RECIST guidelines (version 1.1, see Section 11.0):

3.2.10.1 Measurable disease is defined as at least one lesion that can be accurately measured with the longest diameter as ≥1.0 cm by CT scan or ≥1.0 cm with calipers by clinical examination. The exceptions to these criteria are pathologic lymph nodes, which must be ≥1.5 cm in the short axis when assessed by CT scans with slice thickness ≤0.5 cm.

3.2.10.2 Non-measurable lesions include the following: small lesions (longest diameter <1.0 cm for all lesions other than pathologic lymph nodes, which are ≥1.0 cm and <1.5 cm in the short axis), bone metastases, pleural effusions, pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitis pulmonis, lymphangitis cutis, and abdominal masses not followed by CT or MRI.

3.2.11 ECOG performance status of 0, 1, or 2.

3.2.12 Life expectancy of >12 weeks.

3.2.13 History of brain metastases as per the following criteria:

3.2.13.1 Patients with a history of resected brain metastases are eligible only if they are asymptomatic and have stable MRI scans for 3 consecutive months, including ≤28 days of study registration.

3.2.13.2 Patients who receive stereotactic radiosurgery or whole brain radiation for brain metastases are eligible only if they are asymptomatic and have stable MRI scans for 3 consecutive months, including ≤28 days of study registration.

3.2.14 Adequate organ function per blood work obtained ≤7 days prior to registration:

3.2.14.1 Absolute neutrophil count ≥1500/μL.

3.2.14.2 Platelet count ≥100,000/μL.

3.2.14.3 Hemoglobin ≥9 g/dL.

3.2.14.4 Total bilirubin ≤1.5 times the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome.

3.1.14.5 SGOT (AST) and SGPT (ALT) ≤3x ULN except in the case of liver metastases, where ≤5x ULN is allowed.

3.2.14.6 Creatinine ≤2.0 mg/dL or creatinine clearance >50 mL/min.

3.2.14.7 QTc interval ≤500 msec on the baseline electrocardiogram.

3.2.15 Negative pregnancy test done ≤72 hours prior to registration for women of childbearing potential only.

Note: All female subjects will be considered to be of child-bearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause), or have been sterilized surgically (*i.e.*, bilateral tubal ligation ≥1 menstrual cycle prior to randomization, or have undergone a hysterectomy and/or bilateral oophorectomy).

Female subjects of child-bearing potential must agree to use highly effective contraception during the study treatment and for 3 months after the final dose of study treatment. Female subjects exempt from this requirement are subjects who practice total abstinence. If currently abstinent, the subject must agree to use a double barrier method of contraception (*i.e.*, condom and occlusive cap [diaphragm or cervical/vault caps]) with spermicide or until they are established on highly effective contraception for at least one menstrual cycle if they become sexually active during the study treatment and for 3 months after the final dose of study treatment.

Highly effective contraception includes:

- Placement of intrauterine device or system
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) with spermicide
- Vasectomized partner with confirmed azoospermia

Male subjects and their female partner who are of child-bearing potential (as defined above), and are not practicing total abstinence, must agree to use highly effective contraception during study treatment and for 3 months after the final dose of study treatment. If currently abstinent, the subject must agree to use a double barrier method of contraception if they become sexually active, or until they are established on highly effective contraception as described above.

3.2.16 Ability to complete questionnaire(s) independently or with assistance.

3.2.17 Willingness to provide blood and tissue samples for correlative research purposes (see Sections 6.1.2, 14.0, and 17.0). [**Note:** These tissue samples are from archived tissue, if available; new biopsies are not required.]

3.2.18 Ability to comprehend and respond to questions using a telephone keypad.

3.3 Exclusion criteria

3.3.1 Prior malignancy, other than carcinoma in situ of the cervix and non-melanoma skin cancers, unless the prior malignancy was diagnosed and definitively treated ≥5 years previously, there is no subsequent evidence of recurrence, and the patient is considered by a physician to be at <30% risk of relapse.

3.3.2 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or Women of childbearing potential who are unwilling to employ adequate contraception

3.3.3 Presence of a serious nonhealing wound, ulcer, or bone fracture.

3.3.4 History of CTCAE grade ≥3 hypersensitivity to paclitaxel or Cremophor® EL.

3.3.5 Pre-existing peripheral neuropathy grade ≥2 at registration.

3.3.6 Significant cardiovascular impairment (*e.g.*, New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia).

3.3.7 Subjects with known positive HIV status.

3.3.8 History of stroke or transient ischemic attack ≤6 months prior to registration.

3.3.9 History of uncontrolled seizures. [**Note:** Patients are eligible for the study if the seizures are well controlled with standard medications.]

3.3.10 Severe or uncontrolled intercurrent illness/infection.

3.3.11 Concurrent administration of any other investigational agent considered to have potential efficacy in the treatment of breast cancer.

3.3.12 Prior exposure to eribulin mesylate.

4.0 Test Schedule

Tests and procedures	Baseline/ Pre-treatment (≤7 days prior to randomization unless noted otherwise)	Active Monitoring/Treatment				Follow-up/ Observation[10] (Every 12 weeks until progression unless otherwise specified)
		Days 1, 8 for Arm A Days 1, 8, and 15 for Arm B (unless otherwise specified)	Prior to each new cycle, starting with cycle 2 (≤7 days)	Every 12 weeks (+/- 7 days)	At end of treatment (PD, withdrawal, or removal)[10]	
History, physical examination (including measurements of clinically evident disease), weight, BSA	X		X		X	X[11]
ECOG Performance Status (PS)	X		X		X	
Height	X					
Adverse event assessment[13,14]	X		X		X	X[11]
Pregnancy test (serum or urine β-HCG)[1]	X					
Hematology: CBC w/ diff and platelets	X	X			X	
Chemistries: SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, creatinine, calculated creatinine clearance[16], Ca, glucose, Na, K	X		X		X	
Contrast enhanced CT scans of chest/abdomen/pelvis (see Section 11.0)[4]	X[2]			X		X
Bone scan[17]	X[2]			X[3]		X[3,12]
Brain MRI with gadolinium[5]	X			X		X
Concomitant medications	X		X		X	
Electrocardiogram	X		X[18]			
Mandatory blood samples (see Section 14.0)[6,R]	X			X	X	
Mandatory archived tissue sample (see Section 17.0)[7,R]	X					
EORTC QLQ-CIPN20 (see Appendix IV)[8]	X		X		X	
PRO-CTCAE (see Appendix V, VI, & VII)	X[9]	X[9]			X[15]	X

1. For women of childbearing potential only. Must be performed ≤72 hours prior to registration.
2. Must be performed ≤28 days prior to registration.
3. For patients with a history of bone metastases or for whom there is clinical suspicion of bone metastases at study entry.

4. For patients with a documented allergy to iodine, shellfish, or CT contrast, noncontrast enhanced CT scans of the chest AND gadolinium enhanced MRI of the abdomen and pelvis may be performed.
5. For patients with known brain metastases, or if clinically indicated.
6. Use of study kits is required (see Section 14.0). May also be drawn on cycle 1 day 1 prior to the administration of chemotherapy.
7. Must be submitted within 90 days of registration unless the site can provide documentation of their unsuccessful efforts to obtain the required tissue.
8. The EORTC QLQ-CIPN20 questionnaire will be administered via paper form.
9. Items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be administered prior to the initiation of study treatment and then weekly during study treatment via a telephone Interactive Voice Response System (IVRS).
10. For patients who discontinue study treatment without disease progression (see Section 13.8.1). Follow-up can be discontinued after 2 years if the patient is no longer receiving study treatment. If the patient remains on study treatment as of September 30, 2021, follow-up will be discontinued.
11. Information may be obtained through phone calls to the patient or office notes from health care providers (see Section 13.6).
12. Every 24 weeks (sooner if clinically indicated).
13. Patient PRO-CTCAE scores should be printed from the PRO-CTCAE web system and provided to the clinician at the time of clinical grading of adverse events during treatment and at the end of treatment (see Section 1.1in Appendix VI).
14. All adverse events observed during study participation will be reported on the eCRF. All adverse events, regardless of relationship to the study drug, will be collected beginning from the time the subject signs the study ICF through the last visit and for 30 days after last dose. Serious adverse events will be collected for 30 days after the last dose, or any time if the investigator considers it related to study drug. After the 30 days, only those adverse events related to peripheral neuropathy need to be collected.
15. There will be a 12 week follow-up survey administered one time via booklet (see appendix VII).
16. Cockcroft-Gault GFR = (140-age) * (wt. in kg) * (0.85 if female) / (72 * Cr)
17. F-18 (sodium fluoride) PET imaging or Tc99 radionuclide bone scans, per physician discretion.
18. Prior to cycle 2 only.

R. Research funded (see Section 19.0).

5.0 Stratification Factors (documented at the time of registration)

5.1 Prior taxane exposure: Yes *versus* no.

5.2 ER/PR status: ER or PR positive *versus* ER and PR negative.

5.3 Planned line of chemotherapy on study: First-line *versus* second-line.

6.0 Registration/Randomization Procedures

6.1 Pre-registration procedures (Step 1)

6.1.1 Documentation of IRB approval and ongoing IRB approval (no less than annually) must be on file at the Registration Office [redacted] before a site investigator may pre-register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). Sites must also have approval of regulatory documents and have completed required training. Please refer to the Study Completion Guidelines (access the ACCRU web page and click on Regulatory) for a complete list of requirements. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved. [**Note:** When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.]

6.1.2 To pre-register a patient, fax [redacted] a completed pre-registration eligibility checklist to the Registration Office between 8:00 AM and 4:30 PM Central Time Monday through Friday.

Confirmation of pre-registration will be received via email at the time pre-registration is complete. If this email is not received, you can contact the Registration Office at [redacted] to confirm pre-registration.

6.1.3 **All patients who sign and date an informed consent document must be pre-registered, regardless of whether they proceed to Registration (Step 2).**

6.1.3.1 If the patient does not go on to registration, the completed screening disposition form must be faxed to the Registration Office [redacted] If the patient did not meet the eligibility criteria, then the Inclusion/Exclusion Criteria Form must also be faxed to the Registration Office.

6.2 Registration procedures (Step 2)

6.2.1 Upon confirmation of patient pre-registration, the site will register the patient as follows:

Fax [redacted] a completed eligibility checklist and the screening disposition form to the Registration Office between 8:00 AM and 4:30 PM Central Time Monday through Friday.
Confirmation of registration will be received via fax at the time registration is

complete. If this fax is not received, you can contact the Registration Office at [redacted] to confirm registration.

