COMIRB #15-0659

TITLE: A Phase I/Ib Study of Eribulin in Combination with Oral Irinotecan for Adolescent and Young Adult Patients with Relapsed or Refractory Solid Tumors

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Commercially Available Agents:
Eribulin (Halaven®, Eisai Inc., Woodcliff Lake, NJ)
Irinotecan (Camptosar®, Pfizer, New York City, NY)

IND Sponsor: Exempt from IND requirement

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SUMMARY

This Phase I trial will establish the recommended phase II dose of eribulin in combination with fixed doses of oral irinotecan in adolescents and young adults with relapsed or refractory solid tumors. Eribulin will be administered intravenously on days 1 and 8 of a 21-day cycle, while irinotecan will be administered orally on days 1-5. The oral antibiotic cefixime will be used to reduce irinotecan-associated diarrhea, starting two days prior to each cycle and continuing through day 8. Patients will be assigned an eribulin dose level at the time of enrollment using a 3 + 3 Phase I design, and there will be no intrapatient dose escalation. Once the RP2D is defined, there will be 10 patients enrolled in a dose expansion cohort.

Treatment Schema

Day	Cefixime	Eribulin	Oral Irinotecan
-1	X		
0	X		
1	X	X	X
2	X	--	X
3	X	--	X
4	X	--	X
5	X	--	X
6	X	--	--
7	X	--	--
8	X	X	--
9-19	--	--	--
20	X	--	--
21	X	--	--
NEXT CYCLE			

Dose Escalation Schedule		
Dose Level	**Dose**	
	Oral Irinotecan (mg/m^2/day x 5)	**Eribulin (mg/m^2/dose)**
Level 0	90	0.8
STARTING DOSE: Level 1	**90**	**1.1**
Level 2	90	1.4

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To estimate the recommended phase II dose (RP2D) of eribulin in combination with fixed-dose oral irinotecan in adolescents and young adults with relapsed/refractory solid tumors

1.2 Secondary Objectives

1.2.1 To evaluate the toxicity profile of this combination and define the dose-limiting toxicities
1.2.2 To characterize the pharmacokinetics of eribulin in patients receiving oral irinotecan
1.2.3 To determine the antitumor activity of this drug combination within the confines of a Phase I/Ib trial

2. BACKGROUND

2.1 Introduction

New therapies are desperately needed for adolescents and young adults with metastatic or recurrent solid tumors. For example, less than one-fourth of patients with osteosarcoma, Ewing sarcoma, or rhabdomyosarcoma whose tumor recurs after initial frontline therapy are expected to have long-term survival. Outcomes are also poor for patients who have metastatic disease identified at the time of initial diagnosis. These tumor types are commonly seen not only in teenagers but also in young adults, and new therapeutic strategies will be necessary to improve their outcomes. Particularly attractive approaches include those in which robust preclinical activity has been seen in relevant *in vivo* models, and for which combination with other active agents is rational. With these ideas in mind, we will perform the first study assessing the combination of eribulin and irinotecan. Eribulin is a novel microtubule inhibitor with dramatic preclinical activity against pediatric sarcoma xenograft models, while irinotecan is a camptothecin commonly used in the treatment of a wide variety of solid tumors. Irinotecan has been successfully combined with microtubule inhibitors to treat pediatric sarcoma patients, and the two drugs have distinct and generally non-overlapping toxicity profiles. This study will provide necessary information for the design of a Phase II trial to better estimate the activity of this combination in specific tumor types.

2.2 Eribulin

Eribulin (Halaven; Eisai Inc.) is a synthetic analogue of halichondrin B, a potent compound found in the marine sponge, *Halichondria okadai*. Eribulin is a microtubule inhibitor which inhibits polymerization of tubulin subunits and prevents microtubule growth. This mechanism of action is distinct both from taxanes and epothilones, which disrupts microtubule dynamics by stabilizing microtubules [1] as well as vincristine, which shortens microtubules [2]. This

dysregulation of microtubule dynamics caused by eribulin results in globular aggregates of unstable tubulin polymers, creating a G2-M blockade [3] that leads to apoptosis of treated cells [2, 4, 5].

