Oregon Health & Science University
OHSU Knight Cancer Institute
IRB Protocol #: 17190
Other Protocol #: HAL-IIS-M001-1022

TITLE: A phase 1B trial of preoperative eribulin and radiation for retroperitoneal liposarcoma

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Supplied Agent: Eribulin (Eisai)

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SUMMARY OF CHANGES: Amendment 6

Revised Synopsis section, Table 12-2, Section 13.1, Section 13.4.2, and Section 13.5 to reduce planned number of subjects from 16 to 15.

SUMMARY OF CHANGES: Amendment 5

Revision to Section 9.2.2 and 9.3 to add requirement for chain of custody form for archival tissue samples and research blood samples.

Added clarification to Section 13.4.2 regarding process of operating surgeon and Clavien-Dindo Classification Tool.

Added clarification to Section 11.2 regarding process of pathologist central evaluation and Central Pathology Review form.

Revised title page to remove some Co-Investigators per Knight CRQA Auditor request.

Revised Appendix C: PROMIS Questionnaire, to include a box for name of person completing the survey, signature, and date.

Revised Section 11.5 to indicate a qualified investigator will determine RECIST response.

Revised Section 3.1 and 3.2 to include gender neutral terminology.

Revised Section 7.2 to clarify which AEs will be recorded, including which abnormal labs would need to be recorded.

Added Multigated Acquisition Scan (MUGA) to schedule of events. This has been added if an ECHO is not available.

Table 6.1 revised to state ANC greater than or equal to 1000 rather than greater than 1000.
12.7.3 updated address of ESI Product Safety

SUMMARY OF CHANGES: Amendment 4

Revision to Section 9.2.2 and 9.3 to remove requirement for chain of custody form for archival tissue samples and research blood samples.

Added Echocardiogram (ECHO) and hydration to schedule of events in Section 10.4

Added additional criteria for DLT to Section 5.2

Added additional info to section 5.3.3, Prohibited Concomitant Therapy, in relation to prolong QTc

Added clarification to Section 11.5 regarding investigator determination of RECIST response

Added Inclusion Exclusion criteria 3.1.10 for baseline ejection fraction requirement

Added update to Inclusion Exclusion criteria 3.2.7, to include uncontrolled arrhythmia

Added Inclusion Exclusion criteria 3.2.8 – Use of more than one medication with known risk of Torsades de Pointes

Added hydration details to Section 10.2

Removed "and will be replaced" from Section 13.3 Analysis Populations

Added Appendix E: Medications with Known risk of Torsades de Pointes (TdP)

SUMMARY OF CHANGES: Amendment 3

Revision of exclusion criteria for use of supplements in section 3.2.11 with removal of "nutritional" supplements.

Clarification for use of CTCAE v4.03.

Added LDH to schedule of events in section 10.4.

SUMMARY OF CHANGES: Amendment 2

Revision of pathology criteria after involvement of new pathologist, Jessica Davis, who has also been added as a Co-Investigator.

Added clarification regarding window around Day 8 treatment.

Added details that research blood samples will be shipped to the van de Rijn & West lab at Stanford for circulating tumor DNA (ctDNA) analysis.

Added clarification that liposarcomas of the scrotum/spermatic cord are eligible, which was agreed upon after multidisciplinary discussions with co-investigators. Rationale is that the spermatic cord descends through the retroperitoneum and the blood supply is retroperitoneal.

Added clarification that all abdominal CTs must include pelvis.

SUMMARY OF CHANGES: Amendment 1

Treatment windows extended due to need for flexibility in scheduling when considering the many different departments coordinating on this trial, which should provide subjects with easier schedules without negatively impacting subject safety, treatment efficacy nor data integrity:

- DCE-MRI may occur any time during screening, prior to C1D1 treatment.
- Radiation may begin as soon as C1D8 but no later than C2D1.
- Surgical resection target is 4-6 weeks after completion of radiation. Resection may occur no sooner than 3 weeks but no more than 10 week after completion of radiation.

Clarification of "early surgery" endpoint. "Early surgery" is surgical resection that occurs prior to completion of all planned chemoradiation.

Addition of research blood draws. An additional 3-5mL of plasma will be collected at five time points when subjects will be having blood drawn for clinical testing. Plasma will be stored for future analysis of circulating tumor DNA (ctDNA).

Defined "pathologic response" and revised analysis method. There is minimal established data on necrosis in retroperitoneal liposarcoma and therefore this data will be more descriptive than previous version.

Eribulin dose to be modified based on change in BSA rather than weight to align with standard pharmacy practices (Section 5.1.1).

Added additional details regarding the intraoperative biopsy (Section 10.2).

Modification of legend for Figure 13-2 to add clarity.

Appendix C: Replaced "Pain Intensity" and "Pain Interference" PROMIS questionnaires with the more relevant "Belly Pain" PROMIS questionnaire. Total of 15 questions now, reduced from 19.

Appendix E removed as it is more appropriate in the Operations Manual and not within IRB protocol.

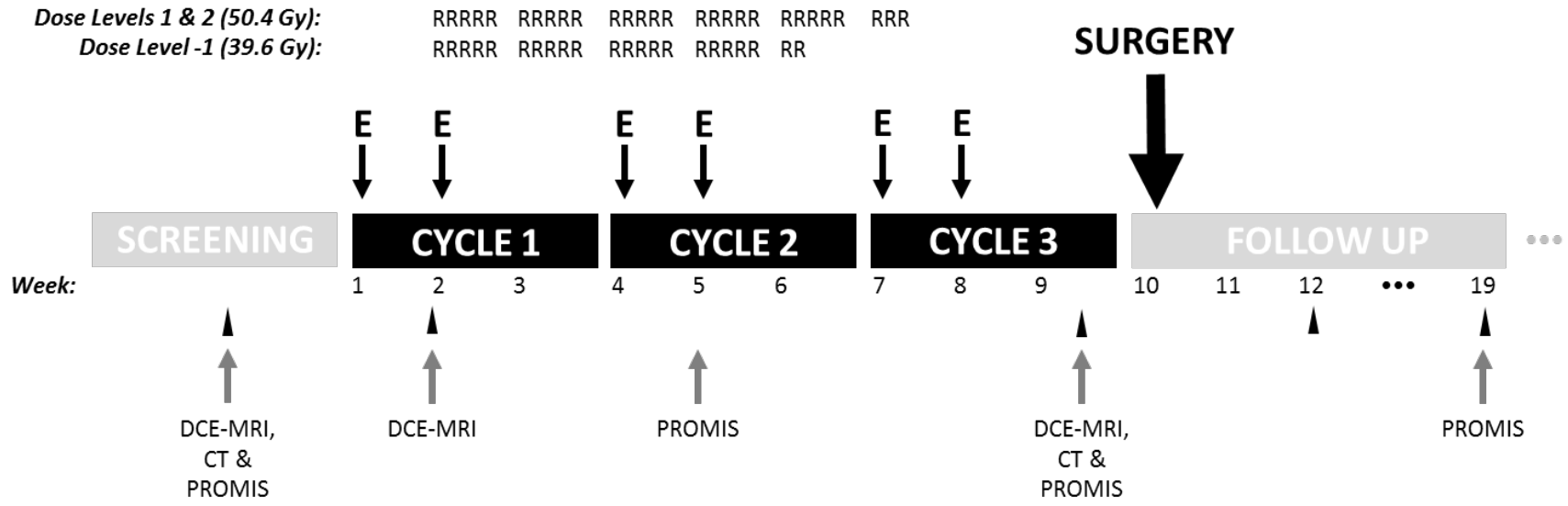
CONTENTS

ABBREVIATIONS

Term	Explanation
AE	Adverse event
ANC	Absolute neutrophil count
AUC	Area under the curve
BSA	Body surface area
C2D8	Cycle 2, Day 8
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum serum concentration
CRF	Case report form
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
FFPE	Formalin fixed paraffin embedded
GTV	Gross Target Volume
IC_{50}	The half maximal inhibitory concentration
IHC	Immunohistochemistry
ITV	Internal Target Volume
IV	Intravenous
LVEF	Left ventricular ejection fraction
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval design
nM	Nanomolar
ORR	Objective response rate
PFS	Progression free survival
PO	Oral
PK	Pharmacokinetic
PTV	Planning Target Volume
QTcF	QT interval corrected by the Fridericia correction formula
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
$t_{1/2}$	Half-life
T_{max}	The time at which the C_{max} is observed
ULN	Upper limit of normal

"Study drug" refers to eribulin
"Protocol therapy" refers to the use of eribulin with radiation as per protocol

SCHEMA



R = IMRT fraction of 1.8 Gy
E = Eribulin IV
DCE-MRI = Dynamic Contrast-Enhanced MRI
PROMIS = Patient- Reported Outcomes Measurement Information System questionnaires
▲ = research blood sample

Dose Level	Dose	
	Radiation (Gy)	Eribulin (mg/m^2)
Level 2	50.4	1.4
Starting Dose (Level 1)	50.4	1.1
Level -1	39.6	1.1

Main Criteria for Inclusion & Exclusion: Subjects with primary or recurrent retroperitoneal liposarcoma of any subtype will be eligible. The tumor must be deemed resectable with acceptable morbidity and targetable with intensity-modulated radiation therapy (IMRT) with acceptable morbidity. Eligible subjects will have no evidence of distant metastases, and will have no history of prior radiation or chemotherapy for their sarcoma.

SYNOPSIS

Rationale:
Liposarcoma is the most common soft tissue sarcoma, and the retroperitoneum is one of the most common locations for liposarcoma to arise. These tumors are particularly difficult to treat due to their location and resections are often quite morbid. The standard of care is *en bloc* surgical resection with wide margins, which can be very difficult to achieve in the retroperitoneum. Unfortunately, even with complete resection, the recurrence rate remains high and repeated resections are common.

This phase 1B trial will assess the safety and tolerability of a preoperative chemoradiotherapy protocol for retroperitoneal liposarcoma, utilizing eribulin and intensity-modulated radiation therapy (IMRT). Eribulin is FDA-approved for the treatment of advanced liposarcoma, and acts by inhibiting microtubule growth, resulting in G2/M cell cycle arrest. In addition, eribulin may decrease tumor hypoxia. The hypothesis is that the combination of eribulin with radiation will be tolerable and may decrease the recurrence rate of retroperitoneal liposarcoma.

Number of Planned Subjects: 15

Length of Study: approximately 18 months to complete accrual; 10 years for survival follow up

Primary Objective: To determine the recommended phase 2 dose (RP2D) of radiation and eribulin when used in combination for the preoperative treatment of retroperitoneal liposarcoma.

Study Design: This is an open-label, phase IB, dose-finding study in which safety and tolerability of radiation in combination with eribulin in subjects with retroperitoneal liposarcomas will be investigated. This study uses a modified toxicity probability interval (mTPI) design with target toxicity rate of 0.2 (see mTPI Decision Table in Section 13.1). The DLT observation period for the purposes of dose-determining will be Cycles 1-2 of therapy (weeks 1-6). Four subjects will be enrolled for the first cohort at each dose, and 3 subjects will be enrolled for subsequent cohorts at the same dose.

Diagnosis and Main Criteria for Inclusion & Exclusion:
Subjects with primary or recurrent retroperitoneal liposarcoma of any subtype will be eligible. The tumor must be deemed resectable with acceptable morbidity and targetable with IMRT with acceptable morbidity. Eligible subjects will have no evidence of distant metastases, and will have no history of prior radiation or chemotherapy for their sarcoma.

Protocol Therapy:
A baseline DCE MRI and abdominal CT will be obtained prior to first dose of chemotherapy. Weeks 1 through 3 will constitute cycle 1, weeks 4 through 6 will constitute cycle 2, and weeks 7 through 9 will constitute cycle 3 (see schema). Eribulin will be given via IV over 2-5 minutes on day 1 and day 8 of each 3 week cycle. Subjects enrolled at dose level 1 or -1 will receive eribulin 1.1 mg/m^2. Subjects enrolled at dose level 2 will receive eribulin 1.4 mg/m^2.

A second DCE MRI will be obtained prior to starting radiation. Subjects enrolled at dose level 1 or 2 will receive IMRT for a total of 28 fractions over 5½ weeks, with a cumulative dose of 50.4 Gy. Subjects enrolled at dose level -1 will receive a total of 22 fractions over 4½ weeks, with a cumulative dose of 39.6 Gy.

A repeat abdominal CT and a third DCE MRI will be obtained prior to surgery. Surgical resection will occur approximately 4-6 weeks after completion of radiation (minimum of 3 weeks, maximum of 10

weeks). Subjects will be followed until death, or until 10 years after completion of study therapy, whichever occurs first.

1.0 Objectives

The primary objective of this study is to determine the recommended phase 2 dose (RP2D) of radiation and eribulin when used in combination for the preoperative treatment of retroperitoneal liposarcoma.

Secondary objectives are: 1) to assess the feasibility of a preoperative chemoradiation protocol for retroperitoneal liposarcoma, 2) to assess the surgical outcomes of retroperitoneal liposarcoma resections after preoperative chemoradiation, and 3) to assess preliminary anti-tumor activity of eribulin in combination with radiation in subjects with retroperitoneal liposarcoma.

Exploratory objectives include obtaining preliminary DCE-MRI data to evaluate changes in perfusion after treatment with chemoradiation and preliminary data on changes in the microenvironment following chemoradiation.