Prior to the initiation of protocol study intervention, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent.

6.2.2 At the time of registration, the following must be recorded:

- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (*e.g.,* diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (*e.g.,* diabetes, Alzheimer's disease, or heart disease).

6.2.3 Correlative research

Mandatory correlative research components are part of this study. The patient will be automatically registered onto this component (see Sections 3.2.17, 14.0, and 17.0).

6.2.4 Prior to accepting the registration/randomization, the registration/randomization application will verify the following:

- Patient eligibility
- Existence of a signed and dated consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Other requirements for registration

6.3.1 Study drugs must be available on site at the time of registration.

6.3.2 Blood draw kits must be available on site at the time of registration.

6.3.3 Patient questionnaire booklets must be available on site at the time of registration. Copies are not acceptable for this submission.

6.3.4 PRO-CTCAE Site Credentialing: At least one staff member from the site is required to obtain credentialing to perform PRO-CTCAE patient training. The staff member should send an e-mail request to the PRO-CTCAE Coordinator at [redacted] to schedule a date and time for live interactive training using the telephone; no instructional videos will be available.

Training will require about 45 minutes and is required only once per site.

Training will include the following: (1) how to register a patient to PRO-CTCAE telephone reporting using the interactive voice response system (IVRS); (2) how to explain and demonstrate the PRO-CTCAE telephone system to patients; (3) how to monitor patients' PRO-CTCAE reporting. The PRO-CTCAE Coordinator will provide e-mail certification of successful credentialing to the site and to the ACCRU Regulatory Office. This office will update their regulatory records to indicate that training has been completed. Sites may check for updates on their status by contacting [redacted]

For any questions or concerns, please send an e-mail to [redacted]

6.3.5 PRO-CTCAE Patient Training: Each patient must be trained to use the telephone symptom reporting system.

Note: Site study staff must clearly convey to the patient that the information regarding symptoms collected by the PRO-CTCAE self-report are for research purposes only and are not monitored by a physician. Study staff must advise patients to directly contact their doctor for any concerning symptoms.

All patients enrolled at U.S. and Canadian sites who can read and speak English or Spanish will be required to participate in PRO-CTCAE reporting by telephone using the PRO-CTCAE interactive voice response system (IVRS). Site study staff will train the patient how to use the IVRS; this training will require about 10 to 20 minutes per patient.

Because patients will self-report PRO-CTCAE symptoms from home, patients will not require access to a telephone during regularly scheduled clinic visits. However, in order for site personnel to train patients, access to a telephone will be required. If this is not possible, the site study staff may provide this training over the telephone by calling the patient after s/he leaves the clinic. Patients reporting by telephone will call telephone number [redacted], enter their user ID and PIN, then answer the verbal questions concerning symptoms and health concerns. This will require about 5 minutes.

A reference card for the telephone IVRS system will be provided to the patient as shown in Appendix VII. This reference card, available in English and Spanish, is available through ACCRU. Both a help line and e-mail address are listed on the [redacted] or call telephone number [redacted].

6.4 Other requirements for the initiation of protocol directed therapy

6.4.1 Protocol directed therapy cannot begin prior to registration and must begin ≤21 days after registration.

6.4.2 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.4.3 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.4.4 Protocol directed chemotherapy must be administered at an ACCRU institution under the supervision of a medical oncologist.

6.5 Randomization procedures

6.5.1 When combined, the stratification factors defined in Section 5.0 create 8 strata groups.

6.5.2 After the patient is registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using Medidata Rave Balance, which is based on the Pocock and Simon[47] dynamic allocation procedure. The goal of this procedure is to maintain arm balance within each of the 8 strata, with the target arm ratio being 1:1.

- Eribulin mesylate
- Paclitaxel

7.0 Protocol Treatment

7.1 Treatment doses and schedule

7.1.1 Pretreatment medications for **paclitaxel** (required)

Agent	Dose	Route	Comments
Dexamethasone	10-20 mg	IV	Administer 30-60 minutes prior to paclitaxel
Diphenhydramine	50 mg	IV or PO	
Famotidine (or equivalent)	20 mg	IV	

7.1.2 Chemotherapy

Arm	Agent	Dose	Route	Day(s)	Cycles
A	Eribulin mesylate	1.4 mg/m^2	IV over 2-5 minutes	1 and 8	q21 days
B	Paclitaxel	90 mg/m^2	IV over 1 hour	1, 8, and 15	q28 days

7.2 The BSA formula of Dubois or of Gehan and George will be used for all chemotherapy dose calculations. Use actual weight.

7.3 The patient must return to the consenting ACCRU institution for chemotherapy administration and clinical evaluation per protocol.

8.0 Dosage Modifications Based on Adverse Events during Protocol Directed Therapy

ALERT: *ADR reporting may be required for some adverse events (See Section 10.0)*

8.1 Dose levels (Based on Adverse Events outlined below).

Dose Level	Eribulin mesylate (mg/m^2)	Paclitaxel (mg/m^2)
0*	1.4	90
-1	1.1	75
-2	0.7	60

* Dose level 0 refers to the starting dose.

8.2 Dose modifications for eribulin mesylate

8.2.1 Guidelines for hematologic toxicity on **day 1**

(CTCAE v4.0 System/Organ/Class [SOC] is INVESTIGATIONS)

8.2.1.1 Delay eribulin mesylate administration for ANC <1000/mm^3 or platelets <75K/mm^3.

8.2.1.2 Discontinue protocol directed treatment if chemotherapy is delayed for >4 weeks due to hematologic toxicity.

8.2.1.3 If the ANC recovers to ≥1000/mm^3 within 4 weeks, resume treatment as follows:

- If the ANC was <500/mm^3 for >7 days, decrease eribulin mesylate by one dose level and maintain for all subsequent doses.
- If the ANC was <1000/mm^3 with fever or infection, decrease eribulin mesylate by one dose level and maintain for all subsequent doses.

8.2.1.4 If the platelets recover to ≥75K within 4 weeks, resume treatment as follows:

- If the platelets were <25K/mm^3, decrease eribulin mesylate by one dose level and maintain for all subsequent doses.
- If the platelets were <50K/mm^3 and required platelet transfusion (per physician discretion), decrease eribulin mesylate by one dose level and maintain for all subsequent doses.

8.2.2 Guidelines for hematologic toxicity on **day 8**

8.2.2.1 Delay eribulin mesylate administration for ANC <1000/mm^3 or platelets <75K/mm^3 until recovery to these values.

8.2.2.2 If recovery occurs before day 15, eribulin mesylate is administered, and that day of treatment will be considered the new day 8. Decrease eribulin mesylate by one dose level and maintain for all subsequent doses.

8.2.2.3 If recovery does not occur before day 15, the eribulin mesylate dose is omitted, and treatment will resume as scheduled on day 1 of the next cycle. Decrease eribulin mesylate by one dose level and maintain for all subsequent doses.

8.2.3 Guidelines for other grade 3 or 4 non-hematologic toxicity

(CTCAE v4.0 System/Organ/Class [SOC] is OTHER UNSPECIFIED ADVERSE EVENTS)

8.2.3.1 For other grade 3 non-hematologic toxicity attributed to chemotherapy, delay chemotherapy administration.

8.2.3.2 If the delay for grade 3 non-hematologic toxicity occurs on day 1 and the toxicity improves to grade 2 or better within 7 days (with or without maximal supportive care), resume treatment with one dose level reduction.

8.2.3.3 If the delay for grade 3 non-hematologic toxicity occurs on day 8 and the toxicity improves to grade 2 or better before day 15, eribulin mesylate is administered, and that day of treatment will be considered the new day 8. Decrease eribulin mesylate by one dose level and maintain for all subsequent doses. Initiate the next cycle no sooner than 2 weeks later.

8.2.3.4 If the delay for grade 3 non-hematologic toxicity occurs on day 8 and the toxicity does not improve to grade 2 or better before day 15, the eribulin mesylate dose is omitted, and treatment will resume as scheduled on day 1 of the next cycle. Decrease eribulin mesylate by one dose level and maintain for all subsequent doses.

8.2.3.5 For other grade 4 non-hematologic toxicity attributed to chemotherapy, protocol participation must be permanently discontinued.

8.2.3.6 If chemotherapy is delayed or skipped for >4 weeks, protocol participation must be permanently discontinued.

8.3 Dose modifications for paclitaxel

8.3.1 Guidelines for hematologic toxicity on **day 1**

(CTCAE v4.0 System/Organ/Class [SOC] is INVESTIGATIONS)

8.3.1.1 Delay paclitaxel administration for ANC <1000/mm^3 or platelets <75K/mm^3.

8.3.1.2 Discontinue protocol directed treatment if chemotherapy is delayed for >4 weeks due to hematologic toxicity.

8.3.1.3 If treatment is delayed for ANC <1000/mm^3 or platelets <75K/mm^3 and the counts recover within 4 weeks, decrease paclitaxel by one dose level and maintain for all subsequent doses.

8.3.1.4 For platelets 75-99K/mm^3, do not delay treatment, decrease paclitaxel by one dose level, and maintain for all subsequent doses.

8.3.2 Guidelines for hematologic toxicity on **day 8 or 15**

8.3.2.1 Skip the day 8 or 15 administration of paclitaxel for ANC <1000/mm^3 or platelets <75K/mm^3. These doses are not made up.

8.3.2.2 If treatment is skipped for ANC <1000/mm^3 or platelets <75K/mm^3, decrease paclitaxel by one dose level and maintain for all subsequent doses.

8.3.2.3 For platelets 75-99K/mm^3, do not delay treatment, decrease paclitaxel by one dose level, and maintain for all subsequent doses.

8.3.3 Guidelines for hepatic dysfunction

(CTCAE v4.0 System/Organ/Class [SOC] is INVESTIGATIONS)

Transaminase level		**Bilirubin level**	**Dose modification**
AST or ALT $\leq$ 2.5	**and**	T. bilirubin $\geq$ 1.5 x ULN, but $\leq$ 3 x ULN	Reduce one dose level♦
AST or ALT $\geq$ 2.5, but $\leq$ 10 x ULN	**and**	T. bilirubin $\leq$ 1.5 x ULN	Reduce one dose level♦
AST or ALT $\geq$ 2.5 but $\leq$ 10 x ULN	**and**	T. bilirubin > 1.5 x ULN, but $\leq$ 3 x ULN	Reduce two dose levels*♦
AST or ALT > 10 x ULN	**or**	T. bilirubin > 3 x ULN	Discontinue protocol therapy

* No reductions below dose level -2.

