A Phase Ib/II Study of Eribulin in Combination with Cyclophosphamide in Patients with Solid Tumor Malignancies

Protocol Number: 11996
Version: 6.0 (May 26, 2017)

Study Drug: Eribulin
IND: Exempt

Coordinating Center: University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center

Principal Investigator: Hope S. Rugo, M.D.
UCSF Helen Diller Family Comprehensive Cancer Center
[redacted]

Statistician: Jimmy Hwang, PhD

Revision History: Version 6.0 (May 26, 2017)
Version 5.0 (May 31, 2013)
Version 4.0 (May 29, 1012)
Version 3.0 (July 1, 2011)
Version 2.0 (June 27, 2011)
Version 1.0 (June 13, 2011)
Version 0.4 (April 18, 2011)
Version 0.2 (April 1, 2011)

STUDY SYNOPSIS:

This is a phase Ib/II trial designed to determine the MTD and DLTs of the combination of eribulin and cyclophosphamide in solid tumors and make preliminary estimates regarding efficacy of this treatment in patients with advanced breast cancer. Phase 1b will be conducted at UCSF. Phase 2 will be conducted at multiple sites to be determined. UCSF will be the coordinating center.

The study drug in this protocol is intravenous eribulin mesylate. Eribulin will be administered on day 1 and 8 in combination with cyclophosphamide 600 mg/m^2 on day 1. Three weeks will constitute one cycle of treatment.

The study includes a standard dose-confirmation schema (phase Ib portion) enrolling 3 to 6 patients/subjects, with any solid tumors, per cohort (3+3 design) with a total of 18 patients. The dose-expansion (phase II portion) will enroll 40 patients with advanced breast cancer to detect an effect size of 15% with a power of 80% with endpoints of safety, efficacy, and clinical benefit rate. A maximum of 58 patients will be enrolled on the phase Ib and II portions of this trial combined and will be treated until disease progression or toxicity mandate treatment change.

Eribulin is a non-taxane microtubule inhibitor that is FDA approved as monotherapy for the treatment of taxane and anthracycline resistant metastatic breast cancer. The combination of docetaxel and cyclophosphamide is a well-accepted adjuvant chemotherapy regimen that has become an increasingly common therapeutic choice for intermediate risk early stage breast cancer. Eribulin has a favorable toxicity profile compared to docetaxel with the most common adverse reactions (incidence ≤25%) including neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. Eribulin appears to have activity in taxane resistant disease, making it an attractive partner with cyclophosphamide.

Neuropathy can be a devastating complication from adjuvant chemotherapy and in the metastatic setting, may limit effective therapy and reduce quality of life. Understanding the host factors that predict risk for neuropathy is critical, as these patients may in particular benefit from the lower risk of neuropathy associated with eribulin therapy. In conjunction with this trial, we have included correlative studies to study the proposed pharmacogenomic factors associated with risk of neuropathy. In this way we will potentially be able to identify patients who could preferentially be treated with less neurotoxic microtubule inhibitors.

Table of Contents

List of Tables and Figures 6
List of Abbreviations 7
1.0 BACKGROUND AND RATIONALE 8
1.1 Breast Cancer 8
1.2 Breast cancer treatment 8
1.3 Toxicity of taxanes 9
1.4 Toxicity of epothilones 9
1.5 Eribulin mesylate and Preclinical data 9
1.6 Clinical data for eribulin mesylate 10
1.7 In Vitro and Vivo Activity Studies 10
1.7.1 Nonclinical Pharmacokinetics 10
1.7.2 Clinical Pharmacokinetics 11
1.7.3 Toxicology 11
1.7.4 Developmental/Reproductive Toxicity: 11
1.8 Cyclophosphamide 12
1.9 Rationale 12
1.9.1 Rationale for eribulin in combination with cyclophosphamide 12
1.9.2 Rationale for Dosing 12
1.9.3 Rationale for Starting Dose 13
1.10 Correlative Studies Background 13
1.10.1 Single-nucleotide polymorphisms 13
1.10.2 Genome Analysis 13
1.10.3 Circulating Tumor Cells 14
1.10.4 Archived Tissue Analysis 15
1.10.5 Quality of life 15
1.10.6 Neuropathy measurements 15
2.0 OBJECTIVES 17
2.1 Phase Ib 17
2.2 Phase II 17
3.0 PATIENT SELECTION 18
3.1 Subject Inclusion Criteria 18
3.2 Subject Exclusion Criteria 19
3.3 Inclusion of Women and Minorities 19
4.0 SUBJECT REGISTRATION AND ENROLLMENT 20
4.1 Subject Recruitment & Study Sites 20
4.2 Registration Procedures 20
4.2.1 Institutional Registration 20
4.2.2 Lead Center Registration 20
5.0 STUDY DESIGN AND TREATMENT PLAN 20
5.1 Dose and schedule 20
5.2 Dose-Limiting Toxicity Phase Ib 21
5.2.1 Hematologic dose-limiting toxicity 22
5.2.2 Non-hematologic dose-limiting toxicity 22
5.3 Duration of Therapy 23
5.4 Conditions for Terminating the Study 23
6.0 TOXICITY MANAGEMENT AND DOSE MODIFICATION 23
6.1 Removal of patients from study: 24
6.2 Concomitant Medications 24
6.3 Supportive Care Guidelines 24
7.0 DRUG INFORMATION 28
7.1 Eribulin mesylate (Halaven™) 28
7.2 Cyclophosphamide (Cytoxan®) 29
8.0 CORRELATIVE/SPECIAL STUDIES 31
8.1 Pharmacokinetic (PK) Studies 31
8.2 Circulating Tumor Cells 31

8.3 Pharmacogenomic (PG studies) 32
8.4 Archived Tissue Analysis 32
9.0 STUDY PROCEDURES 33
9.1 Screening assessments 33
9.2 Assessments and Procedures During Treatment 33
9.3 Study Termination 34
9.4 Follow-up 34
10.0 CRITERIA FOR EVALUATION 37
10.1 Antitumor Effect – Solid Tumors 37
10.1.1 Response Definitions 37
10.1.2 Disease Parameters 37
10.1.3 Methods for evaluation of measurable disease 38
10.1.4 Response Criteria 40
10.1.5 Duration of Response 41
11.0 STATISTICAL CONSIDERATIONS 42
11.1 Study Design/Endpoint Definitions 42
11.2 Accrual Objectives 42
11.2.1 Replacement of Patients: 42
11.3 Stratification Factors 43
11.4 Analysis of Secondary Endpoints 43
11.5 Reporting and Exclusions 43
11.5.1 Evaluation of toxicity. 43
11.5.2 Evaluation of response 43
12.0 MULTI-CENTER GUIDELINES 43
12.1 Responsibilities of the coordinating/lead center 44
12.1.1 Oversight 44
12.1.2 Protocol Distribution 44
12.1.3 Documentation of Distribution 44
12.1.4 Documentation of Protocol Approvals 44
12.2 Responsibilities of other participating sites 44
12.2.1 Study Initiation 45
12.2.2 Patient Enrollment 45
12.2.3 Study Drug Supply and Accountability 45
12.2.4 Approval of Protocol and Amendments 45
13.0 DATA MANAGEMENT 45
14.0 ETHICAL ASPECTS AND REGULATORY CONSIDERATIONS 46
14.1 Conduct of the study 46
14.2 Scientific Review 46
14.3 Institutional Review Board / Independent Ethics Committee 46
14.4 Investigational New Drug Application (IND) 46
14.5 Additional Reporting Requirements 46
15.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 46
15.1 Adverse Event Definitions 46
15.1.1 Adverse Events 46
15.1.2 Serious Adverse Events 47
15.2 Adverse Event Grading 47
15.3 Adverse Event Reporting Period 47
15.4 Adverse Event Reporting and Data Safety Monitoring 48
15.4.1 Oversight and Monitoring Plan 48
15.4.2 Monitoring and Reporting Guidelines 48
15.4.3 Review and Oversight Requirements 48
16.0 REFERENCES 50
APPENDIX A 54
APPENDIX B 55
APPENDIX C 56
APPENDIX D 58

APPENDIX E 60
APPENDIX F 61

List of Tables and Figures

Table 3-1. Adequate Organ Function Values 18
Table 5-1. Dose Escalation Schedule 20
Table 6-1. Toxicity management guidelines for eribulin and cyclophosphamide 26
Table 9-1 Study Calendar 35
Table 10-2. Evaluation of Patients with Measurable Disease (i.e., Target Disease) 41
Table 10-3. Evaluation of Patients with Non-Measurable Disease (i.e., Non-Target Disease) 41

List of Abbreviations

AC	doxorubicin (adriamycin) and cyclophosphamide
aCGH	array comparative genomic hybridization
AE	adverse event
ALDH	aldehyde dehydrogenase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the curve
BID	twice a day
BSA	body surface area
CAEPR	Comprehensive Adverse Event and Potential Risks
CALGB	Cancer and Leukemia Group B
CBC	complete blood count
CBR	clinical benefit rate
CGH	comparative genomic hybridization
CHR	UCSF Committee on Human Research
Cl	plasma clearance
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trials Management System
CV	coefficient of variability
CYP	cytochrome P450
DLT	dose limiting toxicity
DFS	disease free survival
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
E7389	eribulin mesylate
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FACS	fluorescence-activated cell sorting
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FNA	Fine needle aspiration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GOG	Gynecologic Oncology Group
GWAS	genome wide association study
HER-2	human epidermal growth factor receptor 2
HIPPA	The Health Insurance Portability and Accountability Act
HGB	hemoglobin
HR	heart rate
HV	healthy volunteers
IC50	50% inhibitory concentration
IND	investigational new drug
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IB	Investigator's Brochure
IV	intravenous
KPS	Karnofsky Performance Status
MAD	maximum administered dose
MBC	metastatic breast cancer
MRI	Magnetic Resonance Imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New York Heart Association
OS	overall survival
PD	progressive disease
PFS	progression free survival
Pgp	permeability glycoprotein
PgR	progesterone receptor
PHI	personal health information
PI	Principal Investigator
PK	pharmacokinetic
PO	by mouth
PR	partial response
PRC	UCSF Protocol Review Committee
QD	once daily
QID	four times a day
QOD	every other day
QOL	Quality of life
QLQ	Quality of life questionnaire
QTc	QT corrected interval
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RR	response rate
SAE	serious adverse event
SC	subcutaneously
SD	stable disease
SiBP	sitting blood pressure
t ½	elimination half-life
TC	docetaxel and cyclophosphamide
TPC	the physician's choice
ULN	upper limit of normal
Vdss	volume of distribution at steady state
WBC	white blood cell
WGA	whole genome amplification

1.0 BACKGROUND AND RATIONALE

1.1 Breast Cancer

Breast cancer is the most common female cancer in the United States and is estimated to affect 207,090 women in the United States in 2010, with over 40,000 deaths expected (Jemal, Siegel et al. 2010). As many as 20% of patients will develop metastatic disease and most will have received prior adjuvant and/or neoadjuvant chemotherapy. Despite advances in therapies, the overall long-term prognosis of patients with metastatic breast cancer remains poor, with time to progression ranging from 6 to 9 months in the first-line setting and median survival overall of approximately 3 years.

1.2 Breast cancer treatment

For breast cancer, anthracyclines are one of the most commonly administered intravenous chemotherapy agents and are known to cause cardiac toxicity and rare cases of acute leukemia (Patt, Duan et al. 2007) (Du, Xia et al. 2009). The taxanes were introduced in 1990 and quickly became an integral part of chemotherapy regimens. Significant side effects include bone marrow suppression, peripheral neuropathy, nail changes, epiphora, and, less commonly, permanent alopecia (Sparano, Wang et al. 2008). Patients with metastatic disease develop cumulative toxicity from multiple lines of chemotherapy as well as chemotherapy resistance which limits efficacy. Selection of less toxic regimens with improved efficacy is important to achieve the goal of improved outcome without worsening quality of life. Development of agents targeted to the biology that drives tumor growth are a critical step in this process, however, chemotherapy remains the backbone of breast cancer treatment. New agents and new combinations may not only improve response and duration of response, but also could provide an improved backbone for the addition of targeted agents.

The combination of doxorubicin and cyclophosphamide (AC) is a standard contemporary adjuvant chemotherapy regimen based on data from NSABP-15, NSABP-23 and other studies (Fisher, Brown et al. 1990; Fisher, Anderson et al. 2001). Jones and colleagues studied the combination of docetaxel and cyclophosphamide (TC) in patients with early stage breast cancer in order to evaluate a non-anthracycline containing regimen that might avoid the risk of long-term toxicity. 1800 women with stage I and II breast cancer were randomized to receive TC every three weeks for 4 cycles or AC on the same schedule. At a median follow-up of five years, patients treated with TC had a significantly improved disease free survival (DFS) of 86% versus 80% p=0.015, compared to those receiving AC (Jones, Savin et al. 2006). Subsequently, 7 year follow-up data demonstrated a significant improvement in overall survival (OS) favoring TC, 87% versus 82% p=0.032 (Jones, Holmes et al. 2009). Grade 3-4 toxicities were evaluated by age group and anemia was highest in the age group ≥ 65 occurring in 5% of patients who received AC. Febrile neutropenia was 5% with TC and 2.5% with AC. Patients treated with TC also experienced more peripheral edema (1% vs. <1%), diarrhea (5% vs. 1%), myalgia (2% vs. 1%). The AC group had more asthenia (9% vs. 6%), infections (10% vs. 7%), nausea (7% vs. 3%) and vomiting (6% vs. 1%). Four late deaths without breast cancer relapse and probably related to treatment occurred in the AC group: a 45-year-old woman died of cardiomyopathy and congestive heart failure, and two older women died of complications related to myelodysplasia and myelofibrosis. One more patient died of acute leukemia 10 years after AC. No cardiac toxicities or leukemia were observed in the group receiving TC.

Based on this data, TC has become a generally accepted adjuvant chemotherapy regimen for the treatment of lower risk early stage disease. Ongoing or planned studies have incorporated TC as a chemotherapy backbone, including two NSABP trials. NSABP B-46 is a three-arm trial and randomizes women with node-positive or high-risk node-negative breast cancer to 6 cycles of TAC (docetaxel, doxorubicin, and cyclophosphamide), TC, or TC combined with bevacizumab. NSABP B47 is studying the impact of trastuzumab in patients with HER2 normal disease when given with either TC or AC followed by paclitaxel.

1.3 Toxicity of taxanes

Despite the success of taxanes in the treatment of early stage breast cancer, toxicity remains an issue. Mild to moderate peripheral neuropathy is seen in up to 88% of women, with 3% having severe neuropathy, and some suffering from long-term neuropathy (Rowinsky and Donehower 1995). In ECOG 1199, a randomized trial of doxorubicin and cyclophosphamide followed by various schedules of taxane therapy, 27% of patients who received weekly paclitaxel had Grade 2 or greater neuropathy(Sparano, Wang et al. 2008). Other toxicities, such as epiphora, edema, and delayed hair growth, among others, limit time to recovery from adjuvant therapy.