2.0 Background

2.1 Study Disease

Liposarcoma is the most common soft tissue sarcoma, and the retroperitoneum is one of the most common locations for liposarcoma to arise.[1, 2] Over 50% of retroperitoneal sarcomas are liposarcomas.[3-6] The large tumor size and complex anatomy of the retroperitoneum make management of retroperitoneal sarcomas particularly difficult to treat: the standard of care is *en bloc* surgical resection with wide margins, which is often difficult to achieve in the retroperitoneum. Even with complete resection, the recurrence rate remains high and repeat resections are common.[3, 4] Unlike most other sarcomas, the majority of deaths due to retroperitoneal sarcomas result from uncontrolled local disease and not from distant metastases. These factors all contributed to the 2002 NCI CTEP *Sarcoma: State of the Science* recommendation for the initiation of prospective trials to investigate radiation therapy and neoadjuvant targeted therapeutics for retroperitoneal sarcoma.[7] Very little progress has been made since this recommendation. A large, international trial (EORTC 62092, NCT01344018) of surgery with or without radiation therapy ("STRASS") has been ongoing since 2011 with no results reported to date.

At OHSU, patients with a suspected retroperitoneal sarcoma are reviewed and discussed at the Sarcoma Multidisciplinary Tumor Board. Preoperative radiation is considered for each patient, and patients considered good candidates based on the Tumor Board discussion are referred for consultation with sarcoma radiation oncologist Dr. Hung. Chemotherapy is not typically recommended for patients with resectable retroperitoneal sarcoma.

This phase 1B trial will assess the safety and tolerability of a preoperative chemoradiotherapy protocol for retroperitoneal liposarcoma, utilizing eribulin and IMRT. Eribulin is FDA-approved for the treatment of advanced liposarcoma based on a randomized study that demonstrated a statistically significant improvement in overall survival compared with dacarbazine in patients with unresectable, locally advanced or metastatic liposarcoma. Eribulin acts by inhibiting microtubule growth, resulting in G2/M cell cycle arrest and may also decrease tumor hypoxia. The hypothesis is that the combination of eribulin with radiation will be tolerable and may decrease the recurrence rate of retroperitoneal liposarcomas.

2.2 Study Drug: Eribulin

Mechanism of Action

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates.[8, 9] 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.[10]

Microenvironment Changes in Preclinical Models

Eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness *in vitro*. In mouse xenograft models of human breast cancer, eribulin treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype.[11] Funahashi and colleagues used dynamic contrast-enhanced (DCE)-MRI to assess morphological changes in tumor vasculature of human breast cancer MX-1 and MDA-MB-231 xenografts Effects of eribulin on normal cells in the tumor microenvironment were assessed by performing quantitative RT-PCR (qRT-PCR)-based gene expression profiling and focusing on angiogenesis-related and epithelial-mesenchymal transition (EMT)-related pathways. The authors found that eribulin induced tumor vasculature remodeling associated with improved perfusion by increased microvessel density, decreased mean vascular areas and fewer branched vessels in tumor tissues. In addition, eribulin altered the expression of mouse genes in angiogenesis signaling pathways controlling endothelial cell-pericyte interactions, and decreased hypoxia-associated protein expression of mouse vascular endothelial growth factor.

Use in Liposarcoma

Eribulin is approved for the treatment of subjects with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

The efficacy and safety of eribulin were evaluated in an open-label, randomized (1:1), multicenter, active-controlled trial.[12] Eligible subjects were required to have unresectable, locally advanced or metastatic liposarcoma or leiomyosarcoma, at least two prior systemic chemotherapies (one of which must have included an anthracycline), and disease progression within 6 months of the most recent chemotherapy regimen. Subjects were randomized to eribulin 1.4 mg/m2 administered intravenously on Days 1 and 8 of a 21-day cycle or to dacarbazine at a dose of 850 mg/m2, 1000 mg/m2, or 1200 mg/m2 administered intravenously every 21 days (dacarbazine dose was selected by the investigator prior to randomization). Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by histology (liposarcoma or leiomyosarcoma), number of prior therapies (2 vs. > 2), and geographic region (U.S. and Canada vs. Western Europe, Australia, and Israel vs. Eastern Europe, Latin America, and Asia). The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were progression-free survival (PFS) and confirmed objective response rate (ORR) as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Subjects in the dacarbazine arm were not offered eribulin at the time of disease progression.

Of the 143 subjects with liposarcoma, the median age was 55 years (range: 32 to 83); 62% were male, 72% were White; 41% had ECOG PS of 0 and 53% had ECOG PS of 1; 35% were enrolled in Region 1 and 51% were enrolled in Region 2; and 44% received more than two prior systemic chemotherapies. The distribution of subtypes of liposarcoma, based on local histologic assessment, 45% dedifferentiated, 37% myxoid/round cell, and 18% pleomorphic.

Treatment of advanced liposarcoma with eribulin demonstrated a statistically significant improvement in median OS compared with dacarbazine (15.6 mo vs 8.4 mo, HR 0.51, 95%

CI 0.35-0.75). Treatment effects of eribulin were limited to subjects with liposarcoma based on pre-planned, exploratory subgroup analyses of OS and PFS.

Pharmacokinetics

The pharmacokinetics (PK) of eribulin is linear with a mean elimination half-life of approximately 40 hours, a mean volume of distribution of 43 L/m2 to 114 L/m2 and mean clearance of 1.16 L/hr/m2 to 2.42 L/hr/m2 over the dose range of 0.25 mg/m2 to 4.0 mg/m2. The human plasma protein binding of eribulin at concentrations of 100 ng/mL to 1,000 ng/mL ranges from 49% to 65%.

Eribulin exposure after multiple dosing is comparable to that following a single dose. No accumulation of eribulin is observed with weekly administration.

Elimination: Unchanged eribulin was the major circulating species in plasma following administration of 14C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin. Cytochrome P450 3A4 (CYP3A4) negligibly metabolizes eribulin *in vitro*. 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 total eribulin in feces and urine, respectively.
Specific Populations

Age, Sex, and Race/Ethnicity: Based on a population pharmacokinetic analysis with data collected from 340 patients, sex, race, and age do not have a clinically meaningful effect on the exposure of eribulin.

Hepatic Impairment: In a study evaluating the effect of hepatic impairment on the PK of eribulin, eribulin exposures increased by 1.8-fold in patients with mild hepatic impairment (Child-Pugh A; n=7) and by 2.5-fold in patients with moderate (Child-Pugh B; n=5) hepatic impairment as compared to patients with normal hepatic function (n=6). Administration of eribulin at a dose of 1.1 mg/m2 to patients with mild hepatic impairment and 0.7 mg/m2 to patients with moderate hepatic impairment resulted in similar exposure to eribulin at a dose of 1.4 mg/m2 to patients with normal hepatic function.

Renal Impairment: In a study evaluating the effect of renal impairment on the PK of eribulin, patients with moderate (CLcr 30-49 mL/min; n=7) and severe renal impairment (CLcr 15-29 mL/min; n=6) had 1.5-fold higher eribulin dose-normalized exposures compared to that in patients with normal renal function (CLcr ≥ 80 mL/min; n=6). There were no clinically meaningful changes in patients with mild renal impairment (CLcr 50-79 mL/min; n=27)

2.3 Preoperative Radiation for Retroperitoneal Sarcomas

Several retrospective series have suggested a role for preoperative radiation for retroperitoneal sarcomas. No randomized trials of neoadjuvant therapy versus resection alone for retroperitoneal sarcoma have been reported to date, although an international trial (EORTC 62092, the "STRASS" trial) of preoperative radiation is ongoing. Due to the paucity of data in this field, expert opinion usually guides therapy. A recent consensus statement outlines general eligibility criteria to consider prior to using preoperative radiation, and also provides guidance regarding delineation of treatment volumes.[13]

Preoperative radiation therapy to retroperitoneal sarcomas is standard at many large volume sarcoma centers.[5, 6, 14] Each center uses institutional standards for dose and technique,

but most report using IMRT to a dose of 45-50.4 Gy.[13] IMRT is able to deliver a highly conformal dose to the gross disease planning target volume and high risk subclinical disease regions, while dose to surrounding critical structures such as the adjacent normal tissue, bone, testis, spinal cord, kidney and ovary is minimized.

2.4 Study Rationale

The use of preoperative radiation therapy for retroperitoneal sarcoma, in our opinion, should be conducted within a clinical trial whenever possible in order to contribute in a meaningful way to prospective investigations of efficacy and toxicity.

However, patients with retroperitoneal sarcomas continue to relapse at a high rate (estimated at >80%), often despite radiation therapy and R0 surgical resection. We now have a systemic agent, eribulin, which has proven to improve the overall survival of patients with advanced liposarcoma. There is scientific rationale to suggest that this survival benefit is due to unique impacts of eribulin on the liposarcoma microenvironment. In addition, based on the mechanism of action, eribulin is predicted to be a radiosensitizing agent.

The combination of eribulin with radiation has not been studied prospectively. A post-hoc analysis of two previous phase 2 and 3 eribulin trials evaluated the safety profile of subjects who received eribulin alone vs those who also received palliative radiotherapy (RT).[15] Subjects with locally recurrent or metastatic breast cancer who had received 2-5 prior chemotherapy regimens were included in both studies. Eribulin was given at a dose of 1.4mg/m2 IV on Days 1 and 8 of a 21-day cycle and intercurrent palliative RT was permitted for bone pain, bronchial obstruction, or ulcerative skin lesions. The total field for palliative RT was not to exceed >10% of total bone marrow. Eribulin treatment was delayed during palliative RT and then resumed upon recovery from any RT-associated toxicities.

Out of 794 subjects enrolled in both trials, a total of 44 (5.5%) received RT, with the majority (26/44, 59%) having received ≥ 10 Gys. Six out of the 44 subjects (14%) in the RT group continued treatment with eribulin during palliative RT against protocol recommendation. Half (22/44) of subjects started RT 30 days after the start of eribulin treatment. Duration of RT for 33 (75%) subjects was ≤7 days, and for 11 (25%) subjects was 8-20 days. Sites of radiation therapy (frequency at site) included arm/shoulder (3), back/spine (19), brain (whole, 7), chest (3), head/neck (2), leg/hip (17), chest (3) and undisclosed (9); 7 subjects received RT at multiple sites. Events that occurred more frequently in the RT group included bone pain (27% vs 10%) and back pain (27% vs 15%).

Thus, there is preliminary data suggesting that radiation administered during eribulin therapy is safe, even in the highly-pretreated population of metastatic, refractory breast cancer patients.

We hypothesize that the combination of eribulin with radiation will be tolerable and may increase the success rate of retroperitoneal liposarcoma resection. If a safe RP2D is identified through this study, we will then conduct a larger Phase 2 trial investigating efficacy, including long-term patient outcomes.

2.5 Dose Rationale

In this protocol, “study treatment” refers to the addition of the study drug eribulin to radiation.

The standard pre-operative recommended dose of radiation for retroperitoneal sarcomas is 50.4 Gy. Eribulin remains active at a dose of 1.1 mg/m^2 although the approved dose for metastatic liposarcoma is 1.4 mg/m^2. Therefore, the starting dose for this Phase 1B trial will include the standard dose of radiation with a reduced dose of eribulin. The addition of eribulin is anticipated to sensitize the tumor to radiation. Therefore, dose level -1 allows for a reduction in radiation dose to 39.6 Gy, which is the lowest dose that maintains a reasonable likelihood of efficacy.

2.6 Correlative Studies Rationale

This study includes three tiers of correlative studies:

1. Integral. None.

2. Integrated.
   PROMIS (Patient-Reported Outcomes Measurement Information System). We speculate that one reason surgical oncologists do not refer subjects with retroperitoneal sarcomas for preoperative radiation is the concern that delaying surgery may result in prolongation and/or worsening of symptoms. PROMIS is a set of person-centered measures that evaluates and monitors physical, social, and emotional health that can be used with the general population and with individuals living with chronic conditions. We will use the 10 item Global Health Scale and 5 item Belly Pain Scale (total of 15 questions) at four time points: baseline, C2D8, prior to surgery and 9 weeks post-op.

   DCE-MRI. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive method of evaluating vascular changes in the tumor microenvironment. MRI is used to track bolus injections of a paramagnetic gadolinium chelate contrast reagent (CR) as it passes through the tissue under study. Signal intensity time-course data is fitted with pharmacokinetic models and quantitative parameters are derived. DCE-MRI is being actively evaluated as an imaging biomarker for drug effect on perfusion, and correlation between DCE-MRI and clinical measures have been reported.[16-21] The hypothesis in the current study is that changes in tumor perfusion as detected by DCE-MRI will predict pathologic response after preoperative therapy.

3. Exploratory.
   Tumor infiltrating cells. This exploratory endpoint is intended to be hypothesis generating. Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). We will perform IHC for tumor infiltrating lymphocytes and tumor associated macrophages on all paired samples.

   Microvessel density by IHC. There is preclinical evidence to support investigation of alterations in angiogenesis following treatment with eribulin.[11] Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). IHC for CD31 endothelial cells will be analyzed to determine microvessel density, and scored as either high or low density.