♦ Dose reductions stay at the same level unless hepatic function worsens (*i.e.*, for abnormal LFTs that remain at the same level, another dose reduction should not be made).

8.3.4 Guidelines for other grade 3 or 4 non-hematologic toxicity

(CTCAE v4.0 System/Organ/Class [SOC] is OTHER UNSPECIFIED ADVERSE EVENTS)

8.3.4.1 For other grade 3 non-hematologic toxicity attributed to chemotherapy, delay (day 1) or skip (day 8 or 15) chemotherapy administration until the toxicity improves to grade 2 or better and then resume treatment with one dose level reduction.

8.3.4.2 For other grade 4 non-hematologic toxicity attributed to chemotherapy, protocol participation must be permanently discontinued.

8.3.4.3 If chemotherapy is delayed or skipped for >4 weeks, protocol participation must be permanently discontinued.

8.4. Dose modifications for peripheral neuropathy secondary to chemotherapy (eribulin mesylate or paclitaxel)

8.4.1 For intolerable grade 2 peripheral neuropathy, decrease chemotherapy by one dose level and maintain for all subsequent doses.

8.4.2 Skip chemotherapy administration for grade 3 peripheral neuropathy. When the symptoms improve to grade 2 or better, treatment may resume with one dose level reduction for all subsequent doses. (The time to resolution to grade 2 or better should be the adverse event duration used for adverse event reporting.)

8.4.3 Discontinue protocol directed treatment if grade 4 peripheral neuropathy develops.

8.5 General guidelines

8.5.1 Chemotherapy drug dose reductions are permanent. **Once reduced, the dose may not be dose escalated.**

8.5.2 If chemotherapy must be reduced below dose level -2 for toxicity, protocol participation must be permanently discontinued.

8.5.3 If chemotherapy is delayed or skipped for >4 weeks, protocol participation must be permanently discontinued.

8.5.4 For grade $\geq$3 hypersensitivity reactions, protocol participation must be permanently discontinued.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics, antidiarrheals, analgesics, and all other supportive medications may be used at the discretion of the treating physician and in keeping with good clinical practice. All concomitant medications received from the first day of study treatment administration until 30 days after the final dose must be recorded in the medical records.

9.2 Blood products and growth factors should be utilized as clinically warranted and in accordance with institutional policies and recommendations.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse events and other events of interest

10.1.1 Adverse event characteristics

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

All appropriate treatment areas should have access to the CTCAE version 4.0 document, which can be downloaded from the CTEP web site: [redacted]

Site investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

10.2 Expected *versus* unexpected events

10.2.1 The determination of whether an AE is expected or unexpected is based on agent-specific information provided in the Investigator Brochure and/or Section 15.0 of the protocol.

10.2.2 Unexpected AEs are those not listed in the agent-specific information provided in the Investigator Brochure and/or Section 15.0 of the protocol.

10.2.3 An “unexpected adverse experience” refers to any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review, nor mentioned in the consent form.

10.3 Assessment of attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly or probably attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.4 Routine reporting

Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent on separate arms must be reported as defined by the general guidelines.

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) are eribulin mesylate and paclitaxel.

The criteria for identifying AEs are as follows:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.

- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (*e.g.*, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.

- Recurrence of an intermittent medical condition (*e.g.*, headache) not present pretreatment (at baseline).

- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not. A laboratory result should be considered by the site investigator to be an AE if it:

    - Results in the withdrawal of study drug

    - Results in withholding of study drug pending some investigational outcome

    - Results in an intervention, based on medical evaluation (*e.g.*, potassium supplement for hypokalemia)

    - Results in any out of range laboratory value that in the site investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile

All AEs observed during the study will be reported on the CRF (found in the Forms Packet). All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study informed consent form through the last visit and for 30 days after last dose. Serious AEs will be collected for 30

days after the last dose, or any time if the investigator considers it related to study drug. After the 30 days, only peripheral neuropathy AEs need to be collected.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

It is the responsibility of the site investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Every effort must be made by the site investigator to categorize each AE according to its severity and its relationship to the study treatment.

10.5 Serious adverse events and other events of interest

To determine if an adverse event is a serious adverse event, the following criteria must be used. In addition, all adverse events reported using CTCAE classification and graded as 4 or 5 are to be considered serious.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (*i.e.*, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantially disrupts the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

In addition to the above, other events of interest include pregnancy or exposure to study drug through breastfeeding; and AEs associated with study drug overdose, misuse, abuse, or medication error. These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Death, hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer. [**Note:** Disease progression is a study endpoint and should not be captured in the CRF as per the guidelines for disease progression.]

The criteria for assessing severity are different than those used for seriousness (see Serious Adverse Events and Other Events of Interest for the definition of an SAE). Serious AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the Serious Adverse Event Form. The definitions are as follows:

Mild - Discomfort noticed, but no disruption of normal daily activity
Moderate - Discomfort sufficient to reduce or affect normal daily activity
Severe - Incapacitating, with inability to work or to perform normal daily activity

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly or probably attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.6 SAE reporting requirements for the IND agent (eribulin mesylate)

Note: Treatment related SAEs for paclitaxel must be reported by submitting form MedWatch 3500A to the FDA.

[redacted]

The Serious Adverse Event reports must be submitted **within 24 hours** using the Eisai Clinical Study Report Form for Serious Adverse Events & Events of Special Interest (found in the Forms Packet) by following the instructions outlined.

An AE that occurs on a treatment arm using an investigational agent or intervention under an IND must be assessed in accordance with the guidelines for investigational agents. Where indicated, a report must be submitted.

All SAEs occurring ≤30 days after the final dose of study treatment, regardless of causality assessment, **must be reported on a completed SAE form by fax as soon as possible, but no later than 24 hours after awareness. Fax the form to the ACCRU SAE Coordinator at** [redacted] All SAEs must be followed to resolution, or if resolution is unlikely, to stabilization.

Any SAE occurring >30 days after the final dose of study treatment and judged by the site investigator to be related to the study treatment must be reported to ACCRU regardless of the length of time that has passed since study completion. **Deaths and life-threatening events should be reported within 24 hours by faxing the completed SAE form.** The detailed contact information for reporting of SAEs is provided in the Investigator File.

10.6.1 Reporting guidelines

10.6.1.1 For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator File.

10.6.1.2 It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the site investigator's assessment of causality.

10.6.1.3 SAEs need to be reported at each occurrence.

10.6.1.4 Any follow-up information received on SAEs should be forwarded within 24 hoursof its receipt. If the follow-up information changes the site investigator's assessment of causality, this should also be noted on the follow-up SAE form.

10.6.1.5 Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and any supplementary documents requested by ACCRU.

10.6.1.6 The site investigator should notify his/her IRB/IEC of the occurrence of the SAE, in writing, in accordance with local requirements. A copy of this communication must be forwarded to ACCRU.

10.6.2 Death

10.6.2.1 Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND, requires SAE reporting within 24 hours.

10.6.2.2 Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires SAE reporting within 24 hours.

10.6.2.3 Reportable categories of death including the following:

- Death attributable to a CTCAE term.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

10.6.2.4 Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.6.3 Secondary malignancy

10.6.3.1 A secondary malignancy is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

10.6.3.2 All secondary malignancies that occur following treatment with an agent under an IND/IDE are to be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, Acute Myelogenous Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

10.6.3.3 Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.6.4 Second malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require only routine reporting.

10.6.5 Reporting of pregnancy

10.6.5.1 Any pregnancy where the estimated date of conception occurs either prior to the study termination visit or within 90 days of the last study treatment must be reported. If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. An induced abortion or a spontaneous abortion is considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs).

10.6.5.2 Pregnancies must be reported as soon as possible but no later than 24 hours by fax or email. The contact information for the reporting of pregnancies is provided in the Investigator File. The Pregnancy Report Form (see Forms Packet) must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than 1 business day.

10.6.5.3 A subject who becomes pregnant must be withdrawn from the study.

10.6.6 Reporting of Other Events of Interest: Overdose

10.6.6.1 Study drug overdose >10% is the accidental or intentional use of the drug in the amount higher than the starting dose being studied.

10.6.6.2 Any study drug overdose during the study should be noted on the CRF (AE Log found in the Forms Packet).

10.6.6.3 All AEs associated with an overdose should both be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of SAEs, even if the events do not meet serious criteria. If the AE associated with an overdose does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as non-serious on the SAE form and the Adverse Event CRF.

10.6.7 Additional instructions

10.6.7.1 Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via expedited mechanisms if the event occurs following treatment on a trial under an IND.

10.6.7.2 Use the ACCRU protocol number and the protocol-specific patient ID provided during trial registration on all reports.

10.6.7.3 **Mayo Clinic Cancer Center (MCCC) Institutions:** Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the ACCRU Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the ACCRU SAE Coordinator for submission to Eisai Inc.

10.6.7.4 **Non-Mayo ACCRU sites:** Once the ACCRU SAE Coordinator receives the report via fax, the ACCRU SAE Coordinator will forward a copy of the above expedited reports to Eisai Inc. at [redacted] The ACCRU SAE Coordinator will forward to [redacted] as appropriate. The ACCRU IND Coordinator will assist the investigator in notifying the FDA if required.

10.7 Other Required Reporting for routine CRFs

10.7.1 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse Event/Symptoms	Baseline	Each evaluation
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	Aspartate aminotransferase increased	X	X
	Alanine aminotransferase increased	X	X
	Blood bilirubin increased	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal disorders	Nausea	X	X
	Vomiting	X	X
	Constipation	X	X
Skin and subcutaneous tissue disorders	Alopecia	X	X
Nervous systems disorders	Peripheral sensory neuropathy	X	X
Blood and lymphatic system disorders	Anemia	X	X
Immune system disorders	Allergic reaction	X	X
Psychiatric disorders	Depression	X	X
	Insomnia	X	X

Note: For this trial ALL adverse events (not just AEs listed in the table) will be collected by date of occurrence regardless of greatest grade or nadir event. A reasonable effort should be made to collect a resolution date for those patients that discontinue treatment with peripheral neuropathy as an AE.

10.7.2 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (*i.e.*, compliance with Test Schedule in Section 4.0).