1.4 Toxicity of epothilones

Epothilones also target microtubules and stabilize their polymerization, but differ from taxanes in that they demonstrate less susceptibility to Pgp-mediated efflux and retain antitumor activity even in the setting of tubulin mutations (Rivera and Gomez 2010). Phase II studies for the mostly widely studied epothilone, ixabepilone, when given as monotherapy, has shown overall response rates (ORR) for metastatic breast cancer patients not previously treated with taxanes of 41.5 and 57% and in taxane-pretreated patients ORR of 11.5 to 22% (Denduluri, Low et al. 2007) (Low, Wedam et al. 2005) (Perez, Lerzo et al. 2007) (Roche, Yelle et al. 2007) (Thomas, Gomez et al. 2007). In a phase II study with 113 patients, grade 3/4 adverse events included 14% of patients with peripheral sensory neuropathy, 54% with neutropenia, 14% with fatigue and grade 3 myalgia/arthralgia in 14% (Perez, Lerzo et al. 2007). Based on this toxicity profile, newer, less toxic agents are still needed.

1.5 Eribulin mesylate and Preclinical data

Eribulin mesylate (E7389) is a nontaxane, microtubule dynamic inhibitor with a novel mechanism of action. Eribulin suppresses polymerization, has no effect on microtubule depolymerization, and sequesters tubulin into nonfunctional aggregates (Kuznetsov, Towle et al. 2004; Jordan, Kamath et al. 2005; Okouneva, Azarenko et al. 2008) (Towle, Salvato et al. 2001).

Results of in vitro studies demonstrate that eribulin inhibits cell growth with sub- to low-nmol/L half-maximal inhibitory concentration (IC50) values in a wide range of established human cancer cell lines, including breast, colon, prostate, ovarian, small cell lung, and non-small cell lung cancers, histiocytic lymphoma, promyelocytic leukemia, head and neck carcinoma, melanoma, and uterine sarcoma. Eribulin exerts its anticancer effects via a tubulin-based antimitotic mechanism, leading to G2/M (GAP 2/mitosis stages of cell cycle) cell cycle blocks, disruption of mitotic spindles, and ultimately apoptotic cell death after prolonged mitotic blockage. Among tubulin-targeted agents, eribulin is a mechanistically unique inhibitor of microtubule dynamics, leading to inhibition of microtubule growth in the absence of effects on microtubule shortening, and formation of non-productive tubulin aggregates. This unique pattern of inhibitory effects on microtubule dynamics is not shared by other known tubulin-targeted agents.

Preclinical studies have also demonstrated antitumor activity in cell lines that are taxane resistant as a result of β-tubulin mutations (Cortes and Lorca 2011) (Kuznetsov et al. abstract ESMO 2007). In addition, eribulin appears to have less neurotoxicity than other microtubule antagonists. A murine model compared the effect on nerve conduction of paclitaxel and ixabepilone to eribulin. This data, presented at the annual European Society for Medical Oncology found that treatment with paclitaxel and ixabepilone resulted in a reduction in caudal nerve conduction velocity as well as caudal and digital amplitude, but eribulin had no deleterious effect on these endpoints. Eribulin also caused less severe morphological changes in dorsal root ganglion and sciatic nerves on pathological assessment (Wozniak, Lapidus et al. 2010).

1.6 Clinical data for eribulin mesylate

In two phase II studies, eribulin has demonstrated efficacy in patients with heavily pre-treated metastatic breast cancer. E7389-A001-201 evaluated the safety and efficacy of eribulin in subjects with locally advanced or metastatic breast cancer who had been previously treated with an anthracycline and taxane and had documented progression during or within 6 months following the last dose of chemotherapy. 103 patients with a median of 4 prior chemotherapy regimens for advanced disease enrolled (Vahdat, Pruitt et al. 2009). 70 subjects received 1.4 mg/m^2 eribulin administered as an IV bolus on days 1, 8, and 15 of a 28-day cycle; another 33 subjects received eribulin administered as an IV bolus on days 1 and 8 of a 21-day cycle. The 21-day cycle cohort was added because 63% of subjects in the 28-day cycle cohort experienced dose delays, reductions, or omissions due to neutropenia; in most cases the day 15 dose was being omitted. The response rate (RR) was 11.5% (all PR), the clinical benefit rate (CBR) was 17.2%, and progression free survival (PFS) was 2.6 months. The second phase II trial, E7389-A001-211, enrolled 299 patients with locally advanced or metastatic breast cancer who had received anthracycline, taxane, and capecitabine as prior therapy, and were refractory to their last chemotherapy regimen as documented by progression on or within 6 months of therapy (Cortes, Vahdat et al. 2010). All patients received 1.4 mg/ m^2 on day 1 and 8 every 21 days. Results were similar by independent review, with RR of 9.3%, CBR of 17.1% and PFS of 2.6 months. Between the two trials, OS ranged from 9 to 10.4 months. The most common drug-related grades 3/4 toxicities were neutropenia (54-64%), fatigue (5-10%), peripheral neuropathy (5-6.9%), and febrile neutropenia (4-5.5%).

The results of a phase III trial comparing eribulin to treatment of physician's choice (TPC) in patients with anthracycline and taxane pre-treated MBC and at least two prior chemotherapy regimens for advanced disease recently led to FDA approval of this novel chemotherapy agent (Twelves, Cortes et al. 2010). The EMBRACE trial randomized 508 women to single agent eribulin and 254 women to TPC; the primary endpoint of OS was 13.12 months in the eribulin arm versus 10.65 months in the TPC arm (HR 0.81, p=0.041). The RR was also greater in the eribulin arm (12.2 versus 4.7%, p=0.002), and although PFS was significantly longer by investigator assessment, by central review this was not significantly different, likely due to the inclusion of patients with evaluable rather than solely measurable disease (3.7 versus 2.2 months, HR 0.87, p=0.14). Subset analysis suggested benefit from eribulin across identified risk groups. 144 patients were identified with ER/PgR/HER2 negative disease, determined locally, and in this group the PFS for eribulin was 2.23 months, compared to 1.9 months for TPC. In the overall study, grade 3/4 toxicities that were higher in the eribulin arm included higher rates of neutropenia (21% versus 14%) and leukopenia (11.7% versus 5%) as well as febrile neutropenia (3% versus 0.8%). However, anemia (1.8 vs 3.2%), asthenia/fatigue (8.2 vs 10.1%), nausea (1.2 vs 2.4%), mucositis (1.4 vs 2%) and hand-foot syndrome (0.4 vs 3.6%) were more prevalent in the TPC arm.

1.7 In Vitro and Vivo Activity Studies

1.7.1 Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of eribulin were examined after single IV administrations in male mice (0.5 or 2 mg/kg), male rats (0.5 or 1 mg/kg), and male dogs (0.08 mg/kg). The PK of eribulin can be characterized by an extensive volume of distribution (7.45 – 12.2 l/kg in mice, 36.3 – 44.1 l/kg in rats, and 18.8 – 20.4 l/kg in dogs), a moderate clearance (2.03 – 2.79 l/hr/kg in mice, 1.61 – 2.04 l/hr/kg in rats, and 0.688 – 1.06 l/hr/kg in dogs), and a relatively slow elimination (t½, 3.55 - 6.88 hours in mice, 15.9 - 27.9 hours in rats, 21.9 - 28.2 hours in dogs). In multiple dose PK studies in which eribulin was administered every four days for three courses no accumulation was observed in both rats and dogs.

The protein binding of eribulin in mouse, rat, dog and human plasma in vitro was investigated. Between 100 and 1000 ng/mL, eribulin was not strongly bound to plasma protein in vitro: mouse (28.47%-35.94%), rat (23.01%-34.09%), dog (15.41%-26.37%), and human plasma (48.92%-65.07%). Cytochrome 3A4 (CYP3A4) appears to be the major enzyme responsible for the human hepatic metabolism of eribulin, and forms mainly isomeric monohydroxylates in vitro.

No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 was detected with eribulin at concentrations up to 5 µmol/L. Eribulin inhibited CYP3A4-mediated R-warfarin 10-hydroxylation, testosterone 6-β hydroxylation, nifedipine dehydration (Ki: 3-17 µmol/L), and exhibited weak inhibitions on the metabolism of carbamazepine, diazepam, paclitaxel, tamoxifen, midazolam, and terfenadine. Eribulin did not alter the activities or the protein expressions of CYP1A, CYP3A, CYP2C9, and CYP2C19 in the primary cultures of human hepatocytes (up to 5 or 10 µmol/L). It is unlikely that eribulin would cause metabolic inhibition of concurrent drugs based on anticipated low therapeutic dose in humans. However, caution will be taken for patients who are taking drugs that are metabolized by CYP3A4 since CYP3A4 was substrate dependant and appears to be the major enzyme responsible for human hepatic metabolism of eribulin in vitro.

1.7.2 Clinical Pharmacokinetics

The pharmacokinetics of eribulin in human subjects is characterized by a rapid distribution phase, with a prolonged elimination phase after intravenous infusion. Plasma concentrations of drug are sufficiently low during the elimination phase to preclude significant accumulation at the dosing intervals being tested. The disposition of eribulin follows linear kinetics over the dose range studied, as shown by consistent dose-independent pharmacokinetic parameters (t½, CI, Vdss) and similar dose-normalized parameters (Cmax/Dose, AUC0-t/Dose and AUC0-∞/Dose) between eribulin doses ranging from 0.25 to 1.4 mg/ m^2 (E7389-A001-101) and from 0.25 to 4.0 mg/ m^2 (E7389-A001-102).

1.7.3 Toxicology

The toxicity of eribulin has been evaluated in rats and dogs with the drug administered in 5% ethanol in 0.9% sodium chloride (NaCl) as a slow IV bolus to rats or as a 1-hour IV infusion to dogs once a day on days 1, 5, 9. In range-finding studies, single doses of 0.75 mg/kg/day (4.5 mg/ m^2/day) were lethal to rats and two doses of 0.075 mg/kg/day (1.5 mg/ m^2/day) were lethal to dogs. Bone marrow toxicity appeared to be dose-limiting in both rats and dogs. In the Investigational New Drug Application (IND)-directed, Good Laboratory Practices (GLP) toxicity studies, doses of 0.08 mg/ m^2/day produced no toxicity in dogs or rats, while doses of 0.6 to 0.8 mg/ m^2/day produced reversible bone marrow toxicity in both species. Other toxicities that were considered to be drug-related occurred in the lymphoid tissue, testes, and skeletal muscle. All observed toxicities (except testicular toxicity) were reversible in both dogs and rats. Based on these studies, the recommended starting dose for phase I clinical trials is 0.12 mg/ m^2/day, as dose less than 1/10th the maximum tolerated dose (MTD) in rats (1.2-1.5 mg/ m^2/day) and 1/6th the Toxic Dose Low (0.4 mg/ m^2/day) in dogs.

In vitro bone marrow assays did not demonstrate significant species difference between human, dog, and mouse CFU-G/M cell sensitivity to eribulin. Based on the ratios of human to murine and human to canine IC_{90S} and in vivo MTDs, the calculated human MTD was projected to be 0.9 mg/ m^2/day (based on canine data) and 3.1 mg/ m^2/day (based on murine data.) Similar bone marrow effects were also confirmed by in vitro assays using multipotential stem cells (CFC-GEMM) from mouse, dog and human. The murine CFC-GEMM cells appeared to be less sensitive to the toxic effects, whereas human and canine cells appeared to be equally sensitive. In *in vitro* genotoxicity studies, eribulin was negative in the Ames test with or without S9, but was weakly positive in the L5178Y/$TK_{+/-}$ mouse lymphoma mutagenesis assay.

1.7.4 Developmental/Reproductive Toxicity:

Developmental and reproductive toxicity studies of eribulin have not been performed thus far. Eribulin was not tested in pregnant or breast-feeding women. Women of child-bearing potential and men participating in clinical studies of eribulin must use appropriate contraception, including abstinence and double-barrier methods, throughout eribulin therapy. In preclinical mutagenicity studies, eribulin was neither genotoxic or mutagenic.

1.8 Cyclophosphamide

Cyclophosphamide (Endoxan, Cytoxan, Neosar, Procytox, Revimmune) is a prodrug nitrogen mustard alkylating agent, from the oxazophorines group. It is converted by oxidase enzymes in the liver to active toxic metabolites, 4-hydroxycyclophosphamide and aldophosphamide. Most of the aldophosphamide is oxidized by the enzyme aldehyde dehydrogenase (ALDH) to make carboxyphosphamide. A small proportion of aldophosphamide is converted into phosphoramide mustard and acrolein. Phosphoramide mustard forms DNA crosslinks between (interstrand crosslinkages) and within (intrastrand crosslinkages) DNA strands at guanine N-7 positions. This is irreversible and leads to cell death(Cohen and Jao 1970) (Brock 1989) (Brock 1996).

Phosphoramide mustard is only formed in cells that have low levels of ALDH. Cyclophosphamide has relatively little typical chemotherapy toxicity as ALDH is present in relatively large concentrations in bone marrow stem cells, liver and intestinal epithelium. ALDH protects these actively proliferating tissues against toxic effects phosphoramide mustard and acrolein by converting aldophosphamide to carboxyphosphamide that does not give rise to the toxic metabolites (phosphoramide mustard and acrolein).

Cyclophosphamide has activity in a broad range of human cancer types and has emerged as front line therapy for many advanced cancers including breast cancer. Phase III clinical trials have shown that cyclophosphamide in combination with adriamycin prolongs survival in patients with breast cancer (Fisher, Brown et al. 1990). In early stage breast cancer patients, the regimen of cyclophosphamide and docetaxel has recently been adopted since it is a less toxic regimen and data shows that it improves DFS and OS (Jones, Holmes et al. 2009).

The most common toxicities associated with cyclophosphamide include bone marrow suppression, nausea, vomiting, anorexia, diarrhea, abdominal discomfort, alopecia, mucositis, infertility; and rare cases of hemorrhagic cystitis due to the metabolite acrolein, hemorrhagic colitis, Stevens-Johnson syndrome or interstitial pneumonitis.

1.9 Rationale

1.9.1 Rationale for eribulin in combination with cyclophosphamide

Docetaxel or paclitaxel are well-established active and effective treatments for advanced breast cancer in both the front-line and pre-treated setting. *In vitro* data with taxane resistant cell lines offers a biological basis for the efficacy of eribulin in this setting. Due to the favorable toxicity profile and efficacy seen with the use of eribulin as a single agent, it is feasible to study combinations of eribulin with standard chemotherapeutic agents given in breast cancer. The success of docetaxel combined with cyclophosphamide in the adjuvant setting has led to considerable interest in anthracycline-free chemotherapy options. Given the advantages of eribulin in both toxicity and efficacy, the combination of eribulin and cyclosphosphamide is intriguing. If both efficacy and safety is demonstrated in the metastatic setting, this could be an important combination therapy to test as adjuvant therapy for early stage breast cancer.

1.9.2 Rationale for Dosing

On November 15, 2010, the U. S. Food and Drug Administration granted approval for eribulin mesylate for the treatment of patients with metastatic breast cancer who have previously received an anthracycline and a taxane in either the adjuvant or metastatic setting, and at least two chemotherapeutic regimens for the treatment of metastatic disease. In the phase III trial which led to this approval, eribulin was administered as an intravenous dose of 1.4 mg/ m^2 on days 1 and 8 of a 21-day cycle, with dose delays and reductions for pre-specified toxicities.