   Microenvironment & differentiation profiling by microarray. There is preclinical evidence to support investigation of alterations in the microenvironment and differentiation, particularly in the expression of adipocytic, mesenchymal and angiogenesis genes, following treatment with eribulin.[11] Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). Total RNA will be isolated and hybridized to relevant microarray(s) for all paired samples. This exploratory endpoint is intended to be hypothesis generating.

Circulating tumor DNA (ctDNA). This exploratory endpoint is intended to be hypothesis generating. ctDNA has not been studied in liposarcomas previously but could prove to be an important biomarker of relapse. Plasma will be collected at multiple time points and shipped to the van de Rijn & West lab at Stanford for analysis.

3.0 Study Population

3.1 Inclusion Criteria

A subject must meet ALL of the following criteria in order to be eligible for enrollment in this study:

3.1.1 Pathologically confirmed diagnosis of liposarcoma. All subtypes are eligible.

3.1.2 Sufficient archival tissue available for correlative studies. Submission of FFPE tumor tissue from a previous biopsy or resection is required, and the most recent specimen is preferred. If a FFPE block cannot be provided, then 10 unstained, positively-charged slides of 4-5 µm thickness must be submitted. If insufficient archival tissue is available, a repeat biopsy will be necessary.

3.1.3 Primary or recurrent retroperitoneal, scrotal/spermatic cord or abdominal tumor.

3.1.4 Age ≥ 12 years at time of consent. For subjects between the ages of 12-18 years only, BSA must be ≥1.5 m^2.

3.1.5 All sites of disease must be resectable or borderline resectable as assessed by a surgical oncologist with experience in retroperitoneal sarcoma resection after discussion in our institutional multidisciplinary sarcoma tumor board conference.

3.1.6 All sites of disease must be targetable with IMRT with acceptable morbidity and without exceeding normal tissue dose constraints as assessed by a radiation oncologist.

3.1.7 Measurable disease by RECIST 1.1.

3.1.8 Subjects of childbearing potential must have a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of screening.

3.1.9 QTcF interval on standard 12-lead ECG parameters at screening (defined as the mean of the triplicate ECGs) of <450 msec for males and <470 msec for females.

3.1.10 Ejection Fraction of ≥ 50%

3.1.11 ECOG performance status ≤ 1 (Karnofsky ≥ 70%, see Appendix A)

3.1.12 Individuals ofchildbearing potential must be willing to use adequate contraception throughout the study and for 3 weeks after study drug discontinuation. Adequate contraception is defined in Appendix B.

3.1.13 Normal organ and marrow function as defined below:

Absolute neutrophil count (ANC)	≥ 1 K/cu mm
Platelets (no transfusion within prior 7 days)	≥ 100 K/cu mm
Hemoglobin (no transfusion within prior 7 days)	≥ 9.0 g/dL
Total bilirubin	< ULN, except for subjects with documented Gilbert's syndrome, for which ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
AST(SGOT) and ALT(SGPT)	≤ 2.5 x ULN
Estimated creatinine clearance	> 50 mL/min by Cockcroft-Gault equation

ULN = institutional upper limit of normal

3.1.14 Ability to understand and the willingness to sign a written informed consent document. Subject has signed the Informed Consent (ICF) prior to any screening procedures being performed and is able to comply with protocol requirements.

3.2 Exclusion Criteria

Subjects meeting ANY of the following criteria must NOT be enrolled in this study:

3.2.1 Presence of distant metastases. Intra-abdominal (regional) spread is allowable if meets inclusion criteria 3.1.5 and 3.1.6. Indeterminate or small volume pulmonary nodules may be eligible, if the treating physicians recommend curative-intent resection of the primary tumor despite the presence of possible lung metastases.
3.2.2 Prior radiation or systemic therapy for the diagnosis of liposarcoma.
3.2.3 Prior eribulin.
3.2.4 Grade ≥2 peripheral neuropathy.
3.2.5 Contraindication to MRI, including presence of a pacemaker or aneurysm clip, severe claustrophobia, a known reaction to gadolinium contrast, or body weight exceeding 300 lbs.
3.2.6 Concurrent malignancy or malignancy within 3 years prior to starting study drug, with the exception of malignancies that have completed therapy and are considered by their physician to be at less than 30% risk of relapse. Prior systemic therapy is allowed with the exception of prior eribulin. Prior radiation therapy is allowed with the exception of any abdominal, pelvic or retroperitoneal radiation >10 Gy.
3.2.7 History of uncontrolled arrhythmia, congenital long QT syndrome or torsades de pointes (TdP).
3.2.8 Use of more than one medication with a known risk of TdP. See Appendix E.
3.2.9 Major operation within 14 days prior to starting study drug or not recovered from surgical complications. Neither tumor biopsy nor central line insertion are considered a major operation.
3.2.10 Active infection. Any systemic antimicrobial therapy must be completed ≥5 days prior to initiation of protocol therapy.
3.2.11 Pregnant or nursing (lactating) individuals.
NOTE: Pregnant individuals are excluded from this study because eribulin is an investigational agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the individual with eribulin, breastfeeding should be discontinued. These potential risks may also apply to doxorubicin.
3.2.12 Unable or unwilling to stop the use of herbal supplements. The use of marijuana or its derivatives is allowed. The use of supplements may be allowed after review by a study pharmacist to confirm no significant risk of interaction with eribulin or radiation.

4.0 Registration Procedures

4.1 Subject Registration

Each subject who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the subject throughout the duration of their participation in the trial. All subjects who provide written informed consent will be screened. A subject will be considered registered once eligibility has been determined and a dose is assigned. Registrations from all consented subjects will be entered into the OHSU Clinical Research Management System (eCRIS).

Registration will include a minimum of the following:

- A completed Subject Enrollment Form,
- A completed Eligibility Checklist signed by a study investigator, and
- Signed copies of the most recently IRB-approved informed consent form and HIPPA authorization.
- Dose cohort assignment.

Detailed instructions for subject registration can be found in the separate Study Operations Manual.

4.2 Treatment Assignment

This is a phase IB trial, and there is no randomization for treatment. When a subject is registered, a dose level will be assigned. The first 4 subjects will be assigned to dose level 1. Subsequent dose level assignments will be determined by the dose-determining spreadsheet of the mTPI design (Table 13-2). Four subjects will be enrolled for the first cohort enrolled at any given dose, and 3 subjects will be enrolled for subsequent cohorts at the same dose.

5.0 Treatment Plan

5.1 Agent Administration

REGIMEN DESCRIPTION				
Agent	**Premedications; Precautions**	**Dose/Route**	**Schedule**	**Cycle Length**
IMRT		Levels 1 & 2: 50.4 Gy in 1.8 Gy fractions Level -1: 39.6 Gy in 1.8 Gy fractions	Once daily, five days per week, beginning on Cycle 1, Day 8 (no later thanCycle 2, Day 1).	Levels 1 & 2: 28 fractions Level -1: 22 fractions
Eribulin	Premedicate with ondansetron 4 mg IV	Levels 1 & -1: 1.1 mg/m^2 IV Level 2: 1.4 mg/m^2 IV	Days 1 & 8	21 days

Treatment will be administered on an outpatient basis. Eribulin is not a vesicant or an irritant and therefore may be administered through a peripheral or central venous line.

No investigational or commercial agents or therapies other than those described here may be administered with the intent to treat the subject's malignancy.

Dose cohort assignment to be determined at time of enrollment, per mTPI decision table (Section 13.1).

Dose Cohort	**Dose**	
	Radiation (Gy)	**Eribulin (mg/m^2)**
Level 2	50.4	1.4
Starting Dose (Level 1)	50.4	1.1
Level -1	39.6	1.1

Reported adverse events and potential risks are described in Section 7.

Appropriate dose modifications are described in Section 6.

5.1.1 Eribulin

Eribulin will be administered at the assigned dose intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle for three consecutive cycles. Premedication with ondansetron is

required prior to each dose. Actual body weight should be used when calculating the dose. Dose should be re-calculated for BSA changes >5%.

Eribulin will be supplied by Eisai or its designee in the form of 1 mg/2 mL solution vials as individual subject supply, packaged in cartons.

5.1.2 Radiation

Radiation will be administered at OHSU. Intensity modulated photon therapy should be utilized.

Gross Target Volume (GTV) is defined by CT or MRI T1 plus contrast images. Fusion of MRI and CT is recommended to delineate the GTV for radiotherapy planning whenever possible. If the tumor is near the diaphragm, 4DCT or ABC (Active Breathing Control) should be used. If a 4D CT is used, then an ITV (Internal Target Volume) will be utilized in place of the GTV.

CTV is defined as GTV + 1.5 cm in all directions. Intraabdominal organs that do not show clear invasion from the GTV AND are not planned for resection, should be subtracted from the CTV. Also, areas outside the abdominal cavity and bone should be subtracted from the CTV.

Planning Target Volume (PTV) will include CTV and error of setup. Typically PTV includes CTV plus 5-10 mm depending on tumor location, ABC and/or localization technique.

Dose will be prescribed to cover 95% of the PTV. More than 99% of the GTV should receive > 97% of the prescribed dose. The minimum dose to a point (defined as having a volume of 8.0 mm^3) within the PTV is 90% of the prescription dose and 95% of the PTV is covered with that prescription dose. No point outside of the PTV should receive more than >102%.

The dose to the PTV will be 50.4 Gy given in 28 fractions of 1.8 Gy for subjects enrolled on dose level 1 or 2 and 39.6 Gy given in 22 fractions of 1.8 Gy for subjects enrolled on dose level -1.

Treatments are typically administered as one fraction daily, 5 days per week, with the exception of holiday weeks where the participants may receive 4 fractions. Normal tissue constraints may limit the dose to a portion of the target volumes. Any reason for protocol deviation must be documented clearly in the eCRF.

Radiation dose to normal tissues must be within the accepted normal tissue tolerances (Table 5-1) in the CT based plan. Every effort should be made to avoid treating the anus, vulva, scrotum, or lung, and avoid treating the femoral head/neck if the retroperitoneal sarcoma extends into the thigh through the inguinal canal.

Table 5-1. Normal tissue dose constraints.

Tissue	Max dose (Gy)	Volume
Small bowel*	45 54	50% 20 cc
Colon	60	20 cc
Rectum	60 63	35% 30%
Stomach	45	100%

	50 55	59% 20 cc
Kidney	20	66% of one**
Bladder	60 63	50% 25%
Liver	25 30 50	50% 40% 5%
Spinal cord	45	
Ureter	56	Point dose

* The mobile nature of the small bowel loops in the pre-operative primary case setting make it impossible to identify a specific loop(s) to permit dose constraints to be specified. In addition bowel is generally adjacent to the CTV for these lesions. For this reason it is optimal to reduce the volume as much as possible by restricting the PTV expansion beyond the GTV to 1.5 cm (i.e. CTV of 1.0 cm) in areas where the bowel and GTV approximate, and particularly after 45 Gy in 25 fractions has been administered.
** If both kidneys will remain in place; if nephrectomy is to be performed, maximum dose of 20 Gy to 20% of remaining kidney.

Participants should be immobilized with arms up in stable and comfortable positions to allow accurate repositioning from treatment to treatment and to prevent movement during treatments. A variety of immobilization devises may be utilized. Radiotherapy treatment plans will be generated after immobilization and 4D computerized tomography (CT) simulation. Adjustments of participant position should be made accordingly, if needed prior to treatment. Pretreatment images include orthogonal kilovoltage x-ray or CT.

5.2 Definition of Dose-Limiting Toxicity (DLT)

The DLT observation period will be Cycles 1-2 (weeks 1-6). Toxicity will be monitored throughout the entire treatment course and 9 week post-operative follow up period. A protocol amendment for RP2D de-escalation may occur if excess late toxicity is observed.

Dose-limiting toxicities will be defined as any of the following events that are *probably or definitely attributable* to protocol therapy (either eribulin or radiation). Events not caused by or related to protocol therapy or symptoms determined to be from tumor progression will not be classified as DLTs. Any deaths not clearly due to underlying disease or extraneous causes, as determined by the investigator, will be classified as DLTs.

Management and dose modifications associated with adverse events are outlined in Section 6.

5.2.1 Non-hematologic dose-limiting toxicities

Any CTCAE grade 4 non-hematologic toxicity *definitely or probably attributable* to protocol therapy will be considered a DLT. Any CTCAE grade 3 non-hematologic toxicity *definitely or probably attributable* to protocol therapy that lasts >7 days will be considered a DLT.

5.2.2 Hematologic dose-limiting toxicities

The following hematologic toxicities will be considered dose-limiting, if probably or definitely attributable to protocol therapy:

- CTCAE grade 3-4 febrile neutropenia
- CTCAE grade 3 neutropenia (ANC < 1000) for >7 days
- CTCAE grade 4 anemia (i.e., life threatening)
- CTCAE grade 3 thrombocytopenia with clinically significant bleeding
- CTCAE grade 4 thrombocytopenia (platelets < 25,000)

- Myelosuppression that causes a delay of >7 days for C2D8 eribulin dose

5.3 Concomitant and Supportive Care Measures

No drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-glycoprotein (P-gp) inhibitors. 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.