10.8 PRO-CTCAE administration and data collection

Participants will be registered into the PRO-CTCAE IVRS system and trained to self-report by local study personnel, and will complete a baseline PRO-CTCAE self-report. Subsequently, throughout trial enrollment, weekly, on a day/time selected by the each patient, the patient will be asked to call in to the PRO-CTCAE telephone system and self-report 11 selected symptoms (fatigue, nausea, vomiting, diarrhea, constipation, insomnia, sensory neuropathy, mucositis, pain, anorexia, alopecia) assessed using 20 items (shown in APPENDIX V). The PRO-CTCAE system is hosted and maintained on servers at the NCI and has undergone rigorous security and privacy assessment per NCI requirements. The average length of this call is <5 minutes. Patients who do not call in will receive an automated reminder call. If there is no response to the reminder call, an automatic email notification will be sent to a central PRO-CTCAE Coordinator at MSKCC, who will then attempt to reach the patient (directly or through the local site depending on site preferences or requirements) to conduct the questionnaire and assess reasons for non-compliance.

When patients report severe symptoms, an automated email notification will be sent to local study personnel and local clinical staff.

At each visit requiring clinical AE grading for a given patient, the site will print a customized “shared” patient-clinician AE reporting form, from the PRO-CTCAE system. The form will automatically include that patient’s previously self-reported PRO-CTCAE responses. Clinicians will then record on this customized AE form the clinical CTCAE grades. Additional questions on this form will ask whether the AE form was used at each assessment, whether the patient’s PRO-CTCAE responses were seen and/or used by the individual providing the clinical grades, and whether the patient’s PRO-CTCAE responses impacted the clinical grading of AEs (if they were seen and/or used by the individual providing the grades). All of these questions from the form will then be entered by site staff into Medidata Rave (along with all other case report forms; standard source documentation at sites will be required for all case report forms including the AE form).

After 12 weeks, each participating patient will be given a paper-based questionnaire at a study visit in clinic to assess satisfaction and the usability of the PRO-CTCAE system. A questionnaire will also be administered to site staff and clinicians to assess satisfaction and usability of the PRO-CTCAE system.

As noted above, at the time of the initiation of this trial, the PRO-CTCAE will be available via the NCI-hosted IVRS in English and Spanish. Other languages will not yet be supported, and therefore patients without verbal fluency in one of these languages will not be eligible for this correlative study. We will track the number of patients who are ineligible to participate in this correlative study due to language. We will also track the number of patients who refuse to participate in this correlative study, and the reasons for refusal.

All participating patients will also be asked to complete the EORTC QLQ-CIPN20

questionnaire (paper form; shown in APPENDIX IV) prior to initiating study treatment, once per cycle (on day 1 of cycle 2 and beyond), and at the discontinuation of treatment. These data will be used to provide further validation of the PRO-CTCAE sensory neuropathy items and to compare patient-reported neurotoxicity between treatment arms. The EORTC QLQ-CIPN20 is a validated questionnaire (2, 3) assessing peripheral neuropathic side-effects of chemotherapy over the past week using 20 items each rated by the patient on a 1 (not at all) to 4 (very much) integer scale. The scoring algorithm provided by the scale developers will be used three scales: sensory scale, motor scale, and autonomic scale.

11.0 Treatment Evaluation Using RECIST Guidelines[48]

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline. [**Note:** See the footnote for the table regarding measureable disease in Section 11.4.4, as it pertains to data collection and analysis.]

11.1 Schedule of evaluations: for the purposes of this study, patients must be reevaluated every 12 weeks (+/-7 days).

11.2 Definitions of measurable and non-measurable disease

11.2.1 Measurable Disease

11.2.1.1 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.2.1.2 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (*e.g.*, skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.2.1.3 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 0.5 cm).

11.2.1.4 Tumor lesions in a previously irradiated area are not considered measurable disease unless there is radiographic evidence of progression after irradiation.

11.2.2 Non-Measurable Disease

11.2.2.1 All other lesions (or sites of disease) are considered non-measurable lesions and include the following: small lesions (longest diameter <1.0 cm for all lesions other than pathologic lymph nodes, which are ≥1.0 cm and <1.5 cm in the short axis), bone metastases, pleural effusions, pericardial effusions, ascites, inflammatory breast disease,

leptomeningeal disease, lymphangitis pulmonis, lymphangitis cutis, and abdominal masses not followed by CT or MRI.
[**Note:** "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (*i.e.*, normal) and should not be recorded or followed.]

11.2.3 Special considerations for bone metastases

11.2.3.1 Lytic bone lesions or mixed lytic-blastic bone lesions with an identifiable soft tissue component that is evaluable by cross sectional imaging (*i.e.,* CT or MRI) may be considered measurable disease if the soft tissue component meets the definition of measurability as described above.

11.2.3.2 Blastic bone lesions are considered non-measurable disease.

11.3 Guidelines for the evaluation of measurable disease

11.3.1 Measurement methods

11.3.1.1 All measurements should be recorded in metric notation (*i.e.*, decimal fractions of centimeters) using a ruler or calipers.

11.3.1.2 The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

11.3.1.3 Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable modalities for measurable disease:

11.3.2.1 CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

11.3.2.2 MRI: As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.3.2.3 PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

11.3.2.4 Chest X-ray: Lesions on chest x-ray are acceptable for the documentation of new lesions, but not for the monitoring of measurable disease.

11.3.2.5 Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.3.2.6 FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible "new" disease. A "positive" FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered "negative." New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (*i.e.*, additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.3.3 Measurement at follow-up evaluation:

11.3.3.1 In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks (+/- 7 days) (see Section 11.4.4).

11.3.3.2 The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to

differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.3.3.3 Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (*e.g.*, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of effect

11.4.1 Target lesions and target lymph nodes

11.4.1.1 Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.2.1)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

[**Note:** If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.]

11.4.1.2 Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node), which can be measured reproducibly should be selected.

11.4.1.3 Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

11.4.1.4 Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

11.4.1.5 The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.4.2 Non-target lesions and non-target lymph nodes

11.4.2.1 Non-measurable sites of disease (Section 11.2.2) are classified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.4.3.3.

11.4.3 Response criteria

11.4.3.1 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without remeasuring target lesions and target lymph nodes.

[**Note:** Non-target lesions and non-target lymph nodes should be evaluated at each assessment.]

11.4.3.2 Evaluation of target lesions

a. Complete Response (CR): All of the following must be true:

i. Disappearance of all target lesions.

ii. Each target lymph node must have a reduction in the short axis to <1.0 cm.

b. Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.4.1).

c. Progression (PD): At least one of the following must be true:

i. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

ii. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

iii. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

d. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.4.3.3 Evaluation of non-target lesions including non-target lymph nodes

a. Complete Response (CR): All of the following must be true:

i. Disappearance of all non-target lesions.

ii. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

b. Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

c. Progression (PD): At least one of the following must be true:

i. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

ii. Unequivocal progression of existing non-target lesions and non-target lymph nodes. [**Note:** Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.]

iii. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.4 Overall objective status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease.

Criteria for patients with measurable disease +/- non-measurable disease:

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.4.3.1
** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

Criteria for patients with non-measurable disease only:

Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated*	No	Not Evaluated (NE)
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*See Section 11.4.3.1

12.0 Descriptive Factors – Not applicable

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Patients who achieve a CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 A patient is deemed *ineligible* if after registration it is determined that the patient did not satisfy all eligibility criteria for study entry at the time of registration. The patient will go directly to the event-monitoring phase of the study.

13.4 If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.5 If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A *major violation* occurs if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated such that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. The patient will go directly to the event-monitoring phase of the study, and event monitoring will be required per Section 18.0 of the protocol.

13.8 Follow-up procedures

13.8.1 Survival data will be collected every 12 weeks after the Off-treatment Visit. This data may be collected through a clinic visit, phone call, or written communication. In addition to survival follow-up, the following assessments will be conducted during the Follow-Up Period:

13.8.1.1 Record all the subsequent anti-cancer therapies in the CRF.

13.8.1.2 Subjects with new onset of peripheral neuropathy during the study, or deterioration of pre-existing peripheral neuropathy on study, will be followed until resolution to baseline, the start of a new anti-cancer treatment, or death.

13.8.1.3 For subjects who have discontinued study treatment without disease progression, tumor assessments will be performed at the same frequency as during the Treatment Cycles (*i.e.*, every 12 weeks from the date of randomization) or sooner, if clinically indicated, until disease progression, or before another anti-cancer therapy is initiated. Assessments will utilize the same methodology and acquisition techniques as were used for the Screening Period assessments. Bone scans will be performed every 24 weeks in all subjects, or sooner, if clinically indicated.

13.8.2 The site and date of first new metastasis will be captured for all subjects.

13.8.2.1 For subjects who discontinue protocol directed therapy due to progression with a new site of metastasis, the information will be collected at the time of disease progression on eribulin or paclitaxel.

13.8.2.2 For subjects who discontinue protocol directed therapy due to progression without a new site of metastasis (*i.e.,* disease progression documented by an increase in the size of known lesions), the information will be collected in conjunction with monitoring for overall survival.

13.8.2.3 For subjects who discontinue protocol directed therapy without disease progression and eventually develop a new metastasis, the information will be collected as appropriate during the Follow-Up period.

13.8.3 If a subject fails to attend a scheduled assessment, the PI or designee will make every attempt to contact the subject to determine their status. All contact attempts will be recorded in the subject's medical notes.

13.8.4 Subjects will only be judged as lost to follow-up if documentation is provided of the following:

13.8.4.1 Three unsuccessful attempted telephone contacts, at least 1 month apart for a period of at least 4 months, with the subject, the subject's family, or the primary care (family) doctor [**Note:** The last contact attempt must be at least 4 months after the subject failed to attend a scheduled assessment.]

13.8.4.2 Documented search of [redacted]

13.8.5 If all attempts fail to confirm the subject's status, the subject will be considered as "lost to follow-up", and this will be recorded in the CRF.

14.0 Body Fluid Biospecimens

14.1 Summary table of research blood and blood products to be collected

Biospecimen	Mandatory or optional	Timing	Correlative science justification	Information on submission
EDTA (whole blood)	Mandatory	Serial draws	Pharmacogenetic studies and optional banking (Appendix VI)	Section 14.2
SST (serum)	Mandatory	Serial draws	Circulating marker analyses and optional banking (Appendix VI)	Section 14.2
CellSave (whole blood)	Mandatory	Serial draws	Circulating marker analyses and optional banking (Appendix VI)	Section 14.2

14.2 Blood/Blood Products Handling

14.2.1 **Kits are required for this study.**

(Mayo Clinic Rochester may use Study Refer cards.)