1.9.3 Rationale for Starting Dose

We anticipate the possibility of increased toxicity, including bone marrow suppression, when eribulin is combined with standard dose cyclophosphamide (600 mg/m^2 on day 1 of a 21-day cycle.) Therefore we plan to test this combination initially with a reduced dose of eribulin (1.1 mg/m^2 days 1 and 8 of a 21-day cycle).

1.10 Correlative Studies Background

1.10.1 Single-nucleotide polymorphisms

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. 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 (Ratain 1992). Response to chemotherapy is also highly variable and may be influenced by both host and tumor specific factors. Variability in hepatic metabolism and membrane transport has been the focus of many studies addressing the sources of interindividual differences in response to medications, particularly chemotherapy. Several CALGB studies have included correlative pharmacogenetics studies to investigate genetic contributions to toxicity and response. The most mature of these studies in breast cancer, CALGB 40101, has recently identified novel genetic predictors of paclitaxel-induced peripheral neuropathy. Surprisingly, polymorphisms in known candidate genes for metabolism and transport did not contribute significantly to toxicity. Results from a genome-wide scan of over 500,000 single nucleotide polymorphisms (SNPs) identified three novel candidate genes, FZD3, FGD4 and EPHA5.

FZD3 encodes a Wnt receptor with a known role in neurite outgrowth (Endo, Beauchamp et al. 2008), suggesting that altered function in individuals carrying the variant allele of this gene may protect against paclitaxel-induced peripheral nerve injury. A COX model was also used to identify genetic predictors of time to developing peripheral neuropathy. Although not reaching genome-wide significance, the two top hits were in genes of biological interest. One SNP was in EPHA5 (p = 9.6 x 10-7; HR = 1.63) and another in FGD4 (p = 2.6 x 10-6; HR = 1.57). EPHA5 encodes an ephrin receptor involved in axon guidance. Studies in mice have shown that EPHA5 is important for neuronal regeneration following injury (Barrette, Calvo et al. 2010). Patients carrying a reduced function EPHA5 allele may have an attenuated repair response following paclitaxel-induced injury. 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 (Stendel, Roos et al. 2007). The more common FGD4 polymorphisms identified in CALGB 40101 may be associated with demyelination of peripheral nerves following paclitaxel treatment. The molecular bases for each of these three genes in paclitaxel-induced peripheral neuropathy are currently under study at Dr. Kroetz' laboratory at USCF. Therefore, in addition to specific hypothesis testing for the above candidate genes, this study will also provide the framework for hypothesis generation investigations of genotype and/or haplotype in additional candidate genes of putative importance to response and toxicity of the agents being evaluated in this study.

For patients who consent, whole blood will be collected prior to the start of treatment. DNA extraction will occur at UCSF Genomics Core Facility, the Cancer Center Genome Analysis Core, the Cancer Center Tissue Core or within the laboratory of Dr. Kroetz. Exploratory SNP analysis will then be performed in Dr. Kroetz laboratory. Data from this trial will be combined with other SNP data for separate larger analysis of pooled patients.

1.10.2 Genome Analysis

In genetic epidemiology, a genome-wide association study (GWA study, or GWAS), also known as whole genome association study (WGA study, or WGAS), is an examination of all or most of the genes (the genome) of different individuals of a particular species to see how much the genes vary

from individual to individual. Different variations can then be associated with different traits, for example diseases or toxicity from treatment. One challenge for successful GWAS in the future will be to apply the findings in a way that accelerates drug and diagnostics development, including better integration of genetic studies into the drug-development process and a focus on the role of genetic variation. One such success was found relating genetic variant with response to anti-hepatitis C virus treatment. For genotype 1 hepatitis C treated with Pegylated interferon-alpha-2a or Pegylated interferon-alpha-2b (brand names Pegasys or PEG-Intron) combined with ribavirin, a GWAS study has shown that genetic polymorphisms near the human IL28B gene, encoding interferon lambda 3, are associated with significant differences in response to the treatment. A later report demonstrated that the same genetic variants are also associated with the natural clearance of the genotype 1 hepatitis C virus (Ge, Fellay et al. 2009).

For purposes of hypothesis generation, we plan to collect whole blood on patients prior to the start of treatment and perform a genome scan in the Genome Analysis Core or the UCSF Genomics Core. Data from this trial will be combined with other genome scan data from UCSF for a separate larger analysis of pooled patients. These samples will not be sent to the National Institutes of Health (NIH) and will not be part of the NIH GWAS database.

1.10.3 Circulating Tumor Cells

The development of techniques to detect circulating tumor cells (CTCs) or micrometastases in the blood of cancer patients provides a new approach to monitoring cancer activity and response to therapy. Numerous studies have demonstrated the utility of using CTC enumeration as a prognostic marker in advanced breast cancer (Cristofanilli, Budd et al. 2004; Cristofanilli, Hayes et al. 2005). More recently, considerable attention has turned to the development of more sophisticated assays to better understand the biology and molecular nature of CTCs. Current models suggest that CTCs may represent tumor cells with metastatic potential, and therefore gene-expression profiling of CTCs may be a rich resource for the identification of biomarkers with therapeutic relevance to micrometastatic disease. In addition, as molecular targeted therapies are being developed, it is imperative that we have strategies to assess target levels in patients, as well as changes in target status during treatment. CTCs offer an ideal focus for such strategies, as they are readily obtainable and can be subjected to further molecular analysis.

Molecular profiling of CTCs is challenging because CTCs are a rare cell population. Isolating CTCs and handling picogram levels of RNA and DNA is extremely difficult and can be wrought with technical complications (Racila, Euhus et al. 1998). Efforts to detect CTCs have involved the use of antibody-based capture methods which greatly enrich the tumor cell component relative to hematopoetic cells, however these current methods still retain a considerable fraction of leukocytes which results in a heterogeneous sample that prevents accurate characterization of isolated CTCs. Dr. John Park's laboratory at UCSF has developed a novel approach using sequential immunomagnetic enrichment and FACS (Fluorescence-activated cell sorting) for CTC isolation. Using this protocol, the Park laboratory has successfully isolated small pools of highly purified CTCs from breast cancer patients. Genomic DNA from these CTCs were subjected to whole genome amplification (Howgate, Gamie et al.) followed by array comparative genomic hybridization (aCGH) for copy number analysis. Their results demonstrate that CTCs can be isolated from hematopoietic cells with high enough purity to perform molecular profiling.

We plan to utilize this novel isolation strategy to perform the following exploratory CTC analyses: 1) enumeration of CTCs prior to starting therapy and if ≥5 CTC/mL, a second sample at cycle 2 day 1; 2) whole genome amplification (Howgate, Gamie et al.) followed by aCGH of isolated CTCs 3) sequencing analysis for beta tubulin mutations as indicated; and 4) gene expression using a 64 gene panel including beta 3 tubulin (#2, 3, will be performed only if an adequate number of CTCs are available.)

1.10.4 Archived Tissue Analysis

Over the past several years, advances in molecular technology have allowed scientists to perform genome-wide queries using oligonucleotide arrays to identify genes that are differentially expressed in tumor metastases, as well as in pre- and post-treatment tissue samples (Ramaswamy and Perou 2003; Weigelt, Glas et al. 2003).

Archived tumor tissue will be collected for the analysis of biomarkers predictive of clinical response to eribulin. This may include, but is not limited to, proteins, phosphoproteins, and RNA expression related to the activity of eribulin may be assessed in this tissue. DNA will be extracted from tissue specimens in order to sequence and genotype the samples, to evaluate the prevalence of genetic polymorphisms of all membrane transporters as well as all other genes of interest which could potentially be interacting with the membrane transporters or having a effect on the expression levels of the membrane transporter genes. Sequencing and genotyping of the tissue samples will be carried out using traditional sequencing methods, or using the genomewide association array chip (Illumina, Affymetrix or others) and/or using the high-throughput DNA sequencing technologies (Illumina Genome Analyzer, 454 technologies and SOLiD) mRNA levels of all membrane transporters and other potential genes of interest will be measured by quantitative PCR, microarray analysis or other cutting edge technologies such as high-throughput RNA sequencing technologies (Illumina Genome Analyzer, 454 technologies and SOLiD). The protein levels of the interested genes in the tissue specimens will be determined by immunohistochemistry and Western Blot analyses using targeted antibodies. RNA/protein levels will be associated with various genotypes to identify genetic variants that have an impact on RNA/protein concentration. Other analysis of tumor tissue may include, but is not limited to, markers of response to treatment or potential for metastasis including, but not limited to, proteins, phosphoproteins, and other biological markers.

1.10.5 Quality of life

We plan to evaluate quality of life endpoints using the standard assessment tool EORTC QLQ-C30. QLQ-30 is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide (Groenvold, Klee et al. 1997; Taenzer, Speca et al. 1997; Apolone, Filiberti et al. 1998; McLachlan, Devins et al. 1998).

This questionnaire will be administered at baseline (within 7 days of cycle 1 day 1), and thereafter at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months after the start of treatment, before drug administration and before any tumor assessments are communicated to the patient. Questionnaires should continue to be completed at the scheduled time-points (including beyond study termination), until the patient has progressive disease or starts a different course of anti-tumor treatment, whichever comes first. One person in each center will be designated to take responsibility for the administration, collection, and verification of the QLQ forms. Further details regarding QLQ administration are provided separately to on-site staff. An online questionnaire may also be available.

1.10.6 Neuropathy measurements

Cellular functions that rely on tubulin, such as axonal transport and cytoskeletal support of transmembrane proteins, may also be affected when cells are treated with microtubule inhibitors. In paclitaxel induced neuropathy, these disruptions lead to axonal atrophy of large diameter peripheral nerve axons (Sahenk, Barohn et al. 1994; Persohn, Canta et al. 2005). Patients with taxane-induced neuropathy present with neuropathic pain, dyesthesias, parathesias in a stocking-and-glove pattern, decreased deep tendon reflexes, increased vibration thresholds, decreased sensory nerve action potential amplitudes, and distal muscle weakness (Lipton, Apfel et al. 1989; Chaudhry, Rowinsky et al. 1994; New, Jackson et al. 1996; Forsyth, Balmaceda et al. 1997).

Investigators at UCSF have developed a 10-point Modified Total Neuropathy Score (mTNS) and validated the measure in a group of 40 patients (Wampler, Miaskowski et al. 2006). It is inexpensive, noninvasive, and can be performed by a health care provider in less than ten minutes.

The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire is an eleven-item subscale (Ntx subscale) that evaluates symptoms and concerns associated specifically with chemotherapy-induced neuropathy. It assesses levels of patient neuropathy, severity of toxicity, and patient quality of life and has been validated (Calhoun, Welshman et al. 2003).

The mTNS and FACT/GOG-NTX assessments will take place by a health care provider at baseline (within 7 days of cycle 1 day 1), and at the start of each cycle and study termination. It will be performed before drug administration and before any tumor assessments are communicated to the patient. Assessments will take place until the patient has progressive disease, starts a different course of anti-tumor treatment, or until 12 months from time of enrollment on study, whichever comes first. One person in each center will be designated to take responsibility for the collection and verification of the mTNS and FACT/GOG-Ntx forms. Further details regarding mTNS and FACT/GOG-Ntx administration are provided separately to on-site staff.

2.0 OBJECTIVES

2.1 Phase Ib

Primary Objective:

1. Determine the maximum tolerated dose (MTD) of eribulin in combination with cyclophosphamide in patients with any solid tumor.

Secondary Objectives:

1. Evaluate the safety of treatment with the combination of eribulin and cyclophosphamide in patients with any solid tumor.
2. Determine the dose-limiting toxicities (DLTs) of eribulin in combination with cyclophosphamide in this cohort.
3. Characterize the pharmacokinetics (Bettmann, Dake et al.), including evaluating the potential for drug-drug interaction of eribulin and cyclophosphamide.
4. Evaluate quality of life endpoints using assessment tools EORTC QLQ-C30, FACT/GOG-Ntx and 10-point Modified Neuropathy Score.
5. Explore the relationships between the combination of eribulin/cyclophosphamide pharmacodynamic, pharmacogenomic and response prediction biomarkers.
    a. Explore single-nucleotide polymorphism (SNP) variations evaluating potential toxicities including peripheral neuropathy and bone marrow suppression.
    b. Perform circulating tumor cell (CTC) analysis to enumerate and sort CTCs, and perform exploratory analyses evaluating WGA and β-tubulin expression in CTCs.
    c. Evaluate archival tumor specimens for exploratory markers of target validation and response, including, but not limited to tubulin mutations and comparative analysis with CTC aCGH analysis.

2.2 Phase II

Primary Objective:

1. Estimate the clinical benefit rate (complete response, partial response, and stable disease) of the combination of eribulin and cyclophosphamide in patients with advanced breast cancer.

Secondary Objectives:

1. Make a preliminary assessment of efficacy of this combination in patients with advanced breast cancer including response rate, duration of response and time to progression.
2. Evaluate the safety of this combination in an expanded cohort of patients.
3. Evaluate quality of life endpoints using assessment tools EORTC QLQ-C30, FACT/GOG-Ntx and 10-point Modified Neuropathy Score.
4. Explore the relationships between the combination of eribulin/cyclophosphamide pharmacodynamic, pharmacogenomic and response prediction biomarkers.
    a. Explore single-nucleotide polymorphism (SNP) variations evaluating potential toxicities including peripheral neuropathy and bone marrow suppression.
    b. Perform circulating tumor cell (CTC) analysis to enumerate and sort CTCs, and perform exploratory analyses evaluating WGA and β-tubulin expression in CTCs.
    c. Evaluate archival tumor specimens for markers of target validation and response, including, but not limited to tubulin mutations and comparative analysis with CTC aCGH analysis.

3.0 PATIENT SELECTION

3.1 Subject Inclusion Criteria

1. Phase Ib: Patient must have histologically or cytologically documented solid tumor malignancies.
   Phase II: Patients must have histologically or cytologically confirmed locally advanced, unresectable or metastatic carcinoma of the breast.

2. Patient is male or female and ≥18 years of age on the day of signing informed consent.

3. Patient must have performance status of 0-2 on the ECOG Performance Scale and life expectancy > 3 months.

4. Patients with ≤ grade 1 peripheral neuropathy are eligible for this trial using the CTCAE v4.0, regardless of use of therapy for neuropathy including gabapentin.

5. Patient must have evaluable disease. Measureable disease is not required

6. Patient must have adequate organ function as indicated by the following laboratory values:

Table 3-1. Adequate Organ Function Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC6	≥1,000/µL
Platelets	≥100,000/µL
Hemoglobin	≥9 g/dL
Renal	
Serum creatinine or calculated creatinine clearance†	≤1.5 x upper limit of normal (ULN) OR ≥60 mL/min for patients with creatinine levels >1.5 x institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 x ULN OR direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤3 x ULN or ≤5 x ULN in patients with known liver metastasis
Metabolic	
Potassium§	in normal range

† Creatinine clearance should be calculated per institutional standard.
§ Patients with hypokalemia at screening must be corrected prior to initiating treatment.