Preclinical activity: Studies using both adult and pediatric cell lines have demonstrated that eribulin has activity against a wide variety of cancers at subnanomolar levels [4, 6]. Additionally, growth of taxane-resistant human tumor cell lines harboring known β-tubulin mutations was also inhibited by eribulin [7], presumably due to its unique mechanism and unique binding site. Eribulin has broad *in vivo* activity as demonstrated by its effects in xenografts models of adult breast, colon, melanoma and ovarian cancers [4]. In particular, compelling *in vivo* activity was seen in mouse xenograft experiments conducted by the Pediatric Preclinical Testing Program (PPTP), a NCI funded system used by CTEP to comprehensively and systematically evaluate new agents for pediatric cancer with the purpose of deciding which drugs move forward in NCI-sponsored national clinical trials. For example, treatment with single-agent eribulin resulted in complete responses of established xenografts in four different tumor types, including some responses which were maintained throughout the entire 12-week observation period. Particularly encouraging findings include the fact that systemic drug exposures in these experiments were similar to those seen in in patients receiving the recommended Phase II dose of eribulin, and that in many models, eribulin was more active than vincristine, which is used for a broad variety of pediatric cancers [6].

Clinical Activity: In addition to the robust preclinical data describing eribulin's activity against a wide variety of tumor cell lines and xenografts, there has also been extensive clinical evaluation of this drug, with 21 trials actively recruiting patients with a wide variety of cancers as of September 2013 (clinicaltrials.gov). Results have been published from thirteen phase II or phase III clinical trials evaluating eribulin in patients with a wide variety of cancers [8-18]. In these studies, eribulin was considered by the investigators to be active in non-small cell lung cancer [13], breast [8, 10, 11, 18], leiomyosarcoma [16], adipocytic sarcoma [16], ovarian [14] and prostate cancers [12].

The greatest clinical benefit of eribulin to date has been in the treatment of metastatic breast cancer, leading to eribulin being approved by the US Food and Drug Administration (FDA) in 2010 for the treatment of late stage metastatic breast cancer in patients who have received two or more prior therapies including an anthracycline and a taxane [19]. FDA approval was based on the encouraging results of a Phase III (EMBRACE) trial comparing eribulin monotherapy versus physician's choice [10].

Pharmacokinetic Data: Eribulin demonstrates linear kinetics, with a rapid distribution phase and slow elimination phase, resulting in a prolonged plasma half-life of 34 -73 hours in phase I studies of patients with solid tumors [20, 21]. The primary route of elimination of eribulin is in feces (82%), with only a small fraction eliminated in the urine (9%). Importantly, approximately 90% of eribulin is excreted unaltered [22], and so does not undergo significant metabolism. In fact, the *in vivo* metabolism of eribulin is quite minimal, with metabolites accounting for <0.6% of unchanged eribulin in the plasma [22].

Since only a small percentage of the drug is metabolized, the potential for drug-drug interactions with eribulin is negligible. No clinically significant change in exposure, measured by $AUC_{0-\infty}$ and C_{max}, of eribulin when given in combination with ketoconazole, a CYP3A4 and P-gp inhibitor [23]. Additionally, the exposure of eribulin was not clinically significantly altered when given in combination with rifampin, an inducer of CPY3A4 [24].

Toxicity: In the Phase III EMBRACE trial, the most common grade 3 and 4 toxicities that occurred more frequently in the eribulin treatment when compared with the Treatment of Physician's Choice (TPC) arm were neutropenia, leukopenia and peripheral neuropathy. Neutropenia occurred in 52% of patients, with 24% experiencing grade 4. Neutropenia was easily managed with dose-reductions, delays or granulocyte colony stimulating factor, and resulted in low incidence of febrile neutropenia (5%). The incidence of grade 3 or 4 peripheral neuropathy was <9% similar to patients treated with taxanes on the TPC arm (5%) [10]. In several other phase I and II trials in patients with advanced solid tumors, prostate cancer, squamous cell carcinoma of the head and neck, and breast cancer, the only grade 3 or 4 toxicities reported with an incidence of greater than 10% were leucopenia, lymphopenia and neutropenia [8, 9, 12, 20].