5.3.1 Supportive Care & Concomitant Therapy

There are no required concomitant medications in this study. No non-protocol cytotoxic therapy or radiotherapy may be used during study treatment. Participants may receive all concomitant therapy deemed necessary to provide optimal support. Hematopoietic growth factors may be used according to ASCO guidelines.[22] Because there is a potential for interaction with concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies

5.3.3 Prohibited Concomitant Therapy

Medications that prolong QTc should be used with caution. Participants may not take more than one medication with a known risk of TdP (Appendix E) during and up to 3 weeks after the last dose of eribulin. Premedication with ondansetron 4 mg IV prior to each eribulin dose is allowed.

No investigational products, non-protocol cytotoxic therapy or radiotherapy may be used during study treatment.

5.4 Duration of Treatment

Subjects will be treated with eribulin for a maximum of 3 cycles.

Radiation therapy duration is dependent on assigned dose level. Radiation therapy must begin no sooner than Cycle 1, Day 8 and no later than Cycle 2, Day 1.

Surgery must be completed at least 3 week but no more than10 weeks after completion of radiation therapy. Surgical resection outside of this window will constitute a deviation from protocol therapy, and the reason must be clearly indicated within the eCRF. Surgical resection prior to completion of all planned chemotherapy and radiation will constitute discontinuation of protocol therapy. The reason for early resection must be clearly indicated within the eCRF.

5.5 Duration of Follow-up

Subjects will be followed until death or until 10 years after completion of study therapy, whichever occurs first.

A follow-up visit will occur 2 weeks (±5 days) and 9 weeks (±7 days) post-op or, if surgery is not performed, 2 weeks (±5 days) and 9 weeks (±7 days) following removal from study. Subjects removed from study treatment for unacceptable adverse event(s) will be followed at least weekly until resolution or stabilization of the adverse event.

If a subject withdraws consent for further treatment, study staff must clarify and document the subject's willingness to continue in the follow-up phase of the study.

5.6 Criterial for Removal from Study (End of Treatment)

Subjects are free to withdraw consent and discontinue participation in the study at any time. The following reasons may lead to discontinuation from the study treatment phase, although follow up assessments should still occur.

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse effects,
- Toxicity that precludes further treatment as defined in Section 6,
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator, or
- For any reason, at the Sponsor or Investigator's discretion

The reason for study removal and the date the subject was removed must be documented in the Case Report Form.

5.7 Study Discontinuation

The study may be terminated by the investigator or other authority for the following reasons:

- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect subject safety.
- Subject enrollment is not proceeding at a pace that is compatible with trial completion within a reasonable amount of time so that the data are informative and the field moves forward.

6.0 Dose Modifications

6.1 General Dose Modification Guidelines

In order to dose eribulin on Day 1 or Day 8, the following criteria must be met:

- ANC $\geq$1,000/mm^3
- Platelets >75,000/mm^3
- Total bilirubin <2.0
- Creatinine clearance >50 mL/min by Cockcroft-Gault equation
- No grade 3 or 4 non-hematological toxicities. In particular, confirm peripheral neuropathy grade $\leq$2.

6.1.1 Delays

The Day 8 dose of eribulin may be delayed for a maximum of 1 week. If toxicities do not resolve or improve to $\leq$ Grade 2 by Day 15, omit the dose. If toxicities resolve or improve to $\leq$ Grade 2 severity by Day 15, administer eribulin at a reduced dose as per Table 6-1 and initiate the next cycle no sooner than 2 weeks later.

Protocol treatment (eribulin or radiation) may be delayed for up to 21 days (one equivalent cycle) to allow subject sufficient time for recovery from protocol therapy-related toxicity. If the subject does not recover from the toxicity within 42 days (2 equivalent cycles) from day 1 of the previous treatment cycle, then the subject must be discontinued from protocol therapy.

6.1.2 Dose modifications

Management of severe or intolerable adverse reactions requires temporary delay and/or dose reduction of study treatment. For subjects who do not tolerate the dosing schedule, dose adjustments are permitted in order to allow the subject to continue protocol therapy.

Table 6-1. Eribulin dose adjustments for toxicity, which may or may not be associated with protocol therapy.

If receiving eribulin 1.4 mg/m²:	***Reduce eribulin to:***
ANC <500/mm³ for >7 days	1.1 mg/m²
ANC <1,000 /mm³ with fever or infection	1.1 mg/m²
Platelets <25,000/mm³	1.1 mg/m²
Platelets <50,000/mm³ requiring transfusion	1.1 mg/m²
Omission or delay of Day 8 dose in previous cycle for non-hematologic toxicity	1.1 mg/m²
If receiving eribulin 1.1 mg/m²:	***Reduce eribulin to:***
ANC <500/mm³ for >7 days	0.7 mg/m²
ANC <1,000 /mm³ with fever or infection	0.7 mg/m²
Platelets <25,000/mm³	0.7 mg/m²
Platelets <50,000/mm³ requiring transfusion	0.7 mg/m²
Omission or delay of Day 8 dose in previous cycle for non-hematologic toxicity	0.7 mg/m²
If receiving eribulin 0.7 mg/m²:	***Reduce eribulin to:***
ANC <500/mm³ for >7 days	Discontinue
ANC <1,000 /mm³ with fever or infection	Discontinue
Platelets <25,000/mm³	Discontinue
Platelets <50,000/mm³ requiring transfusion	Discontinue
Omission or delay of Day 8 dose in previous cycle for non-hematologic toxicity	Discontinue

Any subject who requires a dose reduction will continue to receive the reduced dose for the remainder of the study. Any subject who requires a dose reduction that would result in "Discontinue" per tables above must be discontinued from protocol treatment.

6.1.3 Discontinuation

In general, discontinuation of one part of protocol therapy (either eribulin or radiation) will not necessitate discontinuation of the other part. In the event that eribulin treatment is discontinued for reason of toxicity, the subject may continue treatment with radiation at the discretion of the investigator. In the event that radiation treatment is discontinued for reason of toxicity, the subject may continue treatment with eribulin at the discretion of the investigator.

Study participants who develop intolerable tumor-related symptoms during the course of protocol therapy will be taken off treatment and referred for immediate surgery.

6.2 Dose Modifications for Adverse Events of Interest (Diarrhea, Vomiting, Skin Toxicity)

The following information pertains to dose modifications and delays for diarrhea, vomiting or skin toxicity, which may or may not be attributable to study treatment.

Table 6-2. Dose modifications for diarrhea.

Grade	**Eribulin** **Dose Adjustment and Management**	**Radiation** **Dose Adjustment and Management***
Grade 1 (<4 watery BMs/day over baseline)	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.

Grade 2 (4-6 watery BMs/day over baseline)	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.	If persistently grade 2 after 48 hours of adequate medical therapy, interrupt therapy until recovery to grade ≤1, then resume with intent to give total prescribed dose. If treatment break of >14 days is needed, discontinue radiation.
Grade 3 (hospitalization indicated)	Delay next dose until recovery to grade ≤1. Re-initiate at the next lower dose level. If diarrhea recurs at grade 2, delay eribulin until recovery to grade ≤1 and re-initiate eribulin at the next lower dose level. If diarrhea recurs at grade 3, discontinue eribulin.	Discontinue radiation.
Grade 4 (life-threatening)	Discontinue eribulin.	Discontinue radiation.
Confounding factors and/or alternative causes for diarrhea should be excluded before delay/reduction. They include but are not limited to: concurrent medications (magnesium supplementation, antibiotics); *Clostridium difficile* infection. *Only applicable after initiation of IMRT.		

Table 6-3. Dose modifications for vomiting.

Grade	**Eribulin** **Dose Adjustment and Management**	**Radiation** **Dose Adjustment and Management***
Grade 1 (1-2 emesis/24h)	No dose adjustment recommended. Initiate appropriate medical therapy and increase prophylactic antiemetics for next dose.	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
Grade 2 (3-5 emesis/24h)	Delay next cycle until recovery to grade ≤1. Initiate appropriate medical therapy and increase prophylactic antiemetics for next dose. Re-initiate eribulin at the same dose. If emesis recurs at grade 2, delay eribulin until recovery to grade ≤1 and re-initiate eribulin at the next lower dose level.	If persistently grade 2 after 48 hours of adequate medical therapy, interrupt therapy until recovery to grade ≤1, then resume with intent to give total prescribed dose. If treatment break of >14 days is needed, discontinue radiation.
Grade 3 (hospitalization indicated)	Delay next dose until recovery to grade ≤1. Re-initiate at the next lower dose level. If emesis recurs at grade 2, delay eribulin until recovery to grade ≤1 and re-initiate eribulin at the next lower dose level. If emesis recurs at grade 3, discontinue eribulin.	Discontinue radiation.
Grade 4 (life-threatening)	Discontinue eribulin.	Discontinue radiation.
Confounding factors and/or alternative causes for vomiting should be excluded before delay/reduction.		

*Only applicable after initiation of IMRT.

Table 6-4. Dose modifications for radiation dermatitis.*

Grade	Eribulin Dose Adjustment and Management	Radiation Dose Adjustment and Management
Grade 1 (faint erythema or dry desquamation)	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
Grade 2 (patchy moist desquamation)	Initiate appropriate medical therapy. Delay next cycle until recovery to grade ≤1.	If persistently grade 2 after 3 days of adequate medical therapy, interrupt therapy until recovery to grade ≤1, then resume with intent to give total prescribed dose. If treatment break of >14 days is needed, discontinue radiation.
Grade 3 (moist desquamation in areas other than skin folds)	Delay next dose until recovery to grade ≤1. Re-initiate at the next lower dose level.	Discontinue radiation.
Grade 4 (life-threatening)	Discontinue eribulin.	Discontinue radiation.
Confounding factors and/or alternative causes for dermatitis should be excluded before delay/reduction. *Only applicable after initiation of IMRT.		

6.3 Dose Modifications for Treatment-Related Adverse Reactions

The following general guidelines apply to any AEs that are "probably" or "definitely" related to study treatment as assessed by the investigator and are not addressed in Table 6-1, 6-2, 6-3 or 6-4.

Table 6-5. Dose modifications for toxicities that are *probably* or *definitely* related to protocol therapy.

Grade	Eribulin Dose Adjustment and Management	Radiation Dose Adjustment and Management*
1	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
2	Delay next cycle until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate eribulin at the same dose. If the same toxicity recurs at grade 2, delay eribulin until recovery to grade ≤1. Re-initiate eribulin at the next lower dose level.	No dose adjustment recommended. Initiate appropriate medical therapy and monitor.
3	Delay next cycle until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate eribulin at the next lower dose level. If toxicity recurs at grade 2, delay eribulin until recovery to grade ≤1 and re-initiate eribulin at the next lower dose level.	Interrupt therapy until recovery to grade ≤1, then resume with intent to give total prescribed dose. If the same toxicity recurs at grade 3, discontinue radiation. If treatment break of >14 days is needed, discontinue radiation.

	If toxicity recurs at grade 3, discontinue eribulin.	
4	Discontinue eribulin and treat with appropriate medical therapy.	Discontinue radiation and treat with appropriate medical therapy.
*Only applicable after initiation of IMRT.		

7.0 Adverse Events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of expected AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting.

7.1 Adverse Events and Potential Risks

7.1.1 Study Drug: Eribulin

The following includes all AEs considered to be expected.

Neutropenia: Severe neutropenia (ANC <500/mm^3) lasting > 1 week occurred in 12% of patients with MBC and 12% of patients with liposarcoma or leiomyosarcoma. Febrile neutropenia occurred in 5% of patients with MBC and two patients (0.4%) died from complications. Febrile neutropenia occurred in 0.9% of patients with liposarcoma or leiomyosarcoma and fatal neutropenic sepsis occurred in 0.9% of patients. In patients with MBC with elevated liver enzymes >3 × ULN and bilirubin >1.5 × ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal levels.

Peripheral Neuropathy: Grade 3 peripheral neuropathy occurred in 8% of patients with MBC (Grade 4 = 0.4%) and 22% developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 25-662 days). Neuropathy lasting > 1 year occurred in 5% of patients with mBC. Grade 3 peripheral neuropathy occurred in 3.1% of patients with liposarcoma and leiomyosarcoma receiving eribulin and neuropathy lasting more than 60 days occurred in 58% (38/65) of patients who had neuropathy at the last treatment visit.

QT Prolongation: In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1.

Impact on Reproduction: *Females:* Based on findings from an animal reproduction study and its mechanism of action, eribulin can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with eribulin and for at least 2 weeks following the final dose**.** *Males:* Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with eribulin and for 3.5 months following the final dose. Based on animal data, eribulin may result in damage to male reproductive tissues leading to impaired fertility of unknown duration.

Additionally: In patients with liposarcoma and leiomyosarcoma receiving eribulin the most common adverse reactions (≥25%) reported in patients receiving eribulin were fatigue (62%), nausea (41%), alopecia (35%), constipation (32%), peripheral neuropathy (29%), abdominal pain (29%), and pyrexia (28%). The most common (≥5%) Grade 3-4 laboratory abnormalities reported in patients receiving eribulin were neutropenia (32%), hypokalemia (5.4%), and hypocalcemia (5%). Neutropenia (4.9%) and pyrexia (4.5%) were the most common serious

adverse reactions. The most common adverse reactions resulting in discontinuation were fatigue and thrombocytopenia (0.9% each).