7. Female patient of childbearing potential must have a negative serum or urine pregnancy test β-hCG within 72 hours prior to receiving the first dose of study medication and agree to the use of effective methods of contraception while on study.

8. Any number of prior lines of chemotherapy in the metastatic setting is allowed.

9. Concomitant use of bisphosphonates is allowed.

10. Patients with stable and clinically insignificant CNS disease are allowed. Patients must be off steroids with no new CNS symptoms or findings on radiographic imaging for 1 month.

11. Patients willing and able to complete the questionnaires.

12. Patients willing and able to comply with the study protocol for the duration of the study.

13. Written informed consent prior to any study-specific screening procedures with the understanding that the patient may withdraw consent at any time without prejudice.

3.2 Subject Exclusion Criteria

A patient meeting any of the following criteria is not eligible to participate in this study:

1. Patients who have had chemotherapy or radiotherapy within two weeks, 4 weeks for nitrosoureas, mitomycin C, pegylated-doxorubicin and one half-life for bevacizumab, hormone therapy within one week, trastuzumab within 2 weeks or lapatinib within one week of study Day 1.

2. If the patient has residual toxicity from prior treatment, toxicity must be ≤ Grade 1.

3. Patients with non-healing surgical wounds. Patients must be at least two weeks from a major surgical procedure, and surgical wounds must be completely healed.

4. Patients with known active CNS metastases and/or carcinomatous meningitis. However, patients with CNS metastases who have completed a course of therapy would be eligible for the study provided they are clinically stable for at least 1 month prior to entry as defined as:
    a. no evidence of new or enlarging CNS metastasis
    b. off steroids that are used to minimize surrounding brain edema. Patients with clinically insignificant brain metastases that do not require treatment are eligible.

5. Patients with known hypersensitivity to the components of study drug or its analogs.

6. Significant cardiovascular impairment:
    a. Congestive heart failure, Clinically significant cardiac arrhythmia, history or current evidence of a myocardial infarction during the last 6 months, and/or a current ECG tracing that is abnormal in the opinion of the treating Investigator, or unstable angina
    b. QTc prolongation >480 msec (Bazett's Formula) or congenitally long QT syndrome

7. Severe/uncontrolled concurrent illness/infection

8. Patients with other active, current primary malignancies, other than carcinoma in situ of the cervix or non-melanoma skin cancer

9. Patients with a hypersensitivity to halichondrin B and/or halichondrin B chemical derivative

10. Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

11. Patients with other significant disease or disorders that, in the Investigator’s opinion, would exclude the patient from the study

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 SUBJECT REGISTRATION AND ENROLLMENT

4.1 Subject Recruitment & Study Sites

Patients will be screened by the medical oncologists in the oncology practice clinics at participating sites. Patients to be screened will include those currently followed in these practices, as well as those referred from outside providers.

4.2 Registration Procedures

After eligibility screening, patients selected to participate will be registered with the local study site/institution first, then with the lead/coordinating center at University of San Francisco-California Helen Diller Family Comprehensive Cancer Center.

4.2.1 Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization form/Heath Insurance Portability and Accountability Act (HIPAA) authorization form. Patients must be registered with the institution before beginning any treatment or study activities.

4.2.2 Lead Center Registration

To initiate lead center registration, local study sites/institutions should forward copies of the signed informed consent, research authorization/HIPAA forms, and the completed and signed eligibility checklist and any supporting source documentation to clinical research coordinator (CRC) at the lead center by fax to the number on Page 1. The CRC will check the forms for completeness and contact the site regarding any discrepancies

The lead center will then assign a unique patient study identification number, and send a confirmation of patient registration to the local CRC via electronic mail. A copy of this confirmation will be retained by both the lead center and local institution. All future study documentation related to that patient should include the assigned patient ID number.

A patient cannot be treated until confirmation of enrollment is received.

5.0 STUDY DESIGN AND TREATMENT PLAN

5.1 Dose and schedule

Table 5-1. Dose Escalation Schedule

Dose Level	Dose*		
	Eribulin mesylate (mg/m^2)	Cyclophosphamide (mg/ m^2)	Number of patients
Phase Ib			
Level -1	0.7 day 1, 8	600 day 1	3-6
Level 0 (start)	1.1 day 1, 8	600 day 1	3-6
Level 1	1.4 day 1, 8	600 day 1	3-6
Phase II			
	MTD determined in phase I	600 day 1	40
*Doses are stated as exact dose in units (e.g., mg/m^2, mcg/kg, etc.) rather than as a percentage.			

Phase Ib: The study will follow a standard dose-confirmation schema (phase Ib portion) with 3 to 6 patients per cohort (3+3 design) for a total of 9-18 patients with any solid tumor malignancy. The starting dose level will consist of eribulin mesylate 1.1 mg/ m^2 on days 1 and 8 followed by cyclophosphamide 600 mg/ m^2 on day 1 of a 21-day cycle.

- If no DLTs are observed in the first three patients, the dose of eribulin will be escalated to the next dose level for the subsequent patients.
- If one of three patients experiences a DLT, three additional subjects will be enrolled in that expanded cohort for a total of no more than 6 patients in each cohort.
- If no additional DLT is observed at the expanded dose level, i.e. 5 of 6 do not experience DLT during the first cycle, the dose of eribulin will be escalated to the next level.
- If 2 or more dose-limiting toxicities (DLTs) during the first cycle of therapy at any dose level occur, escalation will cease and cohort expansion will continue at the next lower dose level.
- All patients at a given dose level will be followed on treatment for at least 3 weeks (one cycle) before accrual to the next cohort can commence.
- There will be no intra-patient dose escalation allowed.
- For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level.
- For the purposes of Phase Ib dose escalation, DLTs will be defined as any treatment-related toxicity occurring within the first 21 days of combination therapy as grade 3 or 4 clinically evident non-hematologic toxicity; grade 4 neutropenia or thrombocytopenia lasting > 7 days or febrile neutropenia; or any clinically significant toxicity grade 2 or higher that requires more than 14 days to resolve.
- The highest dose level at which no more than one of six subjects experience DLT defines the MTD. Once the MTD has been defined, enrollment of subjects into the dose-expansion (Phase II) study in advanced breast cancer patients will commence.
- Phase 1b will be conducted at UCSF.

Phase II: The dose-expansion (phase II portion) will enroll 40 patients with advanced breast cancer to detect a clinically meaningful benefit rate (efficacy and response) of at least 25% in the study cohort. Phase 2 will be conducted at multiple sites, to be determined. Using a two-stage Simon's minimax design, the null and alternative hypothesis will be H0: p0 < 10% versus Ha: p1 > 25% for proportion of patients with complete or partial response by RECIST criteria. Based on defined p0=10% and p1=25% under the type I error of 5% and the type II error rate of 20%, the sample size for the first stage will be 22 patients. If 2 or fewer responses are observed in the first 22 patients (after all patients in the first stage have completed at least 2 months of treatment), the study will be terminated in the first stage; otherwise, the study will be expanded by additional 18 patients. If there are 7 or fewer responses are observed by the end of the second stage, no further investigation of the drug is warranted. If the clinical benefit rate is less than 10%, the probability of ending the study during the first stage is 62%. If the clinical benefit rate is greater than 25%, the probability that the study will be stopped in the first stage is 6%.

5.2 Dose-Limiting Toxicity Phase Ib

Toxicities will be graded in severity according to the guidelines outlined in the NCI-CTCAE version 4.0, published date 28-May-2009. Dose-limiting hematologic and non-hematologic toxicities will be defined differently, and will be based on events occurring during the first cycle of study drug administration (weeks 1-3). To be considered a dose-limiting toxicity (DLT), an adverse experience must be related to study drug, and must not be related to disease progression or intercurrent illnesses.

Patients must receive ≥1 of 2 weekly treatments of eribulin during the first cycle in order to be evaluable for DLT. If therapy is delayed >14 days during the first cycle attributable to study drug, this is considered a DLT and the patient will not be replaced. If therapy is delayed due to another reason, the patient will be replaced.

5.2.1 Hematologic dose-limiting toxicity

- Grade 4 neutropenia lasting for ≥7 days in duration despite growth factor support. GCSF (Filgrastim) or Pegylated-GCSF (Neulasta) may be administered. Filgrastim may be used for ANC < 1000 at any time, or as prophylaxis in patients at risk for neutropenia. GCSF may not be administered within 24 hours of a chemotherapy infusion. When administered, this does not constitute a DLT.
- Grade 4 neutropenia with fever >38.5° C and/or infection requiring antibiotic or anti-fungal treatment
- Grade 4 thrombocytopenia (≤25.0 x 10^9/L)
- Grade 3 thrombocytopenia complicated by bleeding and/or requiring platelet or blood transfusion

5.2.2 Non-hematologic dose-limiting toxicity

This will be defined as any Grade ≥3 non-hematologic toxicity, with the specific exception of:

- Grade 3 nausea or Grade 3 vomiting that in the opinion of the investigator/sponsor occurs in the setting of inadequate compliance with supportive care measures and lasts for less than 48 hours.
- Grade 3 diarrhea that in the opinion of the investigator/sponsor occurs in the setting of inadequate compliance with supportive care measures and lasts for less than 48 hours.
- Grade 3 dehydration that in the opinion of the investigator/sponsor occurs in the setting of inadequate compliance with supportive care measures and lasts for less than 48 hours.
- Alopecia
- Asthenia
- Inadequately treated (in the opinion of the investigator/sponsor) hypersensitivity reactions
- Grade 3 elevated transaminases of ≤1 week in duration. In patients with known liver metastases and abnormal LFTs at baseline, grade 3 elevated transaminases of ≤1 week in duration must be ≥2x baseline to meet criteria for DLT.
- Grade 3 total hyperbilirubinemia if <35% is direct component
- Hyperglycemia: isolated non-fasting Grade 3 glucose values or Grade 3 hyperglycemia that in the opinion of the investigator/sponsor occurs in the setting of inadequate compliance with supportive care measures.

The following will be considered DLT:

- ≥ Grade 3 electrolyte (Na, K, Ca, Mg, Cl, phosphate, and bicarbonate) abnormalities due to glucose intolerance and not attributable to another cause

- Symptomatic bradycardia
- Persistent increases in QTc interval (>60 milliseconds from baseline and/or >500ms)
- Treatment delay of greater than 14 days
- Failure to administer ≥75% of the planned study drugs during cycle 1 as a result ≥ Grade 2 treatment-related toxicity

Subjects who fail to complete the first cycle due to reasons other than toxicity will be classified as not evaluable for toxicity, and will be replaced as in Section 5.1. No dose reductions can occur within the DLT window, see Table 6-1.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression
- Need for exclusionary concurrent treatment
- Unacceptable toxicity
- Patient decides to withdraw from the study
- Protocol non-compliance
- Study is completed or terminated

The reason for study removal and the date the patient was removed must be documented in the data management system.

5.4 Conditions for Terminating the Study

The Principal Investigator may terminate the study for any of the following reasons:

- Significant toxicities
- The study treatment is less effective than standard treatment
- Completion of all study data.

6.0 TOXICITY MANAGEMENT AND DOSE MODIFICATION

Toxicities will be graded for management according to NCI-CTCAE version 4.0. Eribulin and cyclophosphamide dose-modification guidelines are outlined in Table 6-1.

Both agents should be held for all instances of febrile neutropenia (ANC < 1000/μL). GCSF (Filgrastim) or Pegylated-GCSF (Neulasta) growth factor support is encouraged for ANC < 1500/ μL and may be used at the discretion of the treating physician in order to maintain adequate blood counts. Filgrastim may be used for ANC < 1000 at any time, or as prophylaxis in patients at risk for neutropenia. Growth factor support is not permitted within 24 hours prior to or following any infusion.

How to administer eribulin and cyclophosphamide when a delay is required: the goal is to administer the agents on the same day whenever possible. See table 6-1 for full details.

6.1 Removal of patients from study:

If toxicity occurs in a patient at the 0.7 mg dose of eribulin, no further reduction will occur and the patient will be discontinued from the study. The dose of cyclophosphamide will not be reduced.

If any treatment is held for >3 weeksdue to delayed toxicity recovery from any of the therapies, the patient will be removed from the study.

After the first cycle, patients are allowed to miss 1 out of every 2 weeks of treatment due to hematologic or non-hematologic toxicity. Treatment delays are made at the discretion of the treating physician. Treatment or visit delays due to public holidays, weather conditions, or natural disasters, do not constitute protocol violations. The following treatment delays are allowable for patient coordination:

- Cycle 1, Day 8 – delay eribulin administration up to 1 day
- Cycle 2+, Day 1 – delay treatment up to 14 days
- Cycle 2+, Day 8 – delay treatment up to 3 days

If a delay of >3 weeks in subsequent cycles (after Cycle 1) is required, the patient must discontinue permanently from the study protocol.

6.2 Concomitant Medications

Concomitant treatments permitted: anti-emetics, anti-diarrheals, anti-allergic medications including antihistamines and steroids, granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor/erythropoietin is allowed in response to cytopenias, palliative radiotherapy, bisphosphonate treatment, weak inhibitors of CYP3A4.

For patients receiving study treatment, any medication (including over-the-counter medications) will be recorded on the CRF (case report form).

Concomitant treatments not permitted: other investigational drugs; anti-tumor therapies including chemotherapy, hormone therapy, radiation therapy (other than required for palliation), gene therapy, biologics, or immunotherapy.

Use of strong CYP3A4 inhibitors should be avoided: ketoconazole, itraconazole, clarithromycin, nefazadone, saquinavir, telithromycin, ritonavir, indinavir, nefinavir. See Appendix B. Grapefruit juice may also increase plasma concentrations of eribulin and should be avoided.

Caution should be used when administering mild or moderate CYP3A4 inhibitors during treatment, and alternative therapeutic agents that do not inhibit CYP3A4 should be considered. Patients receiving CYP3A4 inhibitors during treatment should be monitored closely for acute toxicities (e.g blood counts in between cycles.) See Appendix B.

Caution should be used for CYP3A4 substrates with a narrow therapeutic index.See Appendix B.

6.3 Supportive Care Guidelines

Patients should be treated with supportive care measures at the discretion of the treating physician according to standard practices guidelines.

Diarrhea: Anti-diarrheal agents should not be taken prophylactically. Patients should be instructed to begin taking anti-diarrhea medication at the first sign of poorly formed or loose stool, occurrence of more bowel movements than usual in one day, or unusually high volume of stool. Anti-diarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied with fever. In this setting, an infectious etiology must be considered and excluded.

Rash: Skin rash and can be treated with standard topical steroids and/or oral antibiotics, antihistamines, sulfadiazine, or even a short course of oral steroids (less than 7 days) if clinically indicated.

Nausea/Vomiting: Anti-emetic therapy beyond routine premedication is not necessary, but symptomatic patients should be treated with standard anti-emetic medications including a 5HT3 receptor antagonist.

Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia after the first cycle.

Neutropenia: GCSF (Filgrastim) or Pegylated-GCSF (Neulasta) may be administered to treat ANC < 1000 at any time, or as prophylaxis in patients at risk for neutropenia. GCSF may not be administered within 24 hours of a chemotherapy infusion.