Importantly, the toxicity profile of eribulin is distinct from protracted administration of irinotecan, in which the most common toxicities are diarrhea, abdominal pain, weight loss and electrolyte disturbances. Less than 10% of patients treated with eribulin in the EMBRACE trial developed either abdominal pain or hypokalemia of any grade, and no other electrolyte abnormalities were reported. While 18% of patients treated with eribulin developed diarrhea, this percentage was equal to those patients on the control arm, and so may relate more to the specific patient population. Of note, no patient receiving eribulin on the EMBRACE trial developed grade 3 or higher diarrhea. Mild to moderate weight loss was slightly more common in the eribulin-treated arm, occurring in 21% of the patients treated with eribulin while on 14% of patients in the control arm were noted to have decreased weight. Only 1% of patients treated with eribulin developed grade 3 or higher weight loss [10].

2.3 Irinotecan

Irinotecan is a camptothecin agent which is metabolized into SN-38, a topoisomerase I inhibitor. SN-38 functions by stabilizing the DNA-topoisomerase I complex during DNA replication, resulting in DNA damage in the form of single strand breaks and leading to arrest of the cell cycle and cellular death [25].

Preclinical activity: Several preclinical studies have confirmed the activity of irinotecan in a variety of pediatric tumors including xenografts models of neuroblastoma [26, 27], rhabdomyosarcoma [28], Ewing's sarcoma [26], and CNS tumors [29, 30].

Clinical Activity: Irinotecan has been extensively studied in adults both alone in combination with various agents, and is FDA approved for the treatment of metastatic carcinoma of the colon or rectum. In children, irinotecan has demonstrated activity in wide variety of solid tumors including Ewing sarcoma [31, 32], rhabdomyosarcoma [33-35], hepatoblastoma [36-38] and neuroblastoma [39, 40]. Although single-agent activity of irinotecan has been modest [41], the

lack of significant myelosuppression when given on a protracted schedule makes it an attractive partner for combination studies. Currently, irinotecan is being studied by the Children's Oncology Group (COG) in Phase II or III trials in combination with either vincristine or temozolomide in six different tumor types. Importantly, the combination of vincristine and protracted irinotecan will be part of the standard treatment arm in the next national COG Phase III trial for patients with newly-diagnosed rhabdomyosarcoma.

Rationale for oral administration of irinotecan: When irinotecan is used to treat adults with colorectal cancer, the drug is typically administered once every 1-3 weeks in single large doses. However, the greatest activity in pediatric tumor types has been observed with more protracted scheduling in which smaller dosages are given daily for 5 consecutive days for either one or two weeks [42]. This protracted dosing schedule allows for greater exposure of this S-phase-specific agent over a three-week cycle, and also changes the toxicity profile. For example, while neutropenia and thrombocytopenia may be dose-limiting when irinotecan is given on the adult schedule, protracted administration of irinotecan results in only modest myelosuppression, with grade 4 neutropenia occurring in only 6% of treatment cycles on a large national Phase II trial, and grade 3-4 thrombocytopenia occurring in only 2% [41]. However, protracted administration does increase the likelihood of diarrhea, which is the dose-limiting toxicity when irinotecan is given in a protracted fashion [42].

Although protracted intravenous administration appears to be more efficacious against pediatric tumors compared to less frequent dosing, it is more costly and inconvenient. To circumvent these issues, several investigators have studied the administration of irinotecan given orally on a protracted schedule in both children and adults [40, 43-45]. Oral administration of irinotecan provides a convenient and