14.2.1.1 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.2.1.2 Participating institutions obtain kits by submitting a completed Supply Order Form (found in the Forms Packet) via fax. A small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Additional kits will be supplied on request. Unused kits should not be sent back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource.

14.2.1.3 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.2.1.4 Kits will not be sent via rush delivery service unless the participating institution provides its own FedEx® account or alternate billing number. **ACCRU will <u>not</u> cover the cost for rush delivery of kits.**

14.2.2 Samples should be collected Monday – Thursday. However, if the subject can only be seen on Fridays, please contact the Biospecimen Resource Manager for additional instructions (see protocol resource pages for contact information).

14.2.3 Specimen tube(s) must be labeled with the protocol number, ACCRU patient ID number, time and date of the blood draw.

14.2.4 Blood/blood products must be collected and shipped according to specific instructions provided in the kit and the table below.

Collection tube	Volume to collect per tube (number of tubes to collect)	Blood product being processed and submitted	Timepoints			Additional processing required at site	Storage and shipping conditions[1]
			Baseline	Every 12 weeks	End of treatment		
EDTA tube (purple top)	10 mL (1)	Whole blood for WBC, plasma	X	X	X	Yes	Frozen on dry ice
SST tube (marble top)	8.5 mL (2)	Serum	X	X	X	Yes	Frozen on dry ice
CellSave tube (yellow/purple)	10 mL (2)	Whole blood for circulating tumor cells	X	X	X	None	Ambient temperature

1. See Section 14.2.5 for detailed shipping instructions.

14.2.5 Shipping

14.2.5.1 Verify that ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission Form into the remote data entry system within 7 days after specimen collection (see Forms Packet).

14.2.5.2 Specimens collected in the CellSave tubes should be shipped at ambient temperature on the same day they are drawn.

14.2.5.3 Specimens collected in the EDTA and SST tubes should be processed as directed in the kit instructions, stored at -20ºC for 24 hours, and then shipped frozen with plenty of dry ice. The kit instructions include information on places to obtain dry ice if not available on site.

14.2.5.4 Samples should be shipped to BAP Freezer Mondays – Thursdays according to kit instructions. Samples should not be sent on weekends or just prior to federal holidays. (If samples can only be shipped on Fridays, please contact the Biospecimen Resource Manager for additional instructions.)

14.2.5.5 The BAP kits include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping the specimens to BAP Receiving.

14.2.5.6 BAP Freezer will receive the samples and immediately forward specimens to the [redacted]

14.2.6 BAP Shared Resource will process the specimens.

14.2.6.1 DNA will be extracted from white blood cells, divided into aliquots, and stored at -70ºC by BAP, according to patient consent information. One aliquot of DNA will be provided to [redacted] to validate polymorphisms in *FGD4, EPHA5,* and *FZD3* as predictors of peripheral neuropathy.

14.2.6.2 Serum will be divided into aliquots and stored at -80ºC by BAP, according to patient consent information. Two aliquots will be provided to Dr. Minetta Liu's laboratory at the Mayo Clinic to quantify nucleosomes and the M30 neo-epitope as predictors of treatment benefit.

14.2.6.3 As part of ongoing ACCRU research, we will collect whole blood, white blood cells, DNA, serum, and plasma for future research studies, according to patient consent information. Samples will be stored by BAP until specific analyses are identified and may be used for exploratory biomarker analyses, validation studies, or potential diagnostic development. As protocols are developed, they will be presented through ACCRU for IRB review and approval.

14.2.6.4 Whole blood collected in the CellSave tubes will be provided directly to Dr. Minetta Liu's laboratory at the Mayo Clinic to enumerate and phenotype circulating tumor cells. Any CTCs collected for enumeration will be stored at -20ºC by Dr. Liu's laboratory, according to patient consent information. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

14.3 Return of genetic testing research results

The results generated by the proposed genetic analyses are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND number 126070

Investigator brochure

- The IB will be available on the ACCRU web site.

15.1 Eribulin mesylate

15.1.1 Eisai Inc. will package eribulin mesylate as open-label supplies. Eribulin mesylate will be supplied to the sites in glass vials containing 1.0 mg eribulin mesylate in 2.0 mL of solution. Eribulin mesylate is a clear, colorless, and sterile solution packaged in a glass vial.

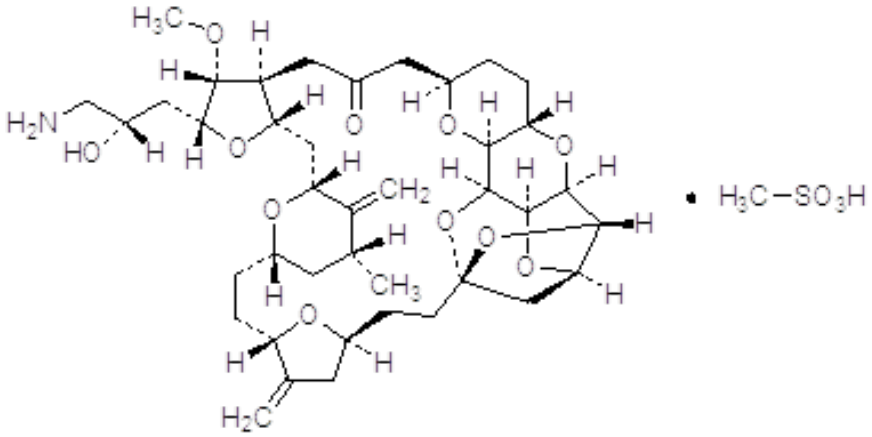
Excipients of the eribulin mesylate formulation are ethanol, hydrochloric acid, sodium hydroxide, and water for injection.

Chemical Name, Structural Formula of Eribulin mesylate

- Test drug code: E7389
- Generic name (INN): eribulin / (USAN): eribulin mesylate
- Chemical name (USAN/INN):

(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one methanesulfonate (salt)

Chemical Structure:



- Molecular formula: $C_{41}H_{63}NO_{14}S$ ($C_{40}H_{59}NO_{11}$ · CH_4O_3S)
- Molecular weight: 826.00

15.1.2 Labeling for Eribulin mesylate

Eribulin mesylate will be labeled in accordance with regulatory compliance of the participating countries and translated into the required language(s) for each country.

The following information will be provided:

- For clinical trial use only
- Name and address of Eisai Inc.
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

15.1.3 Storage Conditions

Eribulin mesylate will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The site investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

Beginning in Fall 2018, a new formula of eribulin will be available which will allow for room temperature storage. Monitor closely when drug is received on site to verify which formulation is received and follow storage recommendations as described within the shipment.

Eisai #	Dosage/Form	Storage Conditions	Total Allowable Excursions
E7389 (eribulin mesylate)	E7389 (eribulin mesylate, 1 mg/vial) **(Refrigerated formula)**	2°C - 8°C	Not less than 2°C or greater than 25°C for a cumulative period of up to 14 days. Temperature excursion down to 0°C for no more than 24 hours.
E7389 (eribulin mesylate)	E7389 (eribulin mesylate,1 mg/vial) **(Ambient formula)**	25°C	Excursions permitted from 15°C to 30°C (59°F to 86°F). Do not freeze or refrigerate.

15.1.4 Preparation

Eribulin mesylate should not be mixed with other drugs or dextrose containing solutions.

15.1.5 Administration

Eribulin mesylate is administered as an IV infusion over 2-5 minutes on days 1 and 8 of each 21 day cycle of therapy.

15.1.6 Potential Drug Interactions

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers, or P-glycoprotein (P-gp) inhibitors. Clinically meaningful differences in exposure (AUC) were not observed when eribulin mesylate was administered with or without ketoconazole and with or without rifampin.

Eribulin mesylate does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 enzymes, or induce CYP1A2, CYP2C9, CYP2C19, or CYP3A4 enzymes at relevant clinical concentrations. Eribulin mesylate is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes.

15.1.7 Toxicities (Nursing Guidelines)

15.1.7.1 Cytopenias are common with neutropenia and anemia being most common. Monitor blood counts prior to each dose.

15.1.7.2 Peripheral neuropathy is common.

15.1.7.3 Warn patients of probable alopecia.

15.1.7.4 Monitor hepatic panel.

15.1.7.5 Gastrointestinal side effects seen include but are not limited to nausea, constipation, dyspepsia, abdominal pain, stomatitis, dry mouth, dysgeusia, diarrhea and mucositis.

15.1.7.6 Monitor renal function.

15.1.8 Drug procurement

Eisai Inc. will supply eribulin to McKesson Specialty Pharmacy. Each participating ACCRU treating location will order eribulin from McKesson Specialty Pharmacy by faxing the Drug Order Request Form (found in the Forms Folder on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of eribulin and will use the Drug Order Request Form to order additional supplies as needed.

All used, unused, and expired eribulin must be destroyed by incineration only, and cannot be destroyed until after reconciliation/accountability has been performed.

15.2 Paclitaxel

15.2.1 Please refer to the FDA-approved package insert for paclitaxel for product information, extensive preparation instructions, and a comprehensive list of adverse events.

15.2.2 Availability

Paclitaxel is commercially available in a concentration of 6 mg/ml in 5 mL, 16.7 mL, 25 mL and 50 mL multidose vials. Each mL of solution also contains 527 mg of polyoxyethylated castor oil and dehydrated alcohol, USP. Please refer to the FDA approved package insert for complete product information.

15.2.3 Preparation

Paclitaxel must be diluted prior to administration with 0.9% sodium chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to1.2 mg/mL. Paclitaxel should be prepared and stored in glass, polypropylene, or polyolefin containers due to leaching of DEHP [di-(2ethylhexyl) phthalate] plasticizer from polyvinyl chloride (PVC) containers. Non-PVC containing tubing and connectors should also be used. Paclitaxel should be administered through an in-line < 0.22 micron filter.

15.2.4 Storage and Stability

Intact vials should be stored at controlled room temperature (20°-25°C; 68°-77°F) in the original package to protect from light, and remain stable until the expiration date on the label. Refrigeration does not adversely affect stability. Upon refrigeration components in the paclitaxel vial may precipitate, but will re-dissolve upon reaching room temperature with little or no agitation. Diluted 0.3-1.2 mg/mL solutions are stable for up to 27 hours at room temperature under normal room lighting. Although solutions may be chemically stable for longer periods in some situations, precipitation may occur unpredictably. The mechanism of this precipitation has not been determined.