Hypersensitivity/Allergic reaction: Hypersensitivity reactions will be managed by the treating physician per standard protocols. Whether to rechallenge the patient or discontinue the offending agent will be decided by the treating physician. Dose reductions will not be made for hypersensitivity reactions.

Table 6-1. Toxicity management guidelines for eribulin and cyclophosphamide

Toxicity	NCI-CTC grade, unless otherwise specified	management of eribulin	eribulin dose upon resumption	management of cyclophosphamide	cyclophosphamide dose upon resumption
Neutropenia (ANC <1000) +/- fever (T>38)	1st episode	hold until afebrile and ANC ≥ 1000	no change and add filgrastim	hold until afebrile and ANC ≥ 1000	no change and add filgrastim
	2nd episode	hold until afebrile and ANC ≥ 1000	no change	hold until afebrile and ANC ≥ 1000	reduce to 500 mg/m^2 and continue filgrastim
	3rd episode	hold until afebrile and ANC ≥ 1000	reduce by one dose level	hold until afebrile and ANC ≥ 1000	continue 500 mg/m^2; continue filgrastim
	4th episode	remove from study	remove from study	remove from study	remove from study
Thrombocytopenia	Grade 2 or greater (<75K)	hold until ≥ 75K	no change	hold until ≥ 75K	reduce to 500 mg/m^2
	Recurrent grade 2 or greater	hold until ≥75K	reduce by one dose level	hold until ≥ 75K	no change
	3rd occurrence grade 2 or greater	hold until ≥ 75K	no change	hold until ≥ 75K	reduce to 400 mg/m^2
	4th occurrence grade 2 or greater	remove from study	remove from study	remove from study	remove from study
Rash	1 or 2	continue treatment; supportive care	no change**	continue treatment	no change
	3	Hold until grade 1 or less; supportive care	no change**	Hold until grade 1 or less	no change
	Recurrent grade 3	Hold until grade1 or less; supportive care	reduce by one dose level	Hold until grade 1 or less	no change
	3rd occurrence grade 3	remove from study; supportive care	remove from study	remove from study	remove from study

Toxicity	NCI-CTC grade, unless otherwise specified	management of eribulin	eribulin dose upon resumption	management of cyclophosphamide	cyclophosphamide dose upon resumption
GI toxicity: diarrhea, nausea, vomiting	1, 2	Continue treatment	no change; maximize supportive treatment	no change; maximize supportive treatment	no change; maximize supportive treatment
	3	Hold until grade 1 or less	no change	hold until grade 1 or less	no change
	recurrent 3	Hold until grade 1 or less	no change	hold until grade 1 or less	reduce to 500 mg/ m^2
	3rd occurrence	Hold until grade 1 or less	reduce by one dose level	hold until grade 1 or less	no change
	4th occurrence grade 3 or 4	remove from study	remove from study	remove from study	remove from study
Liver function abnormalities (ALT, AST, Alk Phos only)	1, 2	Continue treatment	no change	Continue treatment	no change
	3 and > 2x baseline	Hold until less than grade 3	no change	Hold until less than grade 3	Reduce to 500 mg/ m^2
	recurrent 3 and > 2x baseline	Hold until less than grade 3	reduce by one dose level	Hold until less than grade 3	no change
	4th occurrence grade 3 or 4	remove from study	remove from study	remove from study	remove from study
Neuropathy (motor and sensory)	1, 2	continue treatment	no change	continue treatment	no change
	3	Hold until less than grade 3	no change	Hold until less than grade 3	no change
	Recurrent 3	Hold until less than grade 3	reduce by one dose level	Hold until less than grade 3	no change
	3rd occurrence 3	remove from study	remove from study	remove from study	remove from study

* A cycle is a 3-week course. If treatment needs to be held for >48 hours, the dose should be held for that week and resumed the following week. If doses are held for more than 3 weeks, the patients must be removed from study.

** If Grade 2 rash develops but resolves to grade ≤ 1 within 7 days allowing the patient to resume treatment, the patient should be restarted at the same dose.

7.0 DRUG INFORMATION

7.1 Eribulin mesylate (Halaven™)

(Source: FDA-approved product insert, dated 11/2010)

Classification: microtubule inhibitor

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

Metabolism: Eribulin is eliminated primarily in feces unchanged. After administration of 14C-eribulin to patients, approximately 82% of the dose was eliminated in feces and 9% in urine. Unchanged eribulin accounted for approximately 88% and 91% of the dose in feces and urine, respectively.

Storage and Stability: Store at 25°C (77°F); excursions permitted to 15° – 30° C (59° -86° F). Do not freeze. Store the vials in their original cartons.

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

Discard unused portions of the vial.

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

Aseptically withdraw the required amount of eribulin from the single-use vial and administer undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP as IVP over 2-5 minutes.

Patient care implications: Do not dilute in or administer through an intravenous line containing solutions with dextrose. Do not administer in the same intravenous line concurrent with the other medicinal products.

Incompatibilities/Contraindication: No drug-drug interactions are expected P-gp inhibitors. Cytochrome P450 3A4 (CYP3A4) negligibly metabolizes eribulin *in vitro*. Eribulin inhibits CYP3A4 activity in human liver microsomes, but it is unlikely that eribulin will substantially increase the plasma levels of CYP3A4 substrates. However, strong CYP3A4 inhibitors and inducers will be prohibited in this study, see Appendix B.

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

There are no known contraindications.

Side Effects:

Common side effects:

Neutropenia Anemia asthenia/fatigue alopecia	peripheral neuropathy nausea constipation

Less common side effects:

lacrimation	upper respiratory tract infection
dyspepsia	hypokalemia
abdominal pain	muscle spasms, muscular weakness
stomatitis	dysgeusia, dizziness
dry mouth	insomnia, depression
peripheral edema	rash
	liver function test changes

Cardiac toxicity:
QT prolongation has rarely been observed. ECG and electrolyte (potassium and magnesium) monitoring is recommended in patients with history of heart failure or bradyarrhythmias and in patients using drugs known to prolong the QT interval. Eribulin should be avoided in patients with congenital long QT syndrome.

Availability: Eribulin mesylate injection, 1 mg/2 mL, in a single-use vial. One vial per carton. Drug will be provided by Eisai, Inc and will investigationally labeled, but is identical in formulation to the commercial product.

Accountability: Drug accountability records will be maintained by the investigational pharmacy as per standard pharmacy practice. Eisai will request drug accountability confirmation on a periodic basis. Standard information such as drug supply utilized and supply remaining will be requested.

Unused or expired drug will be destroyed by USCF per standard operating procedures and a certificate of destruction (including product lot and expiry, amount destroyed and method of destruction) will be provided to Eisai.

7.2 Cyclophosphamide (Cytoxan®)

Product description: Lyophilized CYTOXAN® (cyclophosphamide for injection, USP) is a sterile white lyophilized cake, or partially broken cake, containing 75 mg mannitol per 100 mg cyclophosphamide (anhydrous). Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards. Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P \cdot H_2O$ and a molecular weight of 279.1. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is soluble in water, saline, or ethanol and has the following structural formula. Please refer to the package insert for complete product details.

Classification: Alkylating agent

Mode of Action: Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites by a mixed function microsomal oxidase system. These metabolites interfere with the growth of susceptible rapidly proliferating malignant cells. The mechanism of action is thought to involve cross-linking of tumor cell DNA.

Metabolism: Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours. It is eliminated primarily in the form of metabolites, but from 5 to 25% of the dose is excreted in urine as unchanged drug. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose.

Storage and Stability: Storage at or below 77°F (25°C) is recommended; this product will withstand brief exposure to temperatures up to 86°F (30°C) but should be protected from temperatures above 86°F (30°C).

Reconstituted Lyophilized CYTOXAN are chemically and physically stable for 24 hours at room temperature or for six days in the refrigerator; it does not contain any antimicrobial preservative and thus care must be taken to assure the sterility of prepared solutions.

Preparation: Refer to the package insert for standard preparation instruction. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Lyophilized CYTOXAN should be prepared for parenteral use by adding Sterile Water for Injection, USP, to the vial and shaking to dissolve. Use the quantity of diluent shown in the package insert.

Administration: Route of administration: Cyclophosphamide will be administered as an IV infusion over 60-120 minutes.

Solutions of Lyophilized CYTOXAN will be infused intravenously in the following: Dextrose Injection, USP (5% dextrose); Dextrose and Sodium Chloride Injection, USP (5% dextrose and 0.9% sodium chloride); 5% Dextrose and Ringer's Injection; Lactated Ringer's Injection, USP; Sodium Chloride Injection, USP (0.45% sodium chloride); Sodium Lactate Injection, USP (1/6 molar sodium lactate).

Patient care implications: To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing CYTOXAN sterile powder for injection. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

Incompatibilities/Contraindications: Continued use of cyclophosphamide is contraindicated in patients with severely depressed bone marrow function. Cyclophosphamide is contraindicated in patients who have demonstrated a previous hypersensitivity to it.

Side Effects:

Myelosuppression	Pain
Liver function test abnormalities	Hemorrhagic cystitis
Impairment of fertility	Hemorrhagic ureteritis
Rash	Urinary bladder fibrosis
Skin pigmentation changes	Renal tubular necrosis
Nail changes	Hemorrhagic colitis
Stevens-Johnson syndrome	Intersititial pnemonitis
Congestive heart failure	Intersititial pulmonary fibrosis
Infusion-related symptoms such as fever, chills, rigors, headache	Jaundice
	Infections
Abdominal discomfort	Secondary malignancy
Nausea	Anemia, thrombocytopenia, leukopenia, neutropenia
Vomiting	
Diarrhea	Anaphylaxis
Mucositis, oral ulceration	SIADH
Alopecia	Malaise
Anorexia	Asthenia

Availability: CYTOXAN® (cyclophosphamide for injection, USP) contains cyclophosphamide monohydrate and is supplied in vials for single-dose use.

Accountability: Drug accountability records will be maintained by the investigational pharmacy as per standard pharmacy practice.

8.0 CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic (PK) Studies

Whole blood for pharmacokinetic assessments of eribulin and cyclophosphamide will be drawn in 6 mL tubes on Cycle 1 Day 1 pre-dose, at the end of eribulin infusion, and at 15 min, 30 min, hour 1, 2, 3, 4, 6 and 8 after the end of eribulin. Participation in the pharmacokinetic assessment portion of the protocol, i.e. recruitment during dose-escalation will be limited to patients enrolled in the Phase Ib portion of the trial.

Description of collection, handling and shipping procedures of PK samples will be provided in Appendix F.

Handling of Specimens(s) – Standard phlebotomy handling

Site(s) Performing Correlative Study – XenoBiotic Laboratories, Inc.

Shipping of Specimen(s) –
Blood will be processed and shipped on dry ice by overnight mail on Monday-Wednesday to:

[redacted]

Notification on the day of shipping should be sent to:

[redacted]

8.2 Circulating Tumor Cells

Collection of Specimen(s)
Three tubes of blood will be collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment (2 CellSave tubes and 1 purple top tube) in each patient. 7.5 mL of blood is required per CellSave tube, it is critical that the tube be completely filled. 10mL is required in each purple top tube. One CellSave tube will be used for CTC enumeration, the second CellSave tube will be used for sorting and WGA with CGH/sequencing. The purple top tube will be used for gene expression if there is adequate sample. If the first sample has ≥ 5 CTC/mL, on Cycle 2 Day 1, 1 CellSave and 1 purple top tube will be collected for CTC enumeration and aCGH/gene expression.

2 CellSave tubes and 1 purple top tube should be obtained at end of study if at all possible.

Handling of Specimens(s) – Standard phlebotomy handling

Site(s) Performing Correlative Study – John Park MD laboratory, UCSF

Shipping of Specimen(s) –
UCSF: No shipment is required. Samples will be hand-delivered at room temperature to the Park laboratory immediately after they are obtained and processed immediately.

Outside sites: Blood will be shipped at room temperature by overnight mail to:

[redacted]

Notification on the day of shipping should be sent to:
[redacted]

Special instructions will be provided for Friday shipping.

8.3 Pharmacogenomic (PG studies)

One 7.5 mL purple top tube will be collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment. DNA extraction and analysis for three novel candidate genes which may relate to development of peripheral neuropathy, FZD3, FGD4 and EPHA5 will be performed. Other exploratory analysis may also be performed. If adequate sample remains, a genome scan at UCSF may also be performed.

Handling of Specimens(s) – Standard phlebotomy handling

Site(s) Performing Correlative Study – Deanna Kroetz laboratory, UCSF

Shipping of Specimen(s) –
UCSF: No shipment is required. Samples will be sent by courierat room temperature to the Kroetz laboratory immediately after they are obtained and processed immediately.

Outside sites: Blood will be shipped at room temperature by overnight mail to:
[redacted]

8.4 Archived Tissue Analysis

Collection of Specimen(s)
FFPE (formalin-fixed paraffin embedded) archived tumor blocks from prior surgery or biopsies with corresponding H&E slides, will be requested for all patients, although they are not required and should not delay enrollment. If necessary, the research team will contact outside institutions to obtain specimens.

All patients consenting to this protocol will be presented with a Tumor Specimen Release Form. These specimens will become the property of UCSF Cancer Center and will be stored at the Cancer Center Tissue Core at UCSF [redacted].

Mutational analyses will be performed on tumor tissue and correlated with results from CTC studies described above.

9.0 STUDY PROCEDURES

9.1 Screening assessments

Screening radiographic studies, EKG, and laboratory studies must be performed within 30 days of starting protocol therapy.

If laboratory studies are performed within 14 days of starting protocol therapy, these can serve as day one values.

- CT scan of chest/abdomen/pelvis
- Bone scan for patients with known or suspected bone metastases
- PET/CT scan with a diagnostic CT may be substituted for the above two scans
- Additional radiographic studies for known sites of disease not evaluated by the above scans
- EKG
- CBC with differential
- Serum biochemical panel including Na, K, HC03-, Cl-, Ca, Mg, Phos, BUN, creatinine, glucose, total bilirubin, AST, ALT, alkaline phosphatase
- Negative serum pregnancy test for females of child-bearing potential
- Concomitant medication review

9.2 Assessments and Procedures During Treatment

Once the patient is confirmed to be eligible based on screening assessments, the following study assessments will be performed (see also study calendar below).

Each cycle will be 21 days (3 weeks). Patients will receive eribulin on day 1 and 8 and cyclophosphamide on day 1 of each cycle. Treatment delay of greater than 7 days or missing >1 out of the 2 weekly doses in the first cycle due to toxicity will be considered a DLT. If a dose is held a week, then that week's dose is omitted and treatment resumes at the next scheduled infusion without prolongation of the 3 week cycle.