Other clinically important adverse reactions occurring in ≥10% of the eribulin-treated patients were:
• **Gastrointestinal Disorders:** nausea (41%); vomiting (19%), diarrhea (17%)
• **General Disorders:** asthenia/fatigue (62%); peripheral edema (12%)
• **Metabolism and Nutrition Disorders:** decreased appetite (19%)
• **Musculoskeletal and Connective Tissue Disorders:** arthralgia/myalgia (16%); back pain (16%)
• **Respiratory Disorders:** cough (18%)

Less Common Adverse Reactions: The following additional clinically important adverse reactions were reported in ≥5% to <10% of the eribulin-treated group:
• **Blood and Lymphatic System Disorders:** thrombocytopenia
• **Eye Disorders:** increased lacrimation
• **Gastrointestinal Disorders:** dyspepsia
• **Metabolism and Nutrition Disorders:** hyperglycemia
• **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, musculoskeletal pain
• **Nervous System Disorders:** dizziness, dysgeusia
• **Psychiatric Disorders:** insomnia, anxiety
• **Respiratory, Thoracic, and Mediastinal Disorders:** oropharyngeal pain
• **Vascular Disorders:** hypotension

7.1.2 Intensity-Modulated Radiation Therapy (IMRT)

Possible acute radiation adverse events depending on tumor location include: fatigue, regional alopecia, diarrhea, skin erythema and desquamation within the treatment fields, nausea, anorexia, vomiting, diarrhea, acute radiation enteritis, dysuria, pneumonitis, wound healing complication, and reduction in blood counts.

Long-term treatment adverse events depending on location include bowel injury, renal/hepatic dysfunction, spinal cord injury, osteoradionecrosis, bony fracture in the radiation field, lymphedema, subcutaneous fibrosis, and joint stiffness of the extremity receiving radiation and surgery. There also is a risk of cancer occurring in a previously irradiated field.

7.2 Adverse Event Characteristics

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:
- Results in death

- Is life-threatening (ie, the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious. (Based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use)

Collection of AEs begins with subject registration. All AEs of interest (section 6.2), all grades neutrophil count decreased, platelets decreased, and all greater than or equal to grade 3 "other" AEs will be recorded.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Adverse Events will be documented as 'Unexpected' or 'Expected' (see Section 7.1 above for expected AEs) based on available safety data.

Attribution for Adverse Events will be documented as follows:

- Definite – the AE *is clearly related* to the study treatment.
- Probable – the AE *is likely related* to the study treatment
- Possible – the AE *may be related* to the study treatment.
- Unrelated – the AE *is clearly NOT related* to the study treatment.

8.0 Pharmaceutical Information

A list of the expected adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage). http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

8.2 Study Agent: Eribulin

Availability: Eribulin is supplied to investigators by the manufacturer Eisai or its designee.

Product description: Eribulin mesylate is a microtubule dynamics inhibitor that is a synthetic analogue of halichondrin B, a product isolated from the marine sponge Halichondria okadai. 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).

Solution preparation: 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. 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.

Storage requirements: 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.

Stability: 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.

Route of administration: Intravenous injection

9.0 Correlative Studies

Details for collection, handling and shipment of specimens and images will be provided in the Operations Manual.

9.1 Integral

None.

9.2 Integrated

9.2.1 Health-Related Quality of Life

Subject-reported symptoms will be evaluated with PROMIS questionnaires at four time points: baseline, C2D8, prior to surgery, and 9 weeks post-op. We will use the 10 item Global Health Scale and 5 item Belly Pain Scale (total of 15 questions) at each time point (see Appendix C). Study staff will administer all questionnaires.

9.2.2 Histologic and Molecular Biomarkers

There is preclinical evidence that treatment with eribulin remodels the abnormal tumor vasculature and reduces microvessel density.[11] Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). CD31 endothelial cells will be stained for with IHC and microvessel density will receive a binary score (high or low density). A chain of custody form to be completed by study staff for intraoperative biopsy specimens can be found in the Operations Manual (appendix F). The Knight BioLibrary & Pathology Shared Resource will assist with tissue collection and processing. The Davis Lab will complete IHC and microvessel density scoring.

9.2.3 Imaging

Subjects will undergo DCE-MRI scanning at three different times during the preoperative period. Baseline DCE-MRI is to be performed during screening. The DCE-MRI will then be repeated approximately 1 week after initiating eribulin (prior to first radiation dose) and then again prior to surgery but at least 1 week after completing radiation.

DCE-MRI will be performed at the OHSU Advanced Imaging Research Center (AIRC) using a 3 Tesla Siemens MRI system. A whole body coil will be used for RF transmit and receive. DCE T1-weighted MRI will be performed using a 3D fast spoiled-GRASS (FSPGR) pulse sequence to acquire 50-60 sets of images of the tumor over the time course of approximately 10 min. The other parameters are: TE = 2.3 ms, TR = 6.0 ms, 10 degree flip angle, and

256x128 matrix size. Each volumetric data set will contain approximately 12-20 image slices with 5 mm slice thickness, resulting in temporal resolution of 8-10s for the time course data. The gadolinium chelate contrast reagent (CR) at dosage of 0.1 mmol/kg will be delivered intravenously at 2 mL/s by a programmable power injector (Medrad, Indianola, PA) at the beginning of the sixth data set acquisition through a peripheral IV or portacath. In addition to DCE-MRI, conventional anatomic images will be taken with standard pulse sequences. The total time for the subject in the scanner is anticipated to be less than 45 minutes.

9.3 Exploratory

Tumor infiltrating cells. This exploratory endpoint is intended to be hypothesis generating. Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). A chain of custody form to be completed by study staff for intraoperative biopsy specimens can be found in the Operations Manual. The Knight BioLibrary & Pathology Shared Resource will assist with tissue collection and processing. The Davis Lab will work with the Coussens Lab to perform IHC for tumor infiltrating lymphocytes and tumor associated macrophages on all paired samples.

Microenvironment & differentiation profiling by microarray. Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). A chain of custody form to be completed by study staff for intraoperative biopsy specimens can be found in the Operations Manual. The Knight BioLibrary & Pathology Shared Resource will assist with tissue collection and processing. Total RNA will be isolated by the Davis Lab and the Gene Profiling Shared Resource will hybridize relevant microarray(s) for all paired samples. This exploratory endpoint is intended to be hypothesis generating.

Circulating tumor DNA (ctDNA). This exploratory endpoint is intended to be hypothesis generating. Plasma (3-5mL) will be collected at multiple time points and shipped to the van de Rijn & West lab at Stanford of ctDNA analysis. A chain of custody form will be completed by study staff for all specimens.

9.4 Analysis

See Section 13.4 for the Statistical Analysis Plan.

The integrated and exploratory correlative data collected in the clinical database will be analyzed by the OHSU Knight Cancer Institute Biostatistics Shared Resource. The analysis of the exploratory biomarker data should be viewed as hypotheses generating; results from such analyses may be used to generate additional hypotheses that must then be verified with subsequent clinical trials.

If the number of samples is inadequate to perform a rigorous data analysis, then only the available data will be listed. Additional analyses that may be performed after the completion of the end-of-study clinical study report will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies. Any additional data analysis will be described in an addendum or in a stand-alone analysis plan document, as appropriate.

The Full Analysis Set will be used for all analyses. Subjects with measureable archival tumor samples will be identified in the summaries and relevant proportions will be calculated against this number of subjects.

DCE-MRI. Data will be transferred anonymously to off-line workstations and analyzed using the shutter-speed model pharmacokinetic analysis software package, which is written in the Matlab language. This model takes into account the two site-water exchange kinetics and allows us to fit the DCE-MRI signal intensity time course and extract pharmacokinetic parameters, such as volume transendothelial CR transfer constant (K^{trans}), extravascular CR leakage space (v_e) and mean intracellular water molecule lifetime (τ_i). The computation of the average K^{trans}, v_e and τ_i values from the lesion region-of-interest (ROI) and pixel-by-pixel parametric mapping of K^{trans}, v_e and τ_i will be performed, and percent changes over the course of drug treatment will be calculated. To account for the heterogeneity of the tumor, histogram analyses of the pixel K^{trans}, v_e and τ_i within the ROI will be performed and the median values of these parameters, as well as their percent changes over treatment course, will be calculated. Anonymized images will be submitted to the National Cancer Archive at Washington University for the purpose of developing a new software package for DCE-MRI analysis.

10.0 Study Procedures & Schedule of Events

Refer to Section 10.4, Schedule of Events.

10.1 Screening/Baseline Visit

Informed consent must be obtained within 4 weeks (28 days) prior to start of protocol treatment. Baseline screening evaluations including imaging are to be conducted within 4 weeks (28 days) prior to starting protocol therapy.

10.2 On-Study Visits

There is a 3 day treatment window for every Day 1. There is a +/- 1 day window for every Day 8 treatment to account for potential subject scheduling issues.

Dose adjustments or the occurrence of hematologic or non-hematologic adverse events may require additional clinical evaluations and/or laboratory studies but should not be any less frequent than the schedule outlined.

Concurrent Medications: All concurrent medications and treatments must be recorded in the case report form (CRF). Any prior medication received up to 30 days prior to the Screening visit will be recorded. Concurrent treatments that are required to manage a subject's medical condition during the study will also be recorded in the CRF. Prior and/or ongoing medications will be reviewed during screening to determine subject eligibility. The medication record will be maintained following enrollment including any changes to the dose or regimen. Prior and concurrent medication including any prescription, over the counter or natural/herbal/multivitamin preparations taken will be recorded.

Adverse event evaluation: Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events 4.0 and relatedness will be assigned as per Section 7.2.

Physical Exam, Vital Signs, Performance Status & Weight: Performed at Screening, C1D1, C1D8, C2D1, C3D1, 2 weeks post-op, and 9 weeks post-op. The physical exam should include General, HEENT, Respiratory, Abdominal and Skin systems at a minimum.

Laboratories: The following labs will be collected as outlined in the table in Section 10.4:

- CBC with differential

- Serum chemistry to include complete metabolic profile (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium), phosphorus and magnesium
- Electrolytes: calcium, potassium, phosphorus and magnesium
- Pregnancy Test: A urine pregnancy test is required for all women of childbearing potential during screening and on Day 1 of each Cycle. If the urine pregnancy test is positive, serum pregnancy tests must be performed per institutional standards.
- Research blood. 7-10mL of blood in Cell-Free DNA BCT tube to yield 3-5mL plasma.

CT Abdomen and Pelvis with Tumor Measurements: Subjects should undergo a CT of the abdomen/pelvis with PO & IV contrast at screening and prior to surgery. If IV contrast cannot be given, oral contrast alone may be used. Target lesions will be defined in accordance with RECIST 1.1 guidelines and followed from baseline.

CT Chest: Subjects should undergo a CT of the chest at screening.

Cardiac evaluations: An ECG will be obtained during Screening and prior to each Day 8 eribulin dose. An ECHO/MUGA will be obtained during Screening

Nursing Assessments: Standard nursing assessment will be performed by a chemotherapy certified nurse prior to eribulin administration.

PROMIS assessments: PROMIS questionnaires will be completed by the patient at four time points: baseline, C2D8, prior to surgery, and 9 weeks post-op.

DCE-MRI: Every possible effort will be made to obtain a DCE-MRI for each subject during screening, prior to first dose of radiation, and prior to surgery.

Intraoperative biopsy: Immediately after removing the tumor from the subject, the surgeon or his/her delegate will collect multiple tumor tissue specimens. Samples of adjacent normal fat will also be collected during surgery.

Hydration: 1 liter of normal saline twice weekly during radiation (IMRT). During hydration visits, electrolytes will be checked and repleted as necessary.

10.3 Follow-up

All registered subjects will be followed until death or until 10 years after completion of study therapy, whichever occurs first.

Two follow-up visits are required, one 2 weeks (±5 days) after surgery and another 9 weeks (±7 days) after surgery. If surgery is not performed, a follow-up visit will occur 2 weeks (±5 days) and 9 weeks (±7 days) following end of treatment.

Any subject who discontinues study treatment but refuses to return for follow-up visits should be contacted for safety evaluations (i.e., assessment of AEs and/or SAEs, concomitant medications) for 30 days after the last dose of study treatment.

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, should be followed at least once a week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event, whichever comes first.

Monitoring for recurrence will begin 6 months after surgery or end of treatment. Follow-up reports will be due every 6 months, and will be limited to monitoring for development of local tumor recurrence, development of distant metastatic disease, survival, and late toxicity.