15.2.5 Administration

Paclitaxel, 90 mg/m^2 administered as an IV infusion over 1 hour, on days1, 8, and 15 of each 28 day cycle of therapy. Please see Section 7.1.1 for premedication regimen.

15.2.6 Toxicities (Nursing Guidelines)

15.2.6.1 Hypersensitivity reactions are common. They are thought to be due, at least in part, to the Cremophor EL® vehicle. Reactions generally occur within the first hour of administration. The most common symptoms observed in severe reactions include dyspnea, flushing, chest pain and tachycardia. Patients should be pretreated to prevent hypersensitivity reactions.

15.2.6.2 Cardiovascular events observed with paclitaxel include hypotension and bradycardia; typically neither discontinuation of paclitaxel nor specific therapy for the event is required.

15.2.6.3 The frequency and severity of neurologic events are dose-dependent. Peripheral neuropathy is rarely severe and may be the cause of paclitaxel discontinuation in 1% of patients. Sensory symptoms usually improve or resolve within several months of completion of treatment. Serious neurologic events such as grand mal seizures, syncope, ataxia and neuroencephalopathy are rare. Pre-existing neuropathies are not a contraindication to treatment with paclitaxel.

15.2.6.4 The most common gastrointestinal toxicities, which include nausea, vomiting, diarrhea and mucositis, are typically mild or moderate in severity. Mucositis occurs more frequently with a 24 hour infusion than with shorter infusion schedules.

15.2.6.5 Although 60% of all patients experience arthralgia and myalgia, there is no consistent relationship between the dose or schedule of paclitaxel and the frequency of these events. The symptoms, which usually begin 2 or 3 days after paclitaxel treatment, are generally transient. Infusion site reactions are more common with 24 hour infusions. They are typically mild, consisting of erythema, tenderness, skin discoloration or swelling at the infusion site. Paclitaxel is generally considered to be an

irritant, but isolated cases of more severe tissue damage following extravasation have been reported.

15.2.6.6 Almost all patients receiving paclitaxel experience alopecia. Nail changes are uncommon. Occasionally edema is seen, usually of mild severity.

15.2.7 Drug procurement:

Sites will obtain the paclitaxel commercially.

16.0 Statistical Considerations and Methodology

16.1 Overview of the statistical design

This is a two arm Phase III trial in first- and second-line HER2 negative patients with locally recurrent or metastatic breast cancer. Patients will be randomized between the experimental and control arm with equal allocation (1:1) within strata defined by prior adjuvant taxanes (yes/no), hormone receptor status (ER or PgR positive/ER and PgR negative), and line of therapy (1st/2nd). Subjects will continue protocol directed therapy until documentation of disease progression, development of unacceptable toxicity, or withdrawal of consent. Those who discontinue study treatment without radiological progression will be followed with repeat imaging studies every 12 weeks. All subjects will be followed until death, withdrawal of consent, or study termination.

The primary endpoint at the time of initial study design was overall survival (OS) with a target accrual of 910 patients to test for the superiority of eribulin mesylate (experimental arm) over standard weekly paclitaxel (control arm).

Subsequent changes in standard practice patterns have had a significant impact on accrual (*e.g.,* the FDA approval of palbociclib in combination with first and second line endocrine therapy) and the availability of first and second line clinical trials for advanced breast cancer (*e.g.,* studies with checkpoint inhibitors for patients with hormone receptor negative, HER2 negative breast cancer). The decision was therefore made to reconfigure objectives with a focus on toxicity as related to PRO-CTCAE and rs7349683 in *EPHA5*, leading to an adjusted target accrual of 200 patients.

16.2 Endpoints

The primary endpoints are (i) to demonstrate that patient-reported PRO-CTCAE data will be able to detect differences in symptoms between participants treated with eribulin and standard weekly paclitaxel at 12 weeks; and (ii) to validate rs7349683 in EPHA5 as a predictor of peripheral neuropathy from treatment with a microtubule targeting agent (*i.e.*, eribulin or paclitaxel). The secondary endpoints include the following: overall survival (OS); progressive free survival (PFS; defined as the time from randomization to progression under RECIST 1.1 criteria, or death due to any cause, whichever occurs first); objective tumor response as defined by RECIST 1.1; duration of tumor response; time to treatment failure; treatment-related toxicity; the clinical value and feasibility of collecting patient-reported symptom toxicity information via PRO-CTCAE in patients receiving eribulin versus standard weekly paclitaxel. In addition, the PRO-CTCAE sensory neuropathy items will be validated specifically and compared to patient-reported

neurotoxicity between arms using the EORTC QLQ-CIPN20 instrument.

16.3 Sample size and power calculations

16.3.1 PRO-CTCAE

For the primary endpoint, the patient-reported maximum score (post baseline) across PRO-CTCAE items for each patient will be computed over the first 12 weeks and compared between arms using a two-sample independent samples t-test. Assuming 85% participation rate and a total accrual of 200 patients, the detectable effect size with 80% and 90% power is 0.43 and 0.50 standard deviation units using a two-sided α=0.05. This study will be able to detect a small (0.2 standard deviations) to moderate (0.5 standard deviations) effect size difference between arms.[49] Subsequent analysis will compare the maximum score for each individual item between arms. P-values adjusted using Hochberg's step-up method will additionally be computed to aid in interpretation across the 20 individual items.

16.3.2 rs7349683 in *EPHA5*

The primary statistical objective for the pharmacogenetic companion of this study is to validate a germline *EPHA5* polymorphism (rs7349683) implicated in drug induced peripheral neuropathy.[14,19,20] The primary statistical endpoint will be the cumulative dose level triggering a grade 2 or higher neuropathy event. Power calculations assume a modest accrual goal of 175-300 patients, evaluable samples from 90% of these patients, and an expected proportion of the population that is self-reported Caucasian as 0.81. Under these assumptions, the expected number of patients available for the pharmacogenomic questions will therefore be 128-219 (64-110 for each arm). To illustrate the power, we will focus on neuropathy triggered within the first six cycles. The patients who do not experience an event will be censored at the cumulative dose level received during the six cycles. The Cox score test will be used to test the association between the cumulative dose level triggering toxicity and the genotype. The goal is to validate the *EPHA5* rs7349683 SNP. The relative minor allele frequency (MAF) for rs7349683 is estimated as 0.36 and the proportion of patients developing CIPN within six cycles is expected to range from 40-50%. The analyses are powered for an additive risk model. The hypothesis will be tested at the one-sided 0.05/3 level. The minimum effect size detectable with a power of 0.8 at this level is shown for sample sizes of 175-300 patients. These effect sizes are similar to the values reported earlier by us and others.[14,19,20]

Sample Size	HR	
	40% Incidence	50% Incidence
175	1.63	1.80
200	1.60	1.70
225	1.55	1.63
250	1.50	1.60
275	1.45	1.58
300	1.43	1.55

The analysis will be more complicated as treatment continues until progression. Therefore, the number of cycles received is subject to an informative censoring mechanism. The pharmacogenetics investigator team is deeply involved in the development of the requisite methodology in the context of CALGB 40502 and will apply the finalized approach to data generated from this study. The analyses will be stratified by regimen (eribulin or paclitaxel).

16.4 Stopping rules

The stopping rule specified below is based on safety profiles reported in related clinical trials: EMBRACE (eribulin *versus* treatment of the physician's choice in patients with $\geq$2 previous regimens for advanced/metastatic breast cancer), BOLD 301 (eribulin *versus* capecitabine as first, second, or third line treatment for advanced/metastatic breast cancer, and CALBG 40502 (paclitaxel *versus* nab-paclitaxel *versus* ixabepilone, each +/- bevacizumab, as first line therapy for locally recurrent / metastatic breast cancer). Since the hematologic safety profiles differ greatly between the eribulin and paclitaxel, the adverse event stopping rule is split into two parts for hematologic adverse events. The stopping rule was determined by taking the observed adverse event rates in these trials and calculating the 95% upper bound. The 95% upper bound was used as the cut point in the stopping rule.

We note that the adverse event stopping rule may be adjusted at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may also choose to suspend accrual because of unexpected adverse events that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment *(i.e.*, an adverse event with attribution specified as "possible", "probable", or "definite") and that satisfy the following:

Hematologic events:

- If more than 50% of the treated patients on the eribulin arm experience a grade 3 or higher neutropenia adverse event.

- If more than 23% of the treated patients on the paclitaxel arm experience a grade 3 or higher neutropenia adverse event.

Non-hematologic events:

- If more than 7% of the treated patients in either the eribulin or paclitaxel arm experience a grade 4 or higher non-hematologic adverse event.

  In addition, we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Study monitoring

The efficacy and toxicity data for this study will be reviewed at least semiannually by the Mayo Clinic Data Safety Monitoring Board (DSMB). Early termination of accrual will be considered if there is evidence of unacceptable toxicity.

16.6 Statistical analysis of secondary and correlative objectives

Analyses of all efficacy endpoints will be intention-to-treat, such that patients will be included in the arm to which they were randomized irrespective of treatment received. Further, patients who withdraw for toxicity, who withdraw consent for continued treatment, or who start off-protocol therapy will continue to be followed for overall survival, progression free survival, and time to new metastasis. Patients who withdraw consent to be followed will be censored. Analysis of objective response will be in evaluable patients with measurable disease. Analyses of toxicity will be conducted in the subset of patients to receive eribulin and standard weekly paclitaxel, respectively.

For the time related secondary endpoints (OS, PFS, TTF, and DOR) and exploratory endpoint (new metastasis free survival), survival functions will be summarized using the Kaplan-Meier method according to treatment group. The primary analysis will use the stratified log-rank tests, as described for overall survival. As a secondary analysis we will use a multivariable Cox proportional hazard model to estimate adjusted hazard ratios for eribulin mesylate over standard weekly paclitaxel, study stratification factors, and covariates for known prognostic factors, including disease free interval and visceral *versus* non-visceral metastases.

For the secondary endpoints of objective response and treatment-related toxicity, the primary analysis will use the Cochran-Mantel-Haenszel chi-squared test with study stratification factors. Secondary analyses will use logistic regression to test differences in proportions while controlling for the covariates listed above.

All tests of secondary objectives will use a two-sided Type I alpha of 0.05, and point estimates will be reported with 95% confidence intervals. Analyses of correlative objectives will be performed as described in Appendix VI.