Cycle 1 (Day 1)

The following assessments will be performed prior to receiving treatment on Cycle 1 Day 1:

- Medical history, physical examination including vital signs, ECOG performance status
- Adverse event and con-med review
- CBC with differential, serum biochemical panel (labs performed for screening within 14 days of treatment start can be used for baseline values)
- EKG – to be read by a cardiologist
- Pharmacokinetic blood work – day 1 only
- Research blood work – at baseline and per schema
- EORTC QLQ-C30
- 10-point Modified Total Neuropathy Score (mTNS)
- FACT/GOG-Ntx

Cycle 1 Day 8

- CBC with differential, serum biochemical panel
- EKG – to be read by clinician. If there is an unanticipated abnormal EKG, a cardiologist will be consulted prior to patient treatment

Cycle 2 and every cycle thereafter

The following assessments will be performed on day 1 and day 8 (or within 24 hours prior) of every cycle:

- CBC with differential, serum biochemical panel

For Phase 2, Day 8 visits will only occur in Cycle 2.

The following assessments will be performed on day 1 of (or within 72 hours prior to) every cycle:

- Medical history and physical exam
- Adverse event and con-med review
- 10-point Modified Total Neuropathy Score (mTNS)
- FACT/GOG-Ntx

Imaging:

Phase 1b (all solid malignancies)
At 6 weeks after study start, then every 6 weeks until end of study therapy

- CT scan of chest/abdomen/pelvis
- Bone scan should be performed as indicated to evaluate change in symptoms
- PET/CT with diagnostic CT scan can substitute for the two above studies
- Additional radiographic studies for known sites of disease not evaluated by the above scans
- Pertinent tumor markers per treating physician's discretion

Phase II (breast cancer only)
At 6 weeks after study start, then every 9 weeks until end of study therapy

- CT scan of chest/abdomen/pelvis
- Bone scan should be performed as indicated to evaluate change in symptoms
- PET/CT with diagnostic CT scan can substitute for the two above studies
- Additional radiographic studies for known sites of disease not evaluated by the above scans
- Pertinent tumor markers per treating physician's discretion

EORTC QLQ-C30
6 weeks, 3 months, 12 months, 18 months, 24 months, and/or at study termination.

9.3 Study Termination

The following assessments will be performed when the patient goes off-study:

- Physical exam
- Adverse event and con-med review
- CBC with differential, serum biochemical panel
- EORTC QLQ-C30
- 10-point Modified Total Neuropathy Score (mTNS)
- FACT/GOG-Ntx
- Radiographic imaging of evaluable and measurable disease

9.4 Follow-up

Patients' clinical data will be collected monthly for the first 3 months after completion of the clinical trial, then every 6 months. These biennial assessments will continue until death or for duration of up to at least ten years. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event and then for at least ten years to obtain recurrence/survival data.

Table 9-1 Study Calendar

Test/Study	Pre-study	Cycle 1 (Days 1-21)		Cycle 2		Cycle 3 and subsequent cycles		Off study
		D1	D8	D1[2]	D8	D1[2]	D8	
Medical History	X[1]	X		X[2]		X[2]		X
Physical Exam[3]	X[1]	X		X[2]		X[2]		X
Informed consent	X[1]							
Inclusion/exclusion	X[1]							
Toxicity assessment (including weight)			X	X	X	X	X[18]	X
PK[4]		X						
PG[5]	X							
EKG[6]	X[1]		X					
CBC, Diff.[7]	X[1]	X[1]	X	X	X	X	X[18]	X
Chemistry[8]	X[1]	X[1]	X	X	X	X	X[18]	X
CTC enumeration and analysis[9]	X			X				X
Genome scan[10]	X							
Archival tumor tissue collection[11]	X							
Eribulin administration[12]		X	X	X	X	X	X	
Cyclophosphamide administration		X		X		X		
Pregnancy Test[13]	X[1]							
Staging Studies (RECIST)[14]	X				X			X
EORTC QOL-C30 questionnaire[15]	X				X			X
Neuropathy assessment[16]	X			X		X		X
FACT-GOG Ntx[17]	X			X		X		X

Evaluations should continue as noted for all subsequent cycles. Day 1 visit procedures for any cycle of therapy are allowed a window of ± 3 days unless otherwise noted.

X[1] Pre-study tests may be used for Day 1 tests if within 2 weeks and no significant changes have occurred.

X[2] D1 physical exam and history in subsequent cycles may be done within 72 hours prior to next cycle.

X[3] Physical Exam includes ECOG status, vital signs, height and weight.

X[4] Pharmacokinetic samples to be collected from patient at study site Day 1 pre-dose, at the end of eribulin infusion, and at 15 min, 30 min, 1, 2, 3, 4, 6 and 8 hours after the end of eribulin in phase Ib and analyzed by an outside vendor.

X[5] Pharmacogenomic samples to be collected from patient at study site will be collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment and analyzed by Dr. Deanna Kroetz' laboratory at UCSF.

X[6] EKG will be performed at baseline and analyzed by a cardiologist. EKG performed on cycle 1 day 8 will be analyzed by the clinician. If there is an unanticipated abnormal EKG, a cardiologist will be consulted prior to patient treatment.

X[7] Hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.

X[8] BUN, creatinine, sodium, potassium, chloride, CO_2 (HCO_3), glucose, calcium, albumin, total protein, total bilirubin, alkaline phosphatase, LDH (melanoma only), AST/SGOT, ALT/SGPT, phosphorous, magnesium. If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed. Biochemistry tests should be obtained after patient has fasted, if possible.

X[9] CTC (circulating tumor cells) will be collected using whole blood by study site and enumerated by Dr. John Park's lab at UCSF using either CellSearch or IE/FACS. The first sample will be collected on cycle 1 day 1 collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment. Baseline/cycle 1 analysis will include genomic profiling and gene expression for tubulin mutations and others. If initial sample shows CTC ≥ 5/mL, a second sample with be enumerated and aCGH/gene expression may be performed on cycle 2 day 1.

X[10] Genome scan to be collected by study site, processed by the DNA bank at UCSF and then analyzed at Dr. Kwok's laboratory at UCSF.

X[11] If available, archival tumor tissue will be collected from the pathology department and analyzed for expression profiling including tubulin mutations and proteomics.

X[12] Treatment delays due to patient coordination are allowed for the following: Cycle 1, Day 8 (eribulin delay up to 1 day), Cycle 2+, Day 1 (treatment delay up to 14 days), and Cycle 2+, Day 8 (delay treatment up to 3 days). Note – treatment or visit delays due to public holidays, weather conditions, or natural disasters, do not constitute protocol violations.

X[13] Pregnancy test is for women of child bearing potential and will be assessed by serum hcg.

X[14] Baseline evaluations should be performed not more than 30 days prior to the beginning of the treatment. Scans should be performed as detailed in section 9.2 every 6 weeks (2 cycles) for phase Ib, and at 6 weeks, then every 9 weeks for phase II until disease progression or end of study therapy for any reason. A 7 day variation in timing before or after the scheduled scan date is allowed to facilitate scheduling. If patients remain on study for more than one year from study start, these assessments will be optional.

X[15] EORTC QLQ-C30 questionnaire will be performed at baseline (within 7 days of cycle 1 day) and thereafter at 6 weeks, 3 months, 12 months, 18 months, 24 months, and/or at study termination. Questionnaires will be completed prior to drug administration.

X[16] Neuropathy will be assessed using the 10-point Modified Total Neuropathy Score (mTNS) at the start of each cycle and at study termination.

X[17] Patient assessment of neuropathy will be assessed using the FACT-GOG-Ntx 11 point questionnaire at the start of each cycle and at study termination.

X[18] Cycle 3+, Day 8 visits are only required for Phase 1. For Phase 2, toxicity assessment will only be done on Day 1 of cycles 3 and beyond.

10.0 CRITERIA FOR EVALUATION

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at 6 weeks (after 2 cycles), then every 6 weeks (phase Ib) or 9 weeks (phase II) until end of study therapy. A one week window in scans is allowable to facilitate scheduling of scans; however every effort should be made to keep the scans on schedule. Confirmatory scans will not be performed since this is a Phase I/II trial and the primary endpoints are safety, toxicity, and clinical benefit rate.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer, Therasse et al. 2009). Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

10.1.1 Response Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first study treatment.

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

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

10.1.2 Disease Parameters

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

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

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

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

10.1.3 Methods for evaluation of measurable disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST 1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST 1.1 measurements. If the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST 1.1 measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published (Bubley, Carducci et al. 1999; Rustin, Quinn et al. 2004; Scher, Halabi et al. 2008). In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer (Vergote, Rustin et al. 2000).

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible new sites of disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). 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, this is not PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. Both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

> **Note**: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.1.4 Response Criteria

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

> **Note**: Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

Evaluation of Best Overall Response

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

Table 10-2. Evaluation of Patients with Measurable Disease (i.e., Target Disease)

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

* See RECIST 1.1 manuscript for further details on evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table 10-3. Evaluation of Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

10.1.5 Duration of Response

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

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

Response Review: N/A

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoint Definitions

The study will follow a standard dose-confirmation schema (phase Ib portion) with 3 to 6 patients per cohort (3+3 design) for a total of 9-18 patients. The starting dose level will consist of eribulin mesylate 1.1 mg/ m^2 on days 1 and 8 followed by cyclophosphamide 600 mg/ m^2 on day 1 of a 21-day cycle. Enrollment to successive cohorts up to dose level +1 will be performed according to the table shown below, to establish the MTD. If 2 or more dose-limiting toxicities (DLTs) are observed at level 0, one dose reduction (to level -1) is built in to the study design. All patients at a given dose level will be followed on treatment for at least 3 weeks before accrual to the next cohort can commence. There will be no intra-patient dose escalation allowed. For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level. For the purposes of Phase I dose escalation, DLTs will be defined as any treatment-related toxicity occurring within the first 21 days of combination therapy as grade 3 or 4 clinically evident non-hematologic toxicity; grade 4 neutropenia or thrombocytopenia lasting > 7 days or febrile neutropenia; or any clinically significant toxicity grade 2 or higher that requires more than 14 days to resolve.

The dose-expansion (phase II portion) will enroll 40 patients to detect a clinically meaningful benefit rate (efficacy and response including complete response, partial response and stable disease) of at least 25% in the study cohort. Using a two-stage Simon's minimax design, the null and alternative hypothesis will be H0: p0 < 10% versus Ha: p1 > 25% for proportion of patients with complete or partial response or stable disease by RECIST criteria. Based on defined p0=10% and p1=25% under the type I error of 5% and the type II error rate of 20%, the sample size for the first stage will be 22 patients. If 2 or fewer responses are observed in the first 22 patients (after all patients in the first stage have completed at least 2 months of treatment), the study will be terminated in the first stage; otherwise, the study will be expanded by additional 18 patients. If there are 7 or fewer responses are observed by the end of the second stage, no further investigation of the drug is warranted. If the clinical benefit rate is less than 10%, the probability of ending the study during the first stage is 62%. If the clinical benefit rate is greater than 25%, the probability that the study will be stopped in the first stage is 6%.

The circulating tumor cell data, pharmacodynamic and pharmacogenomic exploratory analysis will be reported using descriptive statistics only.

11.2 Accrual Objectives

Maximum of 18 patients in phase Ib, 40 in phase II.

11.2.1 Replacement of Patients:

For dose escalation decisions in Cycle 1, each cohort must have at least 3 patients evaluable for toxicity (unless the first 2 patients in the cohort experience a DLT). In Cycle 1, patients are considered non-evaluable and will be replaced if they do not receive at least one dose of eribulin (unless due to a DLT), or if they discontinue from the study prior to completing all safety and toxicity evaluations for 3 weeks. These patients must be replaced unless accrual to the cohort has stopped due to a DLT. Non-evaluable patients will not be included in the cohort total for DLT evaluation.

11.3 Stratification Factors

This is a Phase I/II trial. There will be no planned patient stratification factors.

11.4 Analysis of Secondary Endpoints

Efficacy – Although disease response is not a primary endpoint of the study, it will be assessed by clinical exam at defined time points (see table 9-1) and imaging after 6 weeks on study and then every 9 weeks until end of study treatment. Overall tumor response and time to progression will be assessed using RECIST 1.1 as described in Section 11. Response data will be correlated with dose as well as PD data in a descriptive manner.

Correlative studies – The CTC studies, pharmacogenomics, and evaluation of archived tissue are exploratory. Results will be reported using descriptive statistics only.

11.5 Reporting and Exclusions

11.5.1 Evaluation of toxicity.

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

11.5.2 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions will be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses will not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. The 95% confidence intervals will also be provided.

12.0 MULTI-CENTER GUIDELINES

This study is a multiple-institution, investigator- sponsored trial (IST) coordinated by UCSF. Phase 1 will be conducted at UCSF. Phase 2 will be conducted at multiple-institutions. The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.
The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and

progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

12.1 Responsibilities of the coordinating/lead center

The purpose of this section is to provide the regulatory guidelines needed for the conduct of multicenter investigator-initiated clinical trials where UCSF is the coordinating center. It is the Study Chair's responsibility to ensure that these guidelines are followed.

12.1.1 Oversight

The lead center will coordinate conference calls with participating sites approximately every 1 to 2 weeks to review adverse events, enrollment, safety data, cohort dose escalation, and other study matters. The dose level for ongoing enrollment will be confirmed for new patients scheduled at each site (see section 11 for more information).

The lead center CRC will insure that participating sites are notified of safety events.

Questions regarding the study or reporting of adverse events may be directed to the lead center CRC listed on Page 1 of this protocol.

12.1.2 Protocol Distribution

Upon approval by the coordinating center's IRB, the protocol will be distributed by the Study Chair or designee to the other participating sites via e-mail or private courier. The correspondence will include a description of changes made to the protocol and what action must be taken by the participating site.

If necessary, the Study Chair will forward a copy of the protocol to the drug manufacturer (Eisai) in accordance with the manufacturer's submission requirements.

12.1.3 Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The UCSF-HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol and its updates and safety information are distributed.

12.1.4 Documentation of Protocol Approvals

Documentation of protocol approval at each participating sites will be maintained in a file by the Study Chair or designee; copies must also be provided to the centralized regulatory staff of the UCSF-HDFCCC. It is the responsibility of the Study Chair to review these documents to ensure that participating sites are using the current protocol version.

12.2 Responsibilities of other participating sites

12.2.1 Study Initiation

Before the start of this study, the following documents must be submitted by the each site to the lead center CRC:

- U.S. Food and Drug Administration (FDA) Form 1572, signed by the site's Principal Investigator.
- Current curricula vitae and medical licenses of the site's Principal Investigator and all co-investigators.
- All investigators must also complete all regulatory documentation as required by local regulations.
- Written documentation of local IRB approval.
- Contact information (email, phone number, address) for the research pharmacist and designated contact person(s) (CRC and/or nurse) assigned to this study.

12.2.2 Patient Enrollment

Refer to section 4.0

12.2.3 Study Drug Supply and Accountability

Study drugs will be shipped from the drug manufacturer directly to the site. Each site will be responsible for drug accountability at their site. See Section 7.1 for specific instructions regarding study drug availability.

12.2.4 Approval of Protocol and Amendments

All protocol amendments must be approved by the participating site's IRB within 90 days of receipt. Failure to do so may result in the suspension of study activities at that site.

Upon approval of the protocol or amendment by a participating site's IRB, a copy of the approval documentation must be submitted (electronic or hardcopy) to the Study Chair.