10.4 Schedule of Events

	Screening (≤28 days prior to C1D1)	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 3 Day 1	Cycle 3 Day 8	Pre-Surgery	Day of Surgery	Follow-Up[#]
Eribulin		X	X	X	X	X	X			
IMRT (dose level 1 or 2, 50.4 Gy)			XXXXX XXXXX XXXXX XXXXX XXXXX XXX							
IMRT (dose level -1, 39.6 Gy)			XXXXX XXXXX XXXXX XXXXX XX							
Informed consent	X									
Demographics	X*									
Medical history	X*									
Concurrent medications	X*		----------X----------							
Adverse event evaluation			----------X----------							
Physical exam	X*	X*	X*	X*		X*		X*		X*
Vital signs	X*	X*	X*	X*		X*		X*		X*
Height	X*									
Weight	X*	X*	X*	X*		X*		X*		X*
Performance status	X*	X*	X*	X*		X*		X*		X*
CBC w/diff, CMP, Mg, Phos, LDH	X*	X*	X*	X*	X*	X*	X*	X*		X*
Hydration and electrolyte check			X[f,g]							
Urine β-hCG[a]	X*	X*		X*		X*				
Research blood	X		X					X		X
ECG	X*		X*[b]		X*[b]		X*[b]			
ECHO/MUGA	X									
CT abdomen/pelviswith contrast	X*							X*		
CT chest	X*									
DCE-MRI	X		X[c]					X		
PROMIS	X				X			X		X[e]
Intraoperative biopsy									X[d]	
Estimated visit time (hours):	**5**	**1**	**5**	**1**	**0.5**	**1**	**0.5**	**5**	**variable**	**1**

There is a +/- 3 day treatment window for every Day 1.
There is a +/- 1 day treatment window for every Day 8.
IMRT occurs once daily, five days per week with exceptions for holidays, beginning no sooner than C1D8 and no later than C2D1.
Pre-Surgery evaluations should occur at least 1 week after completion of radiation.
[*] Usual care procedure.
[#] Clinic visit 2 weeks (±5 days) post-op and 9 weeks (±7 days) post-op.
[a] For women of childbearing potential only. If the urine pregnancy test is positive, serum pregnancy test must be performed.
[b] Prior to eribulin dose.

[c] Prior to first dose of radiation.
[d] Occurs on day of surgery immediately after resection (*i.e.*, in operating room after tumor removed en bloc).
[e] At post-op 9 week visit only.
[f] Twice weekly during IMRT portion of trial
[g] Electrolytes: potassium, calcium, magnesium, phosphorus

11.0 Measurement of Effect

11.1 Definitions

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

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

11.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) 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).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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 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 measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, 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 five 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.

Pathologic response. Pathologic response of a resected tumor is assessed by a clinical pathologist after resection. Pathologic response is defined as the overall percentage of treatment change within the tumor, as well as percent necrosis, percent cytodifferentiation and percent fibrosis. A clinical pathologist conducts a central evaluation and directly enters their independent determination in the Central Pathology Review form (located in Study Operations Manual). The Central Pathology Review form records subject information, margin measurement, presence of perineural invasion or lymphovascular invasion, as well as percentages of fibrosis, necrosis, cytodifferentiation, and overall treatment effect.

11.3 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.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-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 measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the

PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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).

Since an effusion may be a side effect of the treatment, 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 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 of possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: 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.
c. 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. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that 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.

11.4 Response Criteria

11.4.1 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.

11.4.2 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).

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.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or principal investigator).

11.4.3 Best Overall Response

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

11.5 Response Review

Response assessment will be determined by a qualified individual, which may be an investigator or, in some cases, a radiology. To avoid bias by the investigator in response determination, the clinical imaging report will be used for identification of target lesions.

12.0 Data Reporting & Regulatory Requirements

12.1 Data Collection and Storage

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Study outcome data will be captured in electronic case report forms (eCRFs) in the following electronic data capture (EDC) system. The web-based system is password protected and encrypted with role-based security, and administered by Knight Clinical Research Quality and Administration (CRQA) informatics staff. Study team members will have login credentials and have been trained in procedures for entering, accessing and storing data. This will facilitate information being stored in a unified format and location. Data from correlative studies will be entered by research personnel at OHSU.

Additional confidentiality will be preserved by limiting PHI captured in an EDC system to just birth date and visit dates. Data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 12.8, OHSU Knight Cancer Institute Data and Safety Monitoring Plan.

12.2 Privacy, Confidentiality and Data Security

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Participants will sign an authorization that includes the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Loss of subject confidentiality is a risk of participation. Study participant identities will be kept confidential except as required by law. Subjects' samples will be identified by code only (i.e. linked, but de-identified). Subject samples will be de-identified at the time and site of collection. Electronic case report forms, participant, and study information will be kept in a password protected database. Additionally, documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location in the Office of Clinical Research.

Subject data collected for this study will be captured in RedCap as described in Section 12.1. All users of the database are assigned a unique ID and username and must complete training appropriate to their role before they are authorized to use the database.

Each subject who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the subject throughout the duration of their participation in the trial. The coded identifier will be used to identify subject specific samples. Tissue samples collected for the purposes of this protocol will be stored until they can be analyzed and will then be destroyed unless the subject consents to participation in the BioLibrary. Blood samples will be shipped to the van de Rijn & West lab at Stanford for analysis. Any remaining samples (tumor) may be stored in the Knight BioLibrary indefinitely and further analyzed to address scientific questions and/or development of biological tests related to cancer.

12.3 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and the appropriate Institutional Review Board (IRB) prior to any subject being consented on this study.

12.4 Informed Consent

Written informed consent will be obtained from all subjects, or the legally authorized representative of the subject, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a subject's signature cannot be obtained, and for all subjects under the age of 18, the investigator must ensure that the informed consent is signed by the subject's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the subject's medical record.

12.5 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator must notify the CRRC and IRB in writing within 5 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

12.6 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Trials Office. Records must be maintained according to sponsor or FDA requirements.

12.7 Reporting of Unanticipated Problems and Adverse Events

12.7.1 OHSU IRB Reporting

Reportable New Information (RNI) and Adverse Events (AE) will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site http://www.ohsu.edu/xd/about/services/integrity/policies/all-irb-documents.cfm.

Fatal and life-threatening events that meet the criteria for an RNI must be reported to OHSU IRB within 5 business days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

All other RNI reports will be submitted to OHSU IRB no later than 5 business days after the PI learns of the event. If the event requires changes as determined by the PI or the IRB) to the protocol or consent form, the PI will make the changes promptly and submit the revised documents to the IRB. RNI and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU IRB.

12.7.2 MedWatch Reporting

For this investigator-initiated study, the investigator is the study sponsor. The investigator / sponsor is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package label), serious adverse experiences with a suspected association to the study drug.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500, the MedWatch Voluntary Reporting form, which is available online at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf

Investigators may also complete Form FDA 3500 online at:
https://www.accessdata.fda.gov/scripts/medwatch/

When the serious adverse event is reported to the FDA, copies of Form FDA 3500 and supporting materials will be submitted to the OHSU Knight Cancer Institute and the IRB. A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

For sponsor-investigators who hold an IND, Form FDA 3500 will be submitted to the IND/IDE associate who will assist the study team in a formal safety report to the FDA.

12.7.3 Additional Reporting Requirements

The Principal Investigator will comply with all safety reporting regulations as set forth in the Code of Federal Regulations. Any correspondence to the FDA regarding adverse events or other safety issues will be simultaneously copied via fax or email to Eisai.

OHSU will notify Eisai of all serious adverse events that are *probably* or *definitely* attributable to the Study Drug (see Section 7.2 for definitions). The notification of a serious suspected adverse drug reaction should occur as soon as possible, but no later than one business day, and should be done by fax or email via the Eisai standard serious adverse event report form (Appendix E). The contact details for the notification are:

Eisai Medical Affairs
200 Metro Boulevard
Nutley, NJ 07110
Tel: 1-888-274-2378
Fax: -1-732-791-1111
Email: ESI_Safety@eisai.com

In addition, OHSU will notify Eisai immediately of any other information that suggests a change to the safety profile of the Study Drug.

12.7.4 Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to Eisai within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Eisai Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Eisai study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

12.8 OHSU Knight Cancer Institute Data and Safety Monitoring Plan (DSMP)

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight Data and Safety Monitoring Committee (DSMC) and/or regulatory authorities.

Quality assurance auditing activities will occur as detailed in the Knight DSMP. All discrepancies, queries, deviations, observations, and findings will be compiled into a final audit report along with a Corrective and Preventative Action Plan.

The investigator-sponsor, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practices (GCP), and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures here.

Locally initiated studies will be audited by OHSU Knight DSMC Auditor. Newly approved studies may be audited any time after enrollment has been initiated. Each OHSU Knight approved interventional protocol will be audited on an annual basis in accordance with the Knight DSMP.

12.9 Inclusion of Women, Minorities and Children

12.9.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 12-1. Oregon population demographics (adapted from US Census Bureau, 2010)

	Sex/Gender		
Ethnic Category	Females	Males	Total
Hispanic or Latino	5.9	5.8	11.7
Not Hispanic or Latino	44.5	43.8	88.3
Ethnic Category: Total of all subjects*	50.4	49.6	100*
Racial Category			
American Indian or Alaskan Native	0.7	0.7	1.4
Asian	1.9	1.8	3.7
Black or African American	0.9	0.9	1.8
Native Hawaiian or other Pacific Islander	0.2	0.1	0.3
White	42.1	41.5	83.6
More than one race	1.9	1.9	3.8
Unknown/Other	2.7	2.6	5.3
Racial Category: Total of all subjects*	50.4	49.5	100*
TOTALS	50.4	49.6	100*

Table 12-2. Projected accrual for the present study

	Sex/Gender			
Ethnic Category	Females	Males	Unknown	Total
Hispanic or Latino	1	1	0	2
Not Hispanic or Latino	6	7	0	13
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	7	8	0	15
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0	0-1
Asian	0-1	0-1	0	0-1
Black or African American	0-1	0-1	0	0-1
Native Hawaiian or other Pacific Islander	0-1	0-1	0	0-1
White	6	6	0	12
More than one race	0-1	0-1	0	0-1
Unknown	0-1	0-1	0	0-1
Racial Category: Total of all subjects*	7	8	0	15

12.9.2 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them.

This study includes subjects ≥12 years of age. Retroperitoneal liposarcomas are rare in adolescents and young adults and exceptionally rare in children.

13.0 Statistical Considerations

The Knight Cancer Institute Biostatistics Shared Resource at OHSU will provide statistical support for this trial. The final data will include all subjects' data up to the time when all subjects have completed treatment or discontinued the study.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

13.1 Study Design

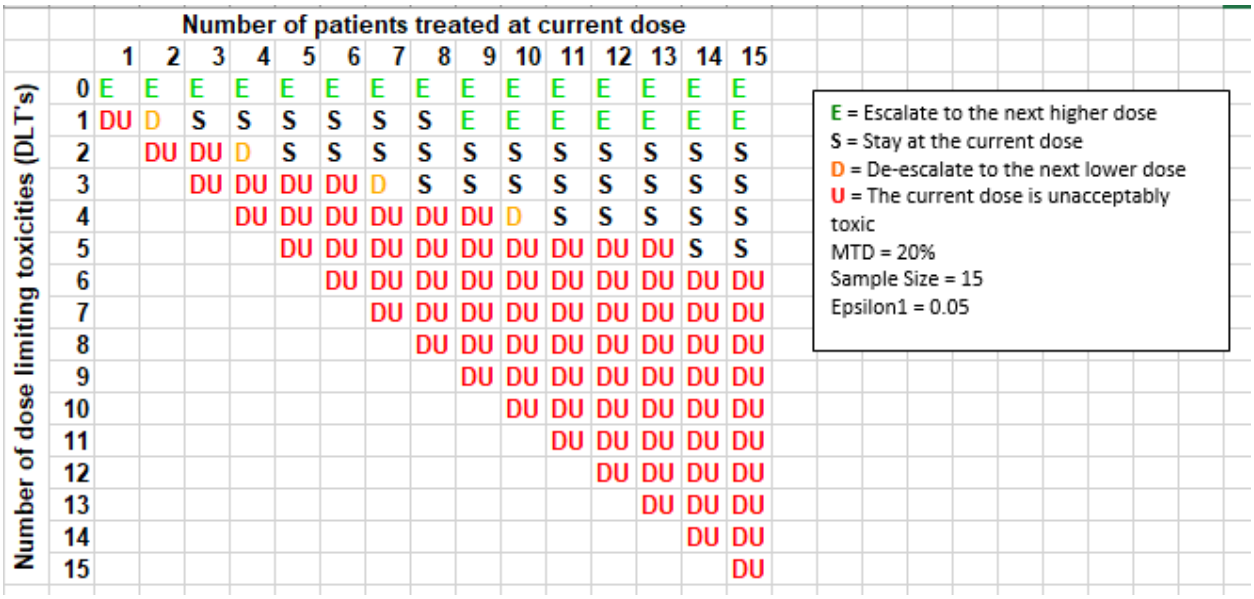
This is an open-label, phase IB, dose-finding study in which safety and tolerability of radiation in combination with eribulin in subjects with retroperitoneal liposarcomas will be investigated.

This study uses a modified toxicity probability interval (mTPI) design with target toxicity rate of 0.2 (see Tables 13-1 and 13-2 below).[23] Four subjects will be enrolled for the first cohort at a given dose, and 3 subjects will be enrolled for subsequent cohorts at the same dose.

Table 13-1. Toxicity probability intervals for mTPI design.

Target Toxicity	Under-dosing interval	Proper dosing interval	Over-dosing interval
0.2	0-0.15	0.15-0.25	0.25-1.00

Table 13-2. mTPI Decision Table with pre-calculated dose-determining decisions. The number of patients treated at the current dose corresponds to the numbered columns. The number of patients experiencing a DLT at the current dose corresponds to the numbered rows. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dose-determining actions. In addition to actions that de-escalate the dose (D), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (DU), which is defined as the execution of the dose-exclusion rule in mTPI.



The DLT observation period for the purposes of dose-determining will be Cycles 1-2 of therapy (weeks 1-6). The dose exclusion rule will not be activated until all subjects in a cohort have completed all planned dose of radiation.