Additional analyses will include the previously described analysis conducted over the first 24 weeks; a comparison of the incidence of patient-reported maximum score ≥3 (*i.e.*, severity reported as "severe" or "very severe"; frequency reported as "frequently" or "almost constantly"; or interference reported as "quite a bit" or "very much") between arms through 12 and 24 weeks using chi-squared testing for each item; and a comparison of the time to patient-reported score ≥3 between arms using Kaplan-Meier and log-rank analyses. Further, these three endpoints (maximum score/grade, incidence of score/grade ≥3, and time to score/grade ≥3) will be compared between patient- and clinician-report

overall and within arms using appropriate paired analyses.

The PRO-CTCAE sensory neuropathy items will be further validated by computing Pearson correlations between each item and the EORTC QLQ-CIPN20 sensory scale score at baseline, 12 and 24 weeks. Note, additional secondary analysis on the EORTC QLQ-CIPN20 scale scores will be performed to further describe differences between arms using analysis of covariance to compare maximum score during treatment between arms while adjusting for baseline score; analysis of covariance to compare scores at 12 and 24 weeks between arms while adjusting for baseline score; and pattern mixture models to compare neuropathy scale scores over time between arms while accounting for informative drop-out.

For analyses related to the secondary hypotheses, descriptive statistics will be used to characterize the proportion of patients in the clinical trial who participate in the PRO-CTCAE correlative study; the proportion of participating patients adhering to scheduled self reports at each time point during the trial; frequency of backup calls; success of backup calls for questionnaire completion; and reasons for missed reports. Patient participants will be asked to complete a satisfaction survey to assess their experiences using the PRO-CTCAE IVRS system. In addition, a CRF will be administered to all participating CRAs/research nurses and clinical investigators at sites regarding technical difficulties encountered and perceived value of the patient reports in clinician reporting and clinical management. In order to assess the feasibility of implementing the PRO-CTCAE at sites, study personnel at 25 selected participating sites will be contacted and invited to participate in semi-structured interviews about their experiences with this new system. The purpose of these interviews will be to explore the barriers and challenges to widespread adoption of the PRO-CTCAE system for use in phase III clinical trials (including cost, technical issues, and administrative burden). These interviews will be conducted by staff members of the PRO-CTCAE project who are based at MSKCC, funded by the NCI PRO-CTCAE contract. Interviews will be conducted with CRAs/research nurses as well as with clinical investigators.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary table of tissue biospecimens to be collected

Biospecimen	Mandatory or optional	Timing	Correlative science justification	Information on submission
Formalin-fixed paraffin-embedded (FFPE) tissue[1]	Mandatory[2]	Within 90 days of registration	Tubulin related analyses (Appendix VI)	Section 17.2

1. 15 slides (five micron sections mounted on charged glass slides) may be sent instead if the local Pathology Department refuses to release the FFPE tissue block.
2. If tissue is available, the site must send to ACCRU. If no tissue sample is available, please document on the CRF.

17.2 Paraffin Embedded Tissue Blocks/Slides

17.2.1 One formalin fixed paraffin-embedded (FFPE) tumor tissue block must be sent from the original diagnosis or from the metastatic site with a corresponding H&E slide.

17.2.2 The FFPE tissue block is preferred. However, those **institutions whose Pathology Departments refuse to provide a tissue block** should provide 15 slides (five micron sections mounted on charged glass slides). **Label the slides with the ACCRU patient ID number, accession number, and order of sections.** Every 10th slide (*i.e.*, slides labeled 1 and 10) should be stained with H&E for central review under the Research Base's protocol for assessing tissue quality. The remaining unstained slides will be processed as described in 17.3. **Do not bake or place cover slips on the slides.**

17.2.3 The following materials are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with a corresponding H&E slide (OR 15 unstained slides with corresponding H&E slides)
- Research Tissue Specimen Submission Form
- Surgical Pathology Report
- Operative Report *(optional)*

Note: Please include the ACCRU patient ID number on all materials listed above.

17.2.4 The block/slides must be appropriately packed to prevent damage (*e.g.*, slides should be placed in an appropriate slide container) and placed in an individual plastic bag. The bag must be labeled with the protocol number, ACCRU patient ID number, and patient initials.

17.2.5 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.2.6 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

[redacted]

17.2.7 If a corresponding H&E slide was not submitted with the block/slides, the ACCRU Operations Office will request that one be processed (*i.e.*, cut from the tissue block and H&E stained as appropriate) and forwarded to the Study Pathologist or designee for review under the Research Base's protocol for assessing tissue quality for the proposed correlative studies. If the tumor tissue is too small, assessment of tissue quality will occur at the time the translational studies are performed.

17.3 Study methodology and storage information

17.3.1 BAP Shared Resource will process the specimens.

17.3.1.1 Total RNA and DNA will be extracted, divided into aliquots, and stored at -80ºC by BAP, according to patient consent information.

17.3.1.2 As part of ongoing ACCRU research, we will bank tumor tissue for future research studies, according to patient consent information. Samples will be stored in the ACCRU Central Operations Office (Attn: Pathology Coordinator) until specific analyses are identified and may be used for exploratory biomarker analyses, validation studies, or potential diagnostic development. As protocols are developed, they will be presented through ACCRU for IRB review and approval.

17.3.2 The institutional pathologist will be notified by the ACCRU Operations Office (Pathology Coordinator) if the block may be depleted.

17.3.3 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.4 Return of genetic testing research results

The results generated by the proposed genetic analyses are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

The Data Management Plan (DMP) defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled, and reviewed.

18.1 Submission timetable

Access the RAVE system through the iMedidata portal at [redacted] All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]
Pre-Registration Material(s) –

Case Report Form (CRF)	**Active Monitoring / Treatment Phase** (Compliance with Test Schedule Section 4.0)
Screening Disposition	Complete for all patients who sign an informed consent form

Case Report Form (CRF)	Active Monitoring / Treatment Phase (Compliance with Test Schedule Section 4.0)
Institutional Contact [**Note:** update form as needed[1]]	≤2 weeks after registration

1. Update the CRF to report any changes, as needed.

Initial Material(s) –

CRF	Active Monitoring / Treatment Phase (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
On-Study: Prior Surgery[2]	
On-Study: Prior Radiation[3]	
On-Study: Prior Systemic Therapy[4]	
Adverse Events: Baseline	
RECIST Measurements: Baseline[6]	
Measurements (Non-Measurable Disease Only): Baseline[6]	
Electrocardiogram (ECG): Baseline	
Supporting Documentation: Baseline[1]	
Patient Status: Baseline	
Specimen Submission: Blood (Baseline) (see Section 14.0)	
Pregnancy Test	
Concomitant Medications **Note:** this is a cumulative log; complete at baseline and update as needed[5]	
Medical History and Current Medical Condition **Note:** this is a cumulative log; complete at baseline and update as needed[5]	
Scans and Photographs for Tumor Assessments (SCANS): Baseline	
OP and Path Reports (see Section 17.0)[1]	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet (EORTC QLQ-CIPN20)	≤2 weeks after registration - Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Booklet Compliance– EORTC QLQ-CIPN20	≤2 weeks after registration - This form **must** be completed only if the booklet contains absolutely **NO** patient provided assessment information.
Specimen Submission: Tissue (see Section 17.0)	≤90 days after registration

1. Attach an electronic copy in RAVE on the Supporting Documentation Form. This is in addition to the pathology material requirements for tissue submission (Section 17.0).
2. Form will be required if the On Study form indicates patient had prior surgery.

3. Form will be required if the On Study form indicates patient had prior radiation.
4. Form will be required if the On Study form indicates patient had prior systemic therapy.
5. Update the CRF to report any changes, as needed.
6. Submit either the RECIST Form for measurable disease, or the Measurements Form for Non-Measurable Disease Only, as applicable (do not submit both forms).

Test Schedule Material(s)

CRF	**Active Monitoring / Treatment Phase** (Compliance with Test Schedule Section 4.0)			
	At each evaluation during treatment	Every 12 weeks	At end of treatment	Follow-up/ Observation (every 12 weeks until PD)[13]
Treatment (Intervention) (Eribulin)	X		X	
Treatment (Intervention) (Paclitaxel)	X		X	
Treatment (Intervention): Dose Modifications, Omission and Delays (Eribulin)	X			
Treatment (Intervention): Dose Modifications, Omission and Delays (Paclitaxel)	X			
Adverse Event Log **Note:** this is a cumulative log[5]	X[4]		X[4]	X
RECIST Measurements		X[1]		X
Measurements (Non-Measurable Disease Only)		X[1]		
Patient Status: Treatment (Intervention)	X			
Patient Status: Clinical Follow-up / Observation				X
Supporting Documentation		X[1]		X[1]
Laboratory Tests and Results	X			
Laboratory Tests and Results End of Treatment			X	
Hematology Test and Results	X			
Specimen Submission: Blood		X		
Specimen Submission: Blood End of Treatment			X	
Concomitant	X			

CRF	Active Monitoring / Treatment Phase (Compliance with Test Schedule Section 4.0)			
	At each evaluation during treatment	Every 12 weeks	At end of treatment	Follow-up/ Observation (every 12 weeks until PD)[13]
Medications **Note:** this is a cumulative log[5]				
Patient Questionnaire Booklet[2] (EORTC QLQ-CIPN20)	X		X	
Booklet Compliance[3] (EORTC QLQ-CIPN20)	X		X	
PRO-CTCAE Feedback Survey[2]		X[6]		
Booklet Compliance[3] (PRO-CTCAE)		X		
Patient Reported Adverse Events (PRO-CTCAE) Status[8]	X			X
Non-Protocol: Surgical Procedure[9]				X
Non-Protocol: Radiation[10]				X
Non-Protocol: Systemic Therapy[11]				X
Electrocardiogram (ECG)	X[12]			
Off Treatment			X	
Medical History and Current Medical Condition **Note:** this is a cumulative log[5]	X		X	X
Notice of New Primary[7]				X
Lost to Follow-Up[7]				X
Scans and Photographs for Tumor Assessments (SCANS)		X		X
Consent Withdrawal (choose appropriate withdrawal form)[7]: • QOL Only • Specimen Only • Clin Follow-Up Only • All Follow-Up	X			X

1. Submit either the RECIST Form for measurable disease, or the Measurements Form for Non-Measurable Disease only, as applicable (do not submit both forms). Attach a copy of documentation of response or progression in RAVE on the Support Documentation Form.

2. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
3. This form must be completed **only** if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information.
4. Patient PRO-CTCAE scores should be printed from the PRO-CTCAE web system and provided to the clinician at the time of clinical grading of adverse events during treatment and at end of treatment. See Section 1.6 in Appendix VI.
5. Update the CRF to report any changes, as needed.
6. There will be a 12 week follow-up survey administered one time via booklet.
7. Submit only if applicable.
8. This form will be completed by the Central PRO-CTCAE Project Coordinator, not by the CRA.
9. Form will be required if Follow-Up Form indicates patient had non-protocol surgery not previously reported.
10. Form will be required if Follow-Up Form indicates patient had non-protocol radiation not previously reported.
11. Form will be required if Follow-Up Form indicates patient had non-protocol systemic therapy not previously reported.
12. Form submitted one time only for testing done prior to cycle 2.
13. Follow-up can be discontinued after 2 years if the patient is no longer receiving study treatment. If the patient remains on study treatment as of September 30, 2021, follow-up will be discontinued.

Follow-up Material(s)

CRF	**Survival**				
	Every 3 months until PD	At PD	Every 3 months after PD[7]	Death	At each event occurrence
Supporting Documentation[1]					X
Patient Status: Survival and Disease Status Follow-Up / Event Monitoring	X	X	X	X	
Lost to Follow-Up[3]					X
Notice of New Primary[3]					X
Medical History and Current Medical Condition **Note:** this is a cumulative log[2]	X	X	X	X	
Non-Protocol: Surgical Procedure[4]					X
Non-Protocol: Radiation[5]					X
Non-Protocol: Systemic Therapy[6]					X
Consent Withdrawal (choose appropriate withdrawal form)[3]: •QOL Only • Specimen Only • Clinical Follow-Up					X

CRF	Survival				
	Every 3 months until PD	At PD	Every 3 months after PD[7]	Death	At each event occurrence
Only • All Follow-Up					

1. Attach a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.
2. Update the CRF to report any changes, as needed.
3. Submit only if applicable.
4. Form will be required if Follow-Up Form indicates patient had non-protocol surgery not previously reported.
5. Form will be required if Follow-Up Form indicates patient had non-protocol radiation not previously reported.
6. Form will be required if Follow-Up Form indicates patient had non-protocol systemic therapy not previously reported.
7. Follow-up can be discontinued after 2 years if patient is no longer taking study treatment.

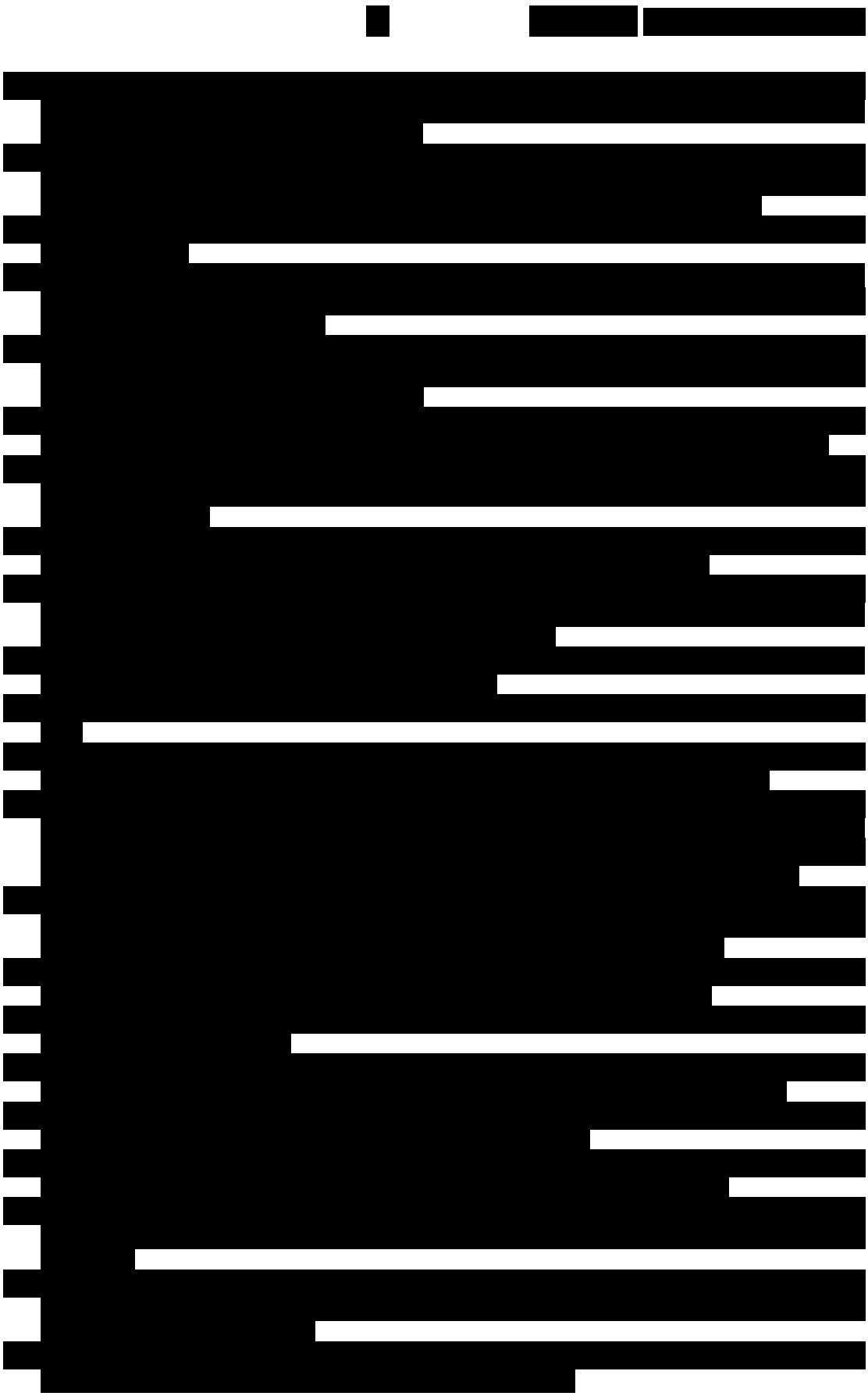
19.0 Budget

19.1 Costs charged to the patient include routine clinical care, including paclitaxel and its administration costs.

19.2 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies to determine which items are considered standard of care versus research at their site. Refer to the payment synopsis for funding provided per accrual to cover study costs, as well as any additional invoiceables that may be allowed.

19.3 Tests that are research funded include research blood kits/collection and tissue collection.

19.4 Eribulin mesylate will be provided free of charge by Eisai Inc.



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

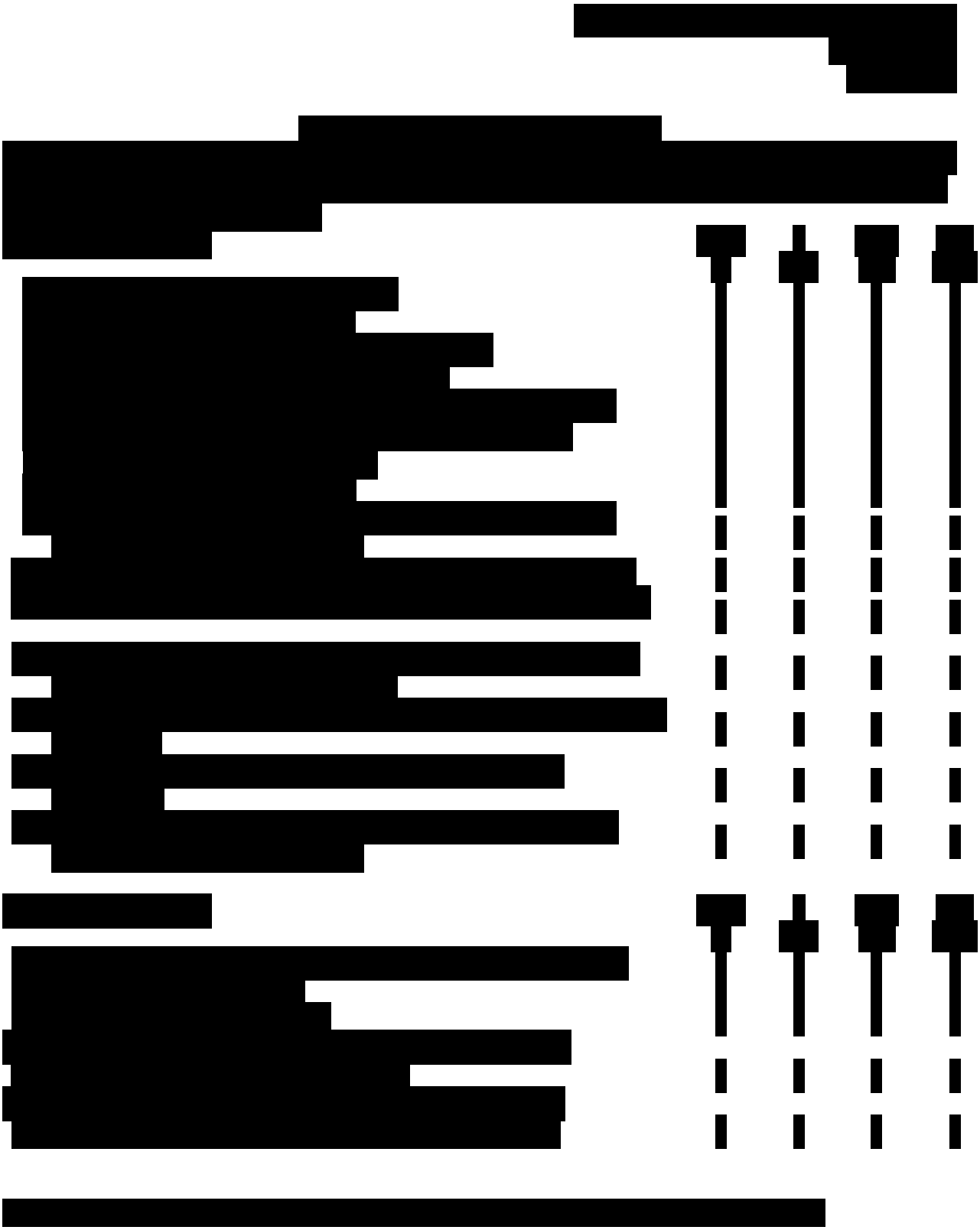
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

PRO-CTCAE
Patient Symptom Reporter

[redacted]