13.0 DATA MANAGEMENT

Case Report Form (CRF) and Source Documentation

- Study data will be entered into OnCore via electronic CRFs and electronic signatures. OnCore meets HIPAA guidelines.
- Source documentation will be kept in separate file folders for each subject.
- All source documentation and CRF data will be made available for monitoring/auditing.

Regulatory Files

- Regulatory files will be maintained by the centralized regulatory office of the UCSF Helen Diller Family Comprehensive Cancer Center.

Record Retention

- All study documentation will be archived as per sponsor/grantor requirements or as per institutional guidelines, whichever is greater.
- The University of California Office of the President (UCOP) recommends that study-related documents be maintained for at least 3 years after completion of the study.

14.0 ETHICAL ASPECTS AND REGULATORY CONSIDERATIONS

14.1 Conduct of the study

This study will be conducted in accordance with ICH GCP guidelines and the Declaration of Helsinki.

14.2 Scientific Review

This study will be reviewed by the UCSF Comprehensive Cancer Center Protocol Review Committee (PRC) for scientific merit. After initial review and approval, the study will be reviewed at least once a year for scientific progress. Any changes to the protocol are to be reviewed and approved by the PRC.

14.3 Institutional Review Board / Independent Ethics Committee

The study will be reviewed by the Committee on Human Research (CHR), UCSF's IRB. After initial review and approval, the study will be reviewed at least once a year as per FDA regulations (21 CFR 56.109). Any changes to the protocol, consent form, and other associated documents are to be reviewed and approved by the CHR.

It is the responsibility of the Principal Investigator to keep the CHR informed of the progress of the study, including changes to the protocol or consent form, exceptions or deviations from the protocol, and any new developments which may affect subject safety or willingness to participate.

14.4 Investigational New Drug Application (IND)

An IND will be filed with the FDA. For non-exempt studies, annual reports will be submitted to the FDA within 60 days of the anniversary date that the IND went into effect, as per FDA regulations (21 CFR 312.33).

14.5 Additional Reporting Requirements

Reporting of Pregnancy to Eisai:
Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient or a male patient(s) partner (spontaneously reported to them) which occurs during the study or within 30 days of completing the study. Women who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to Eisai.

15.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

15.1 Adverse Event Definitions

15.1.1 Adverse Events

Any unfavorable or unintended sign, symptom, or illness that develops or worsens during the course of the study (treatment and follow-up) regardless of causality. This includes abnormal clinical or laboratory findings.

> Laboratory AEs: Laboratory test value abnormalities are recorded as adverse events if they are clinically significant. Laboratory AEs are clinically significant if they are designated as serious, require treatment, cause dose modification/delay or premature withdrawal from the study, or place the subject at risk for other toxicity.

Unexpected AEs: An AE is unexpected if it is not listed in the current labeling for the study drug (Investigator's Brochure, Package Insert, etc.), whether or not it has been previously reported. An unexpected AE may also be one that, although listed in the labeling, is greater in severity or occurs more frequently than expected.

15.1.2 Serious Adverse Events

A serious adverse event (SAE) is one that results in any of the following outcomes regardless of dose (including overdose):

- Death
- Life-threatening (places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred)
- Inpatient hospitalization or prolongs existing hospitalization,
- Persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions),
- Birth defect/congenital anomaly,
- Any important medical event that may not result in prior listed outcomes but, based upon appropriate medical judgment, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the prior listed outcomes.

15.2 Adverse Event Grading

Severity of AEs will be graded as follows:

Grade 1 – Mild (no limitations)
Grade 2 – Moderate (some limitations)
Grade 3 – Severe (requires medical attention; usual activities stop)
Grade 4 – Life-threatening/disabling (requires immediate medical help)
Grade 5 - Death

Causality of AEs will be graded as follows:

Unrelated
Unlikely related
Possibly related
Probably related
Definitely related

AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

15.3 Adverse Event Reporting Period

Reportable AEs are normally those that occur at initiation of study drug and within 6 weeks after the last administration of study drug. Unresolved AEs (those that begin during the reporting period and extended past the 6 week period) should continue to be reported on if the condition worsens or results in death.

AEs that begin after the end of the reporting period (after the 6 week period) are normally not reported, unless they are serious AND the primary investigator has reason to believe the event(s) might be related to study participation. During the last scheduled visit, the investigator should instruct the subject to report any event that the subject or the subject's referring physician believes might reasonably be related to study participation.

15.4 Adverse Event Reporting and Data Safety Monitoring

15.4.1 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (UCSF-HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data in each cohort
- Chairman will issue the approval to continue to the new dose level
- Monitoring every six months (depending on patient accrual)
- Review of all serious adverse events
- Minimum of a yearly audit

15.4.2 Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety at weekly study group or site committee meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include for each dose level the number of patients, significant toxicities as described in the protocol, doses adjustments, and observed responses.

The study coordinator will keep a log of subject(s) at each dose level in the UCSF-HDFCCC clinical trials management system (CTMS). DLTs will be documented in the CTMS. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort's dose, grade 3-5 AEs and SAE reports, and DLTs (if any) as described in the protocol. The report will be reviewed by the chairman or designee (maximum time 5 working days) and written authorization to proceed or a request for more information will be issued.

15.4.3 Review and Oversight Requirements

Adverse Event Monitoring

Adverse Events (AEs) will be recorded on the CTMS. All grade 3-5 expected and unexpected AEs will be recorded and updated at each visit.

Serious Adverse Event Reporting

Serious Adverse Event reporting will be in accordance with the UCSF Committee on Human Research (CHR) Regulations and Code of Federal Regulation (CFR) Title 21 Volume 5 Part 312.32.

UCSF CHR website for guidance in reporting serious adverse events:
http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.pdf

FDA website for guidance in reporting serious adverse events:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

MedWatch forms and information:
http://www.fda.gov/medwatch/getforms.htm

For studies conducted under an IND: Adverse events that are at least possibly related to the study and that are both serious and unexpected will be reported in writing to the FDA as soon as possible but no later than 15 days after first becoming aware of the event (21 CFR 312.32(c)). The sponsor-investigator will use MedWatch FDA Form 3500A for mandatory reporting.

Serious Adverse events will be reported on the MedWatch form. A copy of the MedWatch report and CHR forms must be sent to the DSMC [redacted]. The date the SAE was sent to all required reporting agencies will be documented on the CTMS; hard copies of the report will be maintained in the regulatory files.

All subjects/patients with serious adverse experiences must be followed up for outcome.

If the SAE is death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or his designee via phone or in person within 24 business hours of the Principal Investigator's awareness of the event. The reporting investigator or designee will confirm all verbal communication via e-mail and will copy the email to the DSMC Administrator and DSMC Coordinator.

If any of the above actions occur in a multiple-institutional clinical trial coordinated by the UCSF-HDFCCC, the CRC will ensure that all participating sites are notified.

Review of Adverse Event Rates

If the study has an increase of grade 3 or 4 expected or unexpected AEs above the rate reported in the Investigational brochure or package insert, this will be reported to the DSMC at the time of identifying the increased rate.

If at any time the Investigator stops enrollment or stops the study due to safety issues the DSMC Chair and DSMC Administrator must be notified within 24 business hours via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

If any of the above actions occur in a multiple-institutional clinical trial coordinated by the UCSF-HDFCCC, the CRC will ensure that all participating sites are notified.

Data Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]
Phone [redacted]
Email [redacted]
Box [redacted]

DSMC Monitors
[redacted]
UCSF Helen Diller Family Comprehensive Cancer Center

16.0 REFERENCES

Apolone, G., A. Filiberti, et al. (1998). "Evaluation of the EORTC QLQ-C30 questionnaire: a comparison with SF-36 Health Survey in a cohort of Italian long-survival cancer patients." Ann Oncol **9**(5): 549-557.

Barrette, B., E. Calvo, et al. (2010). "Transcriptional profiling of the injured sciatic nerve of mice carrying the Wld(S) mutant gene: identification of genes involved in neuroprotection, neuroinflammation, and nerve regeneration." Brain Behav Immun **24**(8): 1254-1267.

Bettmann, M. A., M. D. Dake, et al. (2004). "Atherosclerotic Vascular Disease Conference: Writing Group VI: revascularization." Circulation **109**(21): 2643-2650.

Brock, N. (1989). "Oxazaphosphorine cytostatics: past-present-future. Seventh Cain Memorial Award lecture." Cancer Res **49**(1): 1-7.

Brock, N. (1996). "The history of the oxazaphosphorine cytostatics." Cancer **78**(3): 542-547.

Bubley, G. J., M. Carducci, et al. (1999). "Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group." J Clin Oncol **17**(11): 3461-3467.

Calhoun, E. A., E. E. Welshman, et al. (2003). "Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy." Int J Gynecol Cancer **13**(6): 741-748.

Chaudhry, V., E. K. Rowinsky, et al. (1994). "Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies." Ann Neurol **35**(3): 304-311.

Cohen, J. L. and J. Y. Jao (1970). "Enzymatic basis of cyclophosphamide activation by hepatic microsomes of the rat." J Pharmacol Exp Ther **174**(2): 206-210.

Cortes, J. and R. Lorca (2011). "Eribulin mesylate: a promising new antineoplastic agent for locally advanced or metastatic breast cancer." Future Oncology **7**(3): 355-364.

Cortes, J., L. Vahdat, et al. (2010). "Phase II study of the halichondrin B analog eribulin mesylate in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine." J Clin Oncol **28**(25): 3922-3928.

Cristofanilli, M., G. T. Budd, et al. (2004). "Circulating tumor cells, disease progression, and survival in metastatic breast cancer." N Engl J Med **351**(8): 781-791.

Cristofanilli, M., D. F. Hayes, et al. (2005). "Circulating tumor cells: a novel prognostic factor for newly diagnosed metastatic breast cancer." J Clin Oncol **23**(7): 1420-1430.

Denduluri, N., J. A. Low, et al. (2007). "Phase II trial of ixabepilone, an epothilone B analog, in patients with metastatic breast cancer previously untreated with taxanes." J Clin Oncol **25**(23): 3421-3427.

Du, X. L., R. Xia, et al. (2009). "Cardiac toxicity associated with anthracycline-containing chemotherapy in older women with breast cancer." Cancer **115**(22): 5296-5308.

Eisenhauer, E. A., P. Therasse, et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer **45**(2): 228-247.

Endo, Y., E. Beauchamp, et al. (2008). "Wnt-3a and Dickkopf-1 stimulate neurite outgrowth in Ewing tumor cells via a Frizzled3- and c-Jun N-terminal kinase-dependent mechanism." Mol Cell Biol **28**(7): 2368-2379.

Fisher, B., S. Anderson, et al. (2001). "Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23." J Clin Oncol **19**(4): 931-942.

Fisher, B., A. M. Brown, et al. (1990). "Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15." J Clin Oncol **8**(9): 1483-1496.

Forsyth, P. A., C. Balmaceda, et al. (1997). "Prospective study of paclitaxel-induced peripheral neuropathy with quantitative sensory testing." J Neurooncol **35**(1): 47-53.

Ge, D., J. Fellay, et al. (2009). "Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance." Nature **461**(7262): 399-401.

Groenvold, M., M. C. Klee, et al. (1997). "Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement." J Clin Epidemiol **50**(4): 441-450.

Howgate, D. J., Z. Gamie, et al. (2009). "The potential adverse effects of aromatase inhibitors on wound healing: in vitro and in vivo evidence." Expert Opin Drug Saf **8**(5): 523-535.

Jemal, A., R. Siegel, et al. (2010). "Cancer statistics, 2010." CA Cancer J Clin **60**(5): 277-300.

Jones, S., F. A. Holmes, et al. (2009). "Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735." J Clin Oncol **27**(8): 1177-1183.

Jones, S. E., M. A. Savin, et al. (2006). "Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer." J Clin Oncol **24**(34): 5381-5387.

Jordan, M. A., K. Kamath, et al. (2005). "The primary antimitotic mechanism of action of the synthetic halichondrin E7389 is suppression of microtubule growth." Mol Cancer Ther **4**(7): 1086-1095.

Kuznetsov, G., M. J. Towle, et al. (2004). "Induction of morphological and biochemical apoptosis following prolonged mitotic blockage by halichondrin B macrocyclic ketone analog E7389." Cancer Res **64**(16): 5760-5766.

Lipton, R. B., S. C. Apfel, et al. (1989). "Taxol produces a predominantly sensory neuropathy." Neurology **39**(3): 368-373.

Low, J. A., S. B. Wedam, et al. (2005). "Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in metastatic and locally advanced breast cancer." J Clin Oncol **23**(12): 2726-2734.

McLachlan, S. A., G. M. Devins, et al. (1998). "Validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) as a measure of psychosocial function in breast cancer patients." Eur J Cancer **34**(4): 510-517.

New, P. Z., C. E. Jackson, et al. (1996). "Peripheral neuropathy secondary to docetaxel (Taxotere)." Neurology **46**(1): 108-111.

Okouneva, T., O. Azarenko, et al. (2008). "Inhibition of centromere dynamics by eribulin (E7389) during mitotic metaphase." Mol Cancer Ther **7**(7): 2003-2011.

Patt, D. A., Z. Duan, et al. (2007). "Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk." J Clin Oncol **25**(25): 3871-3876.

Perez, E. A., G. Lerzo, et al. (2007). "Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine." J Clin Oncol **25**(23): 3407-3414.

Persohn, E., A. Canta, et al. (2005). "Morphological and morphometric analysis of paclitaxel and docetaxel-induced peripheral neuropathy in rats." Eur J Cancer **41**(10): 1460-1466.

Racila, E., D. Euhus, et al. (1998). "Detection and characterization of carcinoma cells in the blood." Proc Natl Acad Sci U S A **95**(8): 4589-4594.

Ramaswamy, S. and C. M. Perou (2003). "DNA microarrays in breast cancer: the promise of personalised medicine." Lancet **361**(9369): 1576-1577.

Ratain, M. J. (1992). "Therapeutic relevance of pharmacokinetics and pharmacodynamics." Semin Oncol **19**(4 Suppl 11): 8-13.

Rivera, E. and H. Gomez (2010). "Chemotherapy resistance in metastatic breast cancer: the evolving role of ixabepilone." Breast Cancer Res **12 Suppl 2**: S2.

Roche, H., L. Yelle, et al. (2007). "Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy." J Clin Oncol **25**(23): 3415-3420.

Rowinsky, E. K. and R. C. Donehower (1995). "Paclitaxel (taxol)." N Engl J Med **332**(15): 1004-1014.

Rustin, G. J., M. Quinn, et al. (2004). "Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer)." J Natl Cancer Inst **96**(6): 487-488.

Sahenk, Z., R. Barohn, et al. (1994). "Taxol neuropathy. Electrodiagnostic and sural nerve biopsy findings." Arch Neurol **51**(7): 726-729.

Scher, H. I., S. Halabi, et al. (2008). "Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group." J Clin Oncol **26**(7): 1148-1159.

Sparano, J. A., M. Wang, et al. (2008). "Weekly paclitaxel in the adjuvant treatment of breast cancer." N Engl J Med **358**(16): 1663-1671.