If the toxicity rate of the currently used dose level is within the under-dosing interval, the mTPI design will recommend escalating the dose level; in the case of proper dosing, the design will recommend continuing at the current dose; for over-dosing, the mTPI design will recommend de-escalating the dose level.

Four subjects will be entered at the starting dose level. No additional subjects may be enrolled until all four of these subjects have completed all planned doses of radiation, and the dose exclusion rule (according to the pre-calculated mTPI table) will not be activated until all four of these subjects have completed all planned doses of radiation. If the mTPI design recommends a dose change (D or E), four subjects will be entered at the new dose level. No additional subjects may be enrolled until all four subjects have completed all planned doses of radiation. If the mTPI design recommends continuing at the current dose (S), three additional subjects will be enrolled at the same dose level. The dose exclusion rule will be applied again once each additional cohort of three subjects completes all planned doses of radiation.

13.2 Primary and Secondary Endpoints

	Objective	Endpoint
Primary	To determine the recommended phase 2 dose (RP2D) of radiation and eribulin when used in combination for the preoperative treatment of retroperitoneal liposarcoma.	Incidence of dose limiting toxicities (DLTs).
Secondary	To assess the feasibility of a preoperative chemoradiation protocol for retroperitoneal liposarcoma.	Rate of enrollment; rate of early surgery; rate of surgery beyond 10 weeks after completion of radiation; change in subject-reported quality of life.
	To assess the surgical outcomes of retroperitoneal liposarcoma resections	Rate of R0 resection; rate of serious post-operative complications.

	after preoperative chemoradiation.	
	To assess preliminary anti-tumor activity of eribulin in combination with radiation in subjects with retroperitoneal liposarcoma.	Pathologic response; objective response rate (ORR, CR+PR) by RECIST; recurrence free survival (RFS) and overall survival (OS) rates.
Exploratory	To obtain preliminary DCE-MRI data to evaluate changes in retroperitoneal liposarcoma perfusion after treatment with chemoradiation.	Changes in K^{trans} and other imaging parameters by DCE-MRI.
	To obtain preliminary data on changes in the liposarcoma microenvironment with chemoradiation.	Microvessel density by IHC; tumor infiltrating cells by IHC; ctDNA detection; gene expression by PCR array.

13.3 Analysis Populations

The safety analysis set includes all subjects who consent and receive at least one dose of study drug, regardless of how long they stay on study drug. Reason(s) for going off study will be collected on every subject.

The dose-determining set (DDS) consists of a subset of subjects in the safety analysis set who complete protocol therapy through Cycle 2 or discontinue due to DLT. If a subject discontinues study therapy before completing Cycle 2 for reasons other than DLT, that subject is not evaluable. The DLT observation period is Cycles 1- 2, but toxicity will be monitored throughout the entire treatment course and dose modifications will occur as per Section 6.0. Additionally, dose de-escalation may occur if excess late toxicity is observed.

The efficacy analysis set subjects who have measurable disease present at baseline, received at least one dose of eribulin, and had their disease re-evaluated.

13.4 Statistical Analysis Plan

13.4.1 Analysis of primary endpoint

The RP2D will be determined according to interim mTPI monitoring algorithm (Table 13-2). Adverse events will be graded and categorized according to the CTCAE v4.03. All adverse events will be tabulated and summarized by major organ category, grade, anticipation, and drug attribution. SAE specific incidence and exact 95% confidence interval will be provided where appropriate.

13.4.2 Analysis of secondary endpoints

Rate of enrollment. The predicted rate of enrollment is 15 subjects over 18 months. Specific enrollment rate will be provided.

Rate of early resection. The protocol specifies that subjects undergo surgical resection no sooner than 3 weeks after completion of radiation. The proportion of subjects, along with exact two-sided 95% confidence intervals, undergoing surgical resection before the completion of all planned chemotherapy and radiation will be reported for the study.

Rate of resection beyond 10 weeks after completion of radiation. The protocol specifies that subjects undergo surgical resection within 10 weeks of completing radiation. The proportion of subjects, along with exact two-sided 95% confidence intervals, undergoing surgical resection later than planned for any reason will be reported for the study.

Rate of serious post-operative complications. Serious post-operative complications are defined as complications occurring within 9 weeks following surgery and ≥ Grade III per the Clavien-Dindo classification system (Appendix D).[24, 25] This rate, along with exact two-sided 95% confidence intervals, will be reported for the study. The operating surgeon utilizes the Clavien-Dindo classification system in order to rank a complication.

PROMIS symptom measures. We will apply a mixed effects model to analyze changes in PROMIS symptom measurements at four time points: baseline, C2D8, prior to surgery and 9 weeks post-op.

Rate of R0 resection. Margin status will be documented from every surgical resection specimen. The rate of R0 resection is defined as the proportion of surgical specimens with microscopically negative margins. The rate of R0 resection, along with exact two-sided 95% confidence intervals, will be reported for the study.

Pathologic response. Pathologic response is defined as the percentage of tumor with treatment change, including necrosis, cytodifferentiation and fibrosis. Descriptive statistics including mean, median, standard deviation, and 95% confidence interval of pathologic response will be reported for the study.

Objective response rate. The ORR (CR+PR) is defined as the proportion of subjects who achieved a complete response (disappearance of all target tumors) or a partial response (≥30% decrease in the sum of the longest diameters of target tumors) based on RECIST Version 1.1. The ORR, along with exact two-sided 95% confidence intervals, will be reported for the study.

Recurrence-free survival rate. Median recurrence-free survival with 95% CI and survival rates at 2, 5 and 10 years will be estimated using the Kaplan-Meier method for both local and distant recurrence.

Overall survival rate. Median overall survival with 95% CI and survival rates at 2, 5 and 10 years will be estimated using Kaplan-Meier method.

13.4.3 Analysis of exploratory endpoints

Change DCE-MRI parameters. We will apply a mixed effects model to analyze changes in DCE-MRI K^{trans} and other parameters measured at three time points (baseline, pre-radiation, and prior to surgery). A comparison of baseline vs. pre-radiation will capture the effect of eribulin alone, while the comparison between pre-radiation vs. prior to surgical resection will capture the effect of combined preoperative eribulin and radiation.

Microvessel density (MVD). Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). IHC for CD31 endothelial cells will receive a binary score (high or low density). We will apply a paired t-test or Wilcoxon signed-rank test to examine the MVD score in the two biopsy specimens.

Tumor infiltrating cells. This exploratory endpoint is intended to be hypothesis generating. Biopsies will be collected prior to protocol therapy (archival) and after protocol therapy (intraoperative). IHC for tumor infiltrating lymphocytes and tumor associated macrophages will receive a binary score (present or absent). We will apply a paired t-test or Wilcoxon signed-rank test to examine the score in the two biopsy specimens.

Gene expression microarray. This exploratory endpoint is intended to be hypothesis generating. We will initially examine the distribution of each biomarker expression using Shapiro-Wilk test, as well as data visualization techniques. If the normality assumption is violated, we will consider transforming the data or adopting non-parametric approaches. Multivariate analysis will be used to assess biomarkers as predictive factors for secondary endpoints. In addition, we will apply lasso-based elastic net method. The elastic net method is a variable selection procedure by L1 and L2 penalized estimation that enforces variable selection and shrinkage simultaneously. The penalty parameter that controls the shrinkage of fixed terms and the variable selection will be determined by k-fold cross validation. Because of the limited sample size, this data analysis is for exploratory research only.

Circulating tumor DNA. This exploratory endpoint is intended to be hypothesis generating. Plasma will be collected at multiple time points prior to study treatment, during study treatment and during follow up. All samples will be shipped to the van de Rijn & West lab at Stanford for detection of ctDNA and analysis of change in ctDNA levels over time (pending additional funding).

13.4.4 Interim analyses and stopping rules

An mTPI dose-finding algorithm will be followed to insure safety (Table 13-2). The mTPI design has integrated stopping rules for excess toxicity. No formal interim analysis is planned.

13.5 Sample Size and Power

Sample size is based on the mTPI design. The RP2D was defined as the dose corresponding to a target toxicity probability of 0.2 with a maximum possible sample size of 15.

We conducted a simulation study to evaluate the effect of sample size on identification of the correct MTD. A total of 10,000 simulated trials were generated under three dose-toxicity scenarios to evaluate operating characteristics of the study design. In the simulation, uniform prior with early safety termination rule (dose exclusion threshold of 0.95) was used.[26] The MTD was defined as the dose corresponding to a target toxicity probability of 0.2. We considered three dose levels in the simulated trials, with three scenarios for the target toxicity of 0.2. The scenarios assumed the true probabilities of four doses as follows (low to high toxicity): scenario 1 (low toxicity) = (0.05, 0.10, 0.15), scenario 2 (low to moderate toxicity) = (0.10, 0.20, 0.30), scenario 3 (high toxicity) = (0.50, 0.60, 0.70). Simulation results are summarized below in Table 13.3.

Table 13-3. Operating characteristics of the mTPI design.

Scenario	**Dose Level -1** Eribulin 1.1 mg/m^2 + IMRT 39.6Gy	**Dose Level 1** Eribulin 1.1 mg/m^2 + IMRT 50.4Gy	**Dose Level 2** Eribulin 1.4 mg/m^2 + IMRT 50.4Gy	**MTD not selected (%)**	
				Below lowest	Above highest
Scenario 1					
True toxicity	0.05	0.10	0.15		
% selected as MTD	3.34	28.15	1.15	0.03	67.3
Average sample size	12.49				
Overall toxicity	0.083				
Scenario 2					
True toxicity	0.10	0.20	0.30		
% selected as MTD	16.93	55.59	0.37	0.74	25.66
Average sample size	16.95				

Overall toxicity	0.187				
Scenario 3					
True toxicity	0.50	0.60	0.70		
% selected as MTD	11.90	1.09	0.00	86.19	0.20
Average sample size	11.398				
Overall toxicity	0.604				

Scenario	**Dose Level -1** Eribulin 1.1 mg/m^2 + IMRT 39.6Gy	**Dose Level 1** Eribulin 1.1 mg/m^2 + IMRT 50.4Gy	**Dose Level 2** Eribulin 1.4 mg/m^2 + IMRT 50.4Gy	No Dose
Scenario 1				
True Toxicity Rate	0.05	0.1	0.15	
Selection Probability	0.0125	0.2175	0.3565	0.4135
Avg. # of patients Treated	0.204	5.616	7.6155	
Total Patients	13.4355			
Overall Toxicity	0.13349			
Scenario 2				
True Toxicity Rate	0.1	0.2	0.3	
Selection Probability	0.106	0.5085	0.285	0.1005
Avg. # of patients Treated	1.02	8.19	5.349	
Total Patients	14.559			
Overall Toxicity	0.226698			
Scenario 3				
True Toxicity Rate	0.5	0.6	0.7	
Selection Probability	0.1765	0.0615	0	0.762
Avg. # of patients Treated	4.992	5.124	0.243	
Total Patients	10.359			
Overall Toxicity	0.553094			

13.6 Handling of Missing Data

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the subject's data may be excluded entirely or partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any subject is excluded from the analysis due to missing data.

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APPENDIX A: Performance Status Criteria

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

APPENDIX B: Adequate contraception

Females and males of reproductive potential must use a barrier method in addition to a highly effective method of contraception throughout the study and for 3 weeks after study drug discontinuation.

Female subjects of childbearing potential must:

- Agree to use effective contraception from start of screening until 3 weeks following the last dose of eribulin and have a male partner who uses a condom, or
- Practice total abstinence, or
- Have a male partner who is vasectomized

Male subjects with a female partner of childbearing potential must:

- Be vasectomized, or
- Agree to use effective contraception, from first dose of eribulin until 3 weeks following the last dose of eribulin, or
- Have a female partner who is NOT of childbearing potential

Highly effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female subjects: sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment, or a vasectomized male partner who is the sole partner for that subject.
- Male subjects: sterilization at least 6 months prior to screening. A condom is required to be used also by vasectomized male subjects in order to prevent delivery of the drug via seminal fluid.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Note: For female subjects, oral contraceptives are allowed but MUST be used in conjunction with a barrier method of contraception due to potential risk for drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

APPENDIX C: PROMIS Questionnaire

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

	In the past seven days…	**Excellent**	**Very good**	**Good**	**Fair**	**Poor**
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

09 June 2016

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		None	Mild	Moderate	Severe	Very severe
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Name of person completing document:

Signature: Date:

Belly Pain

Please respond to each question or statement by marking one box.

In the past 7 days…

1 GIBX78 How often did you have belly pain?

- ☐ 1 Never → **If Never, go to #5**
- ☐ 2 One day
- ☐ 3 2-6 days
- ☐ 4 Once a day
- ☐ 5 More than once a day

2 GIBX79 At its worst, how would you rate your belly pain?

- ☐ 1 Not bad at all
- ☐ 2 A little bad
- ☐ 3 Somewhat bad
- ☐ 4 Quite bad
- ☐ 5 Very bad

In the past 7 days…

3 GIBXS90 How much did belly pain interfere with your day-to-day activities?

- ☐ 1 Not at all
- ☐ 2 A little bit
- ☐ 3 Somewhat
- ☐ 4 Quite a bit
- ☐ 5 Very much

4 GIBXS91 How much did belly pain bother you?

- ☐ 1 Not at all
- ☐ 2 A little bit
- ☐ 3 Somewhat
- ☐ 4 Quite a bit
- ☐ 5 Very much

5 GIBXS92 How often did you have discomfort in your belly?

- ☐ 1 Never
- ☐ 2 Rarely
- ☐ 3 Sometimes
- ☐ 4 Often
- ☐ 5 Always

Last Updated: 1 September 2016

APPENDIX D: Clavien-Dindo classification of surgical complications
Per Dindo et al, 2004 [24]

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

TABLE 2. Clinical Examples of Complication Grades

Grades	Organ System	Examples
Grade I	Cardiac	Atrial fibrillation converting after correction of K^+-level
	Respiratory	Atelectasis requiring physiotherapy
	Neurological	Transient confusion not requiring therapy
	Gastrointestinal	Noninfectious diarrhea
	Renal	Transient elevation of serum creatinine
	Other	Wound infection treated by opening of the wound at the bedside
Grade II	Cardiac	Tachyarrhythmia requiring β-receptor antagonists for heart rate control
	Respiratory	Pneumonia treated with antibiotics on the ward
	Neurological	TIA requiring treatment with anticoagulants
	Gastrointestinal	Infectious diarrhea requiring antibiotics
	Renal	Urinary tract infection requiring antibiotics
	Other	Same as for I but followed by treatment with antibiotics because of additional phlegmonous infection
Grade IIIa	Cardiac	Bradyarrhythmia requiring pacemaker implantation in local anesthesia
	Neurological	See grade IV
	Gastrointestinal	Biloma after liver resection requiring percutaneous drainage
	Renal	Stenosis of the ureter after kidney transplantation treated by stenting
	Other	Closure of dehiscent noninfected wound in the OR under local anesthesia
Grade IIIb	Cardiac	Cardiac temponade after thoracic surgery requiring fenestration
	Respiratory	Bronchopleural fistulas after thoracic surgery requiring surgical closure
	Neurological	See grade IV
	Gastrointestinal	Anastomotic leakage after descendorectostomy requiring relaparotomy
	Renal	Stenosis of the ureter after kidney transplantation treated by surgery
	Other	Wound infection leading to eventration of small bowel
Grade IVa	Cardiac	Heart failure leading to low-output syndrome
	Respiratory	Lung failure requiring intubation
	Neurological	Ischemic stroke/brain hemorrhage
	Gastrointestinal	Necrotizing pancreatitis
	Renal	Renal insufficiency requiring dialysis
Grade IVb	Cardiac	Same as for IVa but in combination with renal failure
	Respiratory	Same as for IVa but in combination with renal failure
	Gastrointestinal	Same as for IVa but in combination with hemodynamic instability
	Neurological	Ischemic stroke/brain hemorrhage with respiratory failure
	Renal	Same as for IVa but in combination with hemodynamic instability
Suffix "d"	Cardiac	Cardiac insufficiency after myocardial infarction (IVa–d)
	Respiratory	Dyspnea after pneumonectomy for severe bleeding after chest tube placement (IIIb–d)
	Gastrointestinal	Residual fecal incontinence after abscess following descendorectostomy with surgical evacuation. (IIIb–d)
	Neurological	Stroke with sensorimotor hemisyndrome (IVa–d)
	Renal	Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb–d)
	Other	Hoarseness after thyroid surgery (I–d)

TIA, transient ischemic attack; OR, operating room.

APPENDIX E: Medications with known risk of Torsades de Pointes (TdP)

Medications that prolong QTc should be used with caution. Participants may not take more than one medication with a known risk of TdP during and up to 3 weeks after the last dose of eribulin. Premedication with ondansetron 4 mg IV prior to each eribulin dose is allowed.

Refer to www.crediblemeds.org for the most up to date listing of medications with known risk of TdP. The following pages are up to date as of March 31, 2021. Medications with known risk of TdP are noted with "**KR**."

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR). The full description of these categories can be found on the CredibleMeds.org website.

Generic Name	Brand Name
Abiraterone (CR)	Zytiga and others
Alfuzosin (PR)	Uroxatral
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Barhemsys and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others
Amphotericin B (CR)	Fungilin and others
Anagrelide (KR)	Agrylin and others
Apomorphine (PR)	Apokyn and others
Aripiprazole (PR)	Abilify and others
Arsenic trioxide (KR)	Trisenox
Artenimol/piperaquine (PR)	Eurartesim
Asenapine (PR)	Saphris and others
Astemizole (KR)	Hismanal
Atazanavir (CR)	Reyataz and others
Atomoxetine (PR)	Strattera
Azithromycin (KR)	Zithromax and others
Bedaquiline (PR)	Sirturo
Bendamustine (PR)	Treanda and others
Bendroflumethiazide (Bendrofluazide) (CR)	Aprinox and others
Benperidol (PR)	Anquil and others
Bepridil (KR)	Vascor

Generic Name	Brand Name
Betrixaban (PR)	Bevyxxa
Bortezomib (PR)	Velcade and others
Bosutinib (PR)	Bosulif
Buprenorphine (PR)	Butrans and others
Cabozantinib (PR)	Cometriq
Capecitabine (PR)	Xeloda
Ceritinib (PR)	Zykadia
Chloral hydrate (CR)	Aquachloral and others
Chloroquine (KR)	Aralen
Chlorpromazine (KR)	Thorazine and others
Chlorprothixene (KR)	Truxal
Cilostazol (KR)	Pletal
Ciprofloxacin (KR)	Cipro and others
Cisapride (KR)	Propulsid
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others
Clofazimine (PR)	Lamprene
Clomipramine (CR)	Anafranil
Clozapine (PR)	Clozaril and others
Cobimetinib (PR)	Cotellic
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori

Generic Name	Brand Name
Cyamemazine (Cyamepromazine) (PR)	Tercian
Dabrafenib (PR)	Tafinlar
Dasatinib (PR)	Sprycel
Degarelix (PR)	Firmagon and others
Delamanid (PR)	Deltyba
Desipramine (PR)	Pertofrane and others
Deutetrabenazine (PR)	Austedo
Dexmedetomidine (PR)	Precedex and others
Diphenhydramine (CR)	Benadryl and others
Disopyramide (KR)	Norpace
Dofetilide (KR)	Tikosyn
Dolasetron (PR)	Anzemet
Domperidone (KR)	Motilium and others
Donepezil (KR)	Aricept
Doxepin (CR)	Sinequan and others
Dronedarone (KR)	Multaq
Droperidol (KR)	Inapsine and others
Efavirenz (PR)	Sustiva
Eliglustat (PR)	Cerdelga
Epirubicin (PR)	Ellence and others
Eribulin mesylate (PR)	Halaven
Erythromycin (KR)	E.E.S. and others

Generic Name	Brand Name
Escitalopram (KR)	Cipralex and others
Esomeprazole (CR)	Nexium and others
Ezogabine (Retigabine) (PR)	Potiga and others
Famotidine (CR)	Pepcid and others
Felbamate (PR)	Felbatol
Fingolimod (PR)	Gilenya
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluorouracil (5-FU) (PR)	Adrucil and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Furosemide (frusemide) (CR)	Lasix and others
Galantamine (CR)	Reminyl and others
Garenoxacin (CR)	Geninax
Gatifloxacin (KR)	Tequin
Gemifloxacin (PR)	Factive
Granisetron (PR)	Kytril and others
Grepafloxacin (KR)	Raxar
Halofantrine (KR)	Halfan
Haloperidol (KR)	Haldol and others
Hydrochlorothiazide (CR)	Apo-Hydro and others
Hydrocodone - ER (PR)	Hysingla™ ER and others
Hydroxychloroquine (KR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others

Generic Name	Brand Name
Imipramine (Melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lansoprazole (CR)	Prevacid and others
Lapatinib (PR)	Tykerb and others
Lenvatinib (PR)	Lenvima
Leuprolide (Leuprorelin) (PR)	Lupron and others
Levetiracetam (PR)	Keppra
Levofloxacin (KR)	Levaquin and others
Levomepromazine (Methotrimeprazine) (KR)	Nosinan and others
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Lesuride and others
Lithium (PR)	Eskalith and others
Lofexidine (PR)	Lucemyra
Loperamide (CR)	Imodium
Lopinavir/Ritonavir (PR)	Kaletra and others
Lurasidone (PR)	Latuda
Maprotiline (PR)	Ludiomil
Melperone (PR)	Bunil and others
Memantine (PR)	Namenda XR
Mesoridazine (KR)	Serentil
Methadone (KR)	Dolophine and others
Metoclopramide (CR)	Reglan and others

Generic Name	Brand Name
Metolazone (CR)	Zytanix and others
Metronidazole (CR)	Flagyl and others
Mianserin (PR)	Tolvon
Midostaurin (PR)	Rydapt
Mifepristone (PR)	Korlym and others
Mirabegron (PR)	Myrbetriq
Mirtazapine (PR)	Remeron
Moexipril/Hydrochlorothiazide (PR)	Uniretic and others
Moxifloxacin (KR)	Avelox and others
Necitumumab (PR)	Portrazza
Nelfinavir (CR)	Viracept
Nicardipine (PR)	Cardene
Nilotinib (PR)	Tasigna
Norfloxacin (PR)	Noroxin and others
Nortriptyline (PR)	Pamelor and others
Nusinersen (PR)	Spinraza
Ofloxacin (PR)	Floxin
Olanzapine (CR)	Zyprexa and others
Omeprazole (CR)	Losec and others
Ondansetron (KR)	Zofran and others
Osimertinib (PR)	Tagrisso
Oxaliplatin (KR)	Eloxatin
Oxytocin (PR)	Pitocin and others
Paliperidone (PR)	Invega and others
Palonosetron (PR)	Aloxi
Panobinostat (PR)	Farydak
Pantoprazole (CR)	Protonix and others
Papaverine HCl (Intra-coronary) (KR)	

Generic Name	Brand Name
Paroxetine (CR)	Paxil and others
Pasireotide (PR)	Signifor
Pazopanib (PR)	Votrient
Pentamidine (KR)	Pentam
Perflutren lipid microspheres (PR)	Definity and others
Perphenazine (PR)	Trilafon and others
Pilsicainide (PR)	Sunrythm
Pimavanserin (PR)	Nuplazid
Pimozide (KR)	Orap
Pipamperone (PR)	Dipiperon and others
Piperacillin/Tazobactam (CR)	Tazosyn and others
Posaconazole (CR)	Noxafil and others
Primaquine phosphate (PR)	
Probucol (KR)	Lorelco
Procainamide (KR)	Pronestyl and others
Promethazine (PR)	Phenergan
Propafenone (CR)	Rythmol SR and others
Propofol (KR)	Diprivan and others
Prothipendyl (PR)	Dominal and others
Quetiapine (CR)	Seroquel
Quinidine (KR)	Quinaglute and others
Quinine sulfate (CR)	Qualaquin and others
Ranolazine (CR)	Ranexa and others

Generic Name	Brand Name
Ribociclib (PR)	Kisqali
Rilpivirine (PR)	Edurant and others
Risperidone (CR)	Risperdal
Romidepsin (PR)	Istodax
Roxithromycin (KR)	Rulide and others
Saquinavir (PR)	Invirase(combo)
Sertindole (KR)	Serdolect and others
Sertraline (CR)	Zoloft and others
Sevoflurane (KR)	Ultane and others
Solifenacin (CR)	Vesicare
Sorafenib (PR)	Nexavar
Sotalol (KR)	Betapace and others
Sparfloxacin (KR)	Zagam
Sulpiride (KR)	Dogmatil and others
Sultopride (KR)	Barnetil and others
Sunitinib (PR)	Sutent
Tacrolimus (PR)	Prograf and others
Tamoxifen (PR)	Nolvadex and others
Telaprevir (CR)	Incivo and others
Telavancin (PR)	Vibativ
Telithromycin (PR)	Ketek
Terfenadine (KR)	Seldane
Terlipressin (KR)	Teripress and others

Generic Name	Brand Name
Terodiline (KR)	Micturin and others
Tetrabenazine (PR)	Nitoman and others
Thioridazine (KR)	Mellaril and others
Tiapride (PR)	Tiapridal and others
Tipiracil/Trifluridine (PR)	Lonsurf
Tizanidine (PR)	Zanaflex and others
Tolterodine (PR)	Detrol and others
Toremifene (PR)	Fareston
Torsemide (Torasemide) (CR)	Demadex and others
Tramadol (PR)	Crispin and others
Trazodone (CR)	Desyrel and others
Trimipramine (PR)	Surmontil and others
Tropisetron (PR)	Navoban and others
Valbenazine (PR)	Ingrezza
Vandetanib (KR)	Caprelsa
Vardenafil (PR)	Levitra
Vemurafenib (PR)	Zelboraf
Venlafaxine (PR)	Effexor and others
Voriconazole (CR)	VFend
Vorinostat (PR)	Zolinza
Ziprasidone (CR)	Geodon and others
Zotepine (PR)	Losizopilon and others
Zuclopenthixol (Zuclopentixol) (PR)	Cisordinol and others

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. Because, the list changes regularly, we recommend always checking the website at crediblemeds.org for the most up-to-date information. Most drugs have multiple brand names and it is not practical to list them on this form. The CredibleMeds.org website provides a partial list of the more common brands.

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