Stendel, C., A. Roos, et al. (2007). "Peripheral nerve demyelination caused by a mutant Rho GTPase guanine nucleotide exchange factor, frabin/FGD4." Am J Hum Genet **81**(1): 158-164.

Taenzer, P. A., M. Speca, et al. (1997). "Computerized quality-of-life screening in an oncology clinic." Cancer Pract **5**(3): 168-175.

Thomas, E. S., H. L. Gomez, et al. (2007). "Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment." J Clin Oncol **25**(33): 5210-5217.

Towle, M. J., K. A. Salvato, et al. (2001). "In vitro and in vivo anticancer activities of synthetic macrocyclic ketone analogues of halichondrin B." Cancer Res **61**(3): 1013-1021.

Twelves, C., J. Cortes, et al. (2010). "Phase III trials of eribulin mesylate (E7389) in extensively pretreated patients with locally recurrent or metastatic breast cancer." Clin Breast Cancer **10**(2): 160-163.

Vahdat, L. T., B. Pruitt, et al. (2009). "Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane." J Clin Oncol **27**(18): 2954-2961.

Vergote, I., G. J. Rustin, et al. (2000). "Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup." J Natl Cancer Inst **92**(18): 1534-1535.

Wampler, M. A., C. Miaskowski, et al. (2006). "The modified total neuropathy score: a clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer." Supportive Oncology **4**(8): W9-W16.

Weigelt, B., A. M. Glas, et al. (2003). "Gene expression profiles of primary breast tumors maintained in distant metastases." Proc Natl Acad Sci U S A **100**(26): 15901-15905.

Wozniak, K. M., R. G. Lapidus, et al. (2010). "Assessment of neuropathy-inducing effects of eribulin mesylate versus paclitaxel and ixabepilone." European Society of Medical Oncology Annual Meeting.

APPENDIX A

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

APPENDIX B

Strong CYP3A4 Inhibitors that are prohibited during the study

Amprenavir	Fosamprenavir	Itraconazole	Nicardipine
Atazanavir	Grapefruit juice	Ketoconazole (oral)	Posaconazole
Clarithromycin	Imatinib	Nefazodone	Ritonavir
Conivaptan	Indinavir	Nelfinavir	Telithromycin
Delavirdine	Isoniazid	Nevirapine	

Strong CYP3A4 Inducers that are prohibited during the study

Barbiturates	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

CYP3A4 Substrates (caution is advised)

Astemizole	Pimozide		
Cisapride	Quinidine		
Opioid analgesics	Tacrolimus		

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

This list is not comprehensive.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp

APPENDIX C

Modified Total Neuropathy Score Sheet

Sensory Symptoms:

0=no symptoms

1=symptoms limited to the tips of fingers or toes

2=symptoms extend to ankle or wrist

3=symptoms extend to above ankle or above wrist to the level of knee or elbow

4=symptoms above knee or elbow and /or severe disabling symptoms that affect normal functioning and/or neuropathic pain that requires narcotic analgesia

If symptoms are asymmetrical from side-to-side, grade the worst side (L/R).

A. Paresthesias (tingling): _____

B. Numbness ("dental work anesthesia"): _____

C. Neuropathic pain (aching, burning, stabbing): _____

D. Myalgias or Cramps: _____

TOTAL SENSORY SYMPTOM SCORE (0-4)
Use average score from A-D, round up to next whole number

Motor Symptoms:

0=no difficulty

1=with slight difficulty

2=with moderate difficulty

3=require some help or an assistive device

4=total loss of function

A. Hand— Dexterity (buttoning, writing, tying shoe laces, opening tight jars, or inserting key in lock) _____

B. Foot —Walking (unsteady on feet, walking on tip toes or on heels, or operating pedals in car) _____

C. Legs— Climbing steps, or standing up from a chair _____

D. Arms— Combing hair, or reaching up to a high shelf _____

TOTAL MOTOR SYMPTOM SCORE (0-4)
Use average score from A-D, round up to next whole number

Neurological Examination:

SENSORY

0=normal

1=absent/decreased in index finger or great toe

2=absent/decreased up to ankle or wrist

3=absent/decreased up to elbow or knee

4=absent/decreased above the level of knee or elbow

If symptoms are asymmetrical from side-to-side, grade the worst side (L/R).

A. Pin level _____
B. Vibration _____(*From quantitative vibration testing compared to norms in Bloom paper*)

TOTAL SENSORY SCORE (0-8) ☐

MOTOR

0=normal (MMT ≥4+)

1=mild weakness, but can overcome some resistance (MMT 3+ to 4)

2=moderate weakness, can overcome gravity (MMT 3)

3=severe weakness with gravity eliminated (MMT 1 to 2)

4=paralysis (MMT 0)

If symptoms are asymmetrical from side-to-side, grade the worst side (L/R).

A. Ankle DF _____

B. Finger spread _____

C. Wrist EXT _____

TOTAL MOTOR SCORE (0-4)
Use score from weakest muscle group ☐

REFLEXES

	L	R	
Biceps	_____	_____	P=present
Triceps	_____	_____	PR=present with reinforcement
Brachioradialis	_____	_____	A=absent
Knee	_____	_____	
Ankle	_____	_____	

0=all reflexes normal (Biceps, Triceps, Brachioradialis, Knee, and ankle)
1=ankle reflex reduced
2=ankle reflex absent
3=ankle reflex absent, others reduced
4=all reflexes absent

TOTAL REFLEX SCORE (0-4) ☐

TOTAL mTNS SCORE (0-24) ☐

See reference 51, Wampler et al.

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX E

FACT-GOG NTX questionnaire

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

APPENDIX F

Correlative Studies
All specimens will be de-identified prior to sending. Only a study ID # will be on the collection tubes.

Pharmacokinetics-Phase Ia only
Whole blood for pharmacokinetic assessments of pazopanib and PCI24781 will be drawn in 6 mL tubes on the following schedule:

Phase Ia: Cycle 1 Day 1: pre-dose, at the end of eribulin infusion, and at 15 min, 30 min, hour 1, 2, 3, 4, 6 and 8

Handling of Specimens(s) – Standard phlebotomy handling

ALL required labels will be provided by a third-party vendor contracted by the sponsor. Labels will come **pre-filled** with the following information:

- Protocol No.: **11996**
- Treatment: **Cohort/Dose level**
- Nominal Time Point: **Predose, 1, 2 hr, etc.**
- Sample Type: **Blood**, **Plasma (Primary)**, **Plasma (Secondary)**

The SITE is then responsible for entering the following information on each sample label:

- Patient ID Number
- Patient Initials

ALL blood and plasma collection and storage tubes should be labeled **PRIOR** to sample collection.

1. Fill an ice bucket with a sufficient amount of ice to completely immerse all tubes before blood draw.
2. Collect approximately 6 mL of whole blood into a pre-chilled 6-mL Na-Heparin tube.
3. Gently invert the tube 3-5 times and immerse it into the ice immediately to prevent possible compound degradation at room temperature.
4. Record drawing time immediately before proceeding to the next step.
5. Within 15 min. of blood collection, the sample must be processed by centrifuging at 1,500 g (3,000 rpm) for 10 min to obtain plasma.
6. Transfer approximately 1.5 mL plasma into each of the two clean, pre-labeled polypropylene tubes (primary and secondary). Immerse both tubes into the ice immediately to prevent possible compound degradation at room temperature. Note, if short on plasma, ensure that the primary sample tube contains 1.5 mL
7. Transfer both polypropylene tubes into a –70°C/–80°C freezer (within 1 hour of collection), where they will remain stored until shipping.
8. Immediately record time of samples' entry into the freezer.

NOTE: All secondary (backup) samples will be maintained at the collecting site until they are requested by the sponsor to be sent to the bioanalytical laboratory.

Site(s) Performing Correlative Study – XenoBiotic Laboratories, Inc.

Shipping of Specimen(s) –
Blood will be processed as above, frozen and shipped on dry ice by overnight mail on Monday-Wednesday to:

[redacted]

Notification on the day of shipping should be sent to:

[redacted]

- Do not ship samples the day before a holiday.
- Always ship the primary sample set to the bioanalytical lab first per pre-agreed shipping schedule.
- All secondary (used as backup) samples will be stored in a –70°C/–80°C freezer at the collecting site until shipping is requested by the sponsor.
- Arrange sample pick-up(s) (e.g., World Courier)
- **XBL must be contacted via email at least one working day prior to shipment and confirmation of receipt by XBL must be documented at the clinical site.**
- If you do not hear from XBL within 2-3 working days of shipping, please contact the person listed in **above** immediately to ascertain the delivery status of the samples.

Shipping Process

1. Obtain 20 lbs of dry ice pellets. Use as much dry ice as possible to help safeguard against any possible delays.
2. Use a Styrofoam box, for example, a 19” x 19” x 12”. Use a larger one if multiple samples are being shipped.
3. Place a 4” layer of dry ice in the bottom of the Styrofoam box. Package the samples the day of shipping to maximize the effectiveness of the dry ice pellets.
4. Wrap the frozen samples in bundles using an elastic band and place the sample bundles in a plastic freezer bag.
5. Use newspaper or other similar material to insulate the bagged sample bundles from direct contact with the dry ice.
6. Place the sample bundles in the Styrofoam box and fill the excess space with the remaining dry ice pellets.
7. Record the estimated weight of the dry ice used per box.

8. Place the lid on the Styrofoam box and seal around the edges completely with tape.
9. Place the Styrofoam box in a larger cardboard shipping carton. Tape the plastic bag or plastic sleeve that contains essential sample documents from the site on top of the Styrofoam box.
10. Seal the shipping carton securely with tape.

Labeling the Cardboard Box

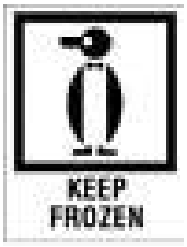
1. Indicate return address and contact person on each carton.
2. Mark the outside of the shipping cartons with tally number e.g., – Box 1 of 3 boxes, Box 2 of 3 boxes, and Box 3 of 3 boxes.
3. Affix the **Biological Substance B** label with the information below to the outside of each box:

   - **One** (1) carbon dioxide label with the weight included. Example:

   Carbon Dioxide Solid UN-1845
   Class 9 PKG GR III
   KG _____

   - **Two** (2) internationally recognized dry ice symbols (Class 9) - one on either side of the box. Example:

   - **One** (1) **KEEP FROZEN** label



   - **One** (1) **PERISHABLE GOODS** label

   PERISHABLE GOODS

Sample Collection Documents to Accompany Shipment(s)

The following documentation/information must accompany ALL shipments:

- A copy of the completed specimen inventory log(s) (i.e., a copy of the completed CRF Specimen Collection page).
- Sponsor Name: **Eisai**

Any missing information may cause a delay in analysis.

Please notify XBL by email or fax immediately after the samples have been collected by the courier. Provide the following information to XBL:

- Name of courier or transport company (i.e., World Courier)
- Date and time the shipment left your premises
- The airway bill number

Single-nucleotide polymorphisms
One 10 mL purple top tube will be collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment.

DNA extraction and analysis for three novel candidate genes which may relate to development of peripheral neuropathy, FZD3, FGD4 and EPHA5 will be performed. Other exploratory analysis may also be performed.

Handling of Specimens(s) – Standard phlebotomy handling

Sites Performing Correlative Study – Deanna Kroetz laboratory, UCSF

Shipping of Specimen(s) –
UCSF: No shipment is required. Samples will be hand-delivered by courier at 4C and shipped on cold packat room temperature to the Kroetz laboratory in batches.

[redacted]

Outside sites: Samples will be stored at 4C and shipped on cold pack at room temperature to the Kroetz laboratory:

[redacted]

Genome Scan
One 10 mL purple top tube will be collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment.

DNA extraction and analysis will be done by the DNA bank at UCSF, and then samples will be sent to Dr. Pui-Yan Kwok's laboratory for genomic profile.

Handling of Specimens(s) – Standard phlebotomy handling

Sites Performing Correlative Study – Pui-Yan Kwok laboratory, CVRI, UCSF

Shipping of Specimen(s) –
UCSF: No shipment is required. Samples will be hand-delivered by courier at room temperature to the DNA bank laboratory immediately after they are obtained and processed immediately. If unable to be sent immediately, samples will be frozen and shipped on dry ice.

[redacted]

Outside sites: Samples will be frozen and will be on shipped on dry ice by overnight mail to:
Shigeshi "Shag" Yamamoto

[redacted]

Circulating Tumor Cells
2 CellSave tubes and 1 purple top tube will be collected at baseline, either during screening assessments or Cycle 1 Day 1 prior to treatment.
If this first sample has ≥ 5 CTC/mL, then on Cycle 2 Day 1, 1 CellSave and 1 purple top tube will be collected for CTC enumeration and aCGH/gene expression.
2 CellSave tubes and 1 purple top tube should be obtained at end of study if at all possible.

7.5 mL of blood is required per CellSave tube, it is critical that the tube be completely filled.
10mL is required in each purple top tube.

One CellSave tube will be used for CTC enumeration, the second CellSave tube will be used for sorting and WGA with CGH/sequencing. The purple top tube will also be used for gene expression if there is adequate sample.

Handling of Specimens(s) – Standard phlebotomy handling

Site(s) Performing Correlative Study – John Park MD laboratory, UCSF

Shipping of Specimen(s) –
UCSF: No shipment is required. Samples will be hand-delivered at room temperature to the Park laboratory immediately after they are obtained and processed immediately.
Outside sites: Blood will be shipped at room temperature by overnight mail to:
Park Lab

[redacted]

Notification on the day of shipping should be sent to:

[redacted]

Special instructions will be provided for Friday shipping.

Archived Tissue Analysis
Once a patient is consented for this study, they will also sign a Tumor Specimen Release Form. Clinical research coordinators will request FFPE (formalin-fixed paraffin embedded) archived tumor blocks from prior surgery or biopsies along with stained H&E slides, for all patients. These specimens

are not required and should not delay enrollment. These specimens will become the property of UCSF Cancer Center and will be stored at the Cancer Center Tissue Core at UCSF under direction of Dr. Stöppler.

[redacted]

Quality of life

EORTC QLQ-30, found in Appendix C, will be self-administered to each patient on the following schedule:

Prior to starting treatment (within 7 days of cycle 1 day 1), then at 6 weeks, 3 months, 12 months, 18 months, 24 months, and/or study termination. Questionnaires may be mailed, emailed, or faxed in advance to patients and/or completed during visits. Questionnaires must be completed by the patient and can be completed up to 7 days prior to drug administration. Translation services may be used for completion of questionnaires. Results will be compiled by research staff.

Neuropathy measurements

1. 10-point modified neuropathy score (mTNS), found in Appendix D, will be performed by research staff at the start of each cycle and at study termination. Results will be compiled by research staff.

2. FACT/GOG-NTX questionnaire, found in Appendix E, will be self-administered to each patient on the following schedule: at the start of each cycle and at study termination. Questionnaires may be mailed, emailed, or faxed in advance to patients and/or completed during visits. Questionnaires must be completed by the patient and can be completed up to 7 days prior to drug administration. Translation services may be used for completion of questionnaires. Results will be compiled by research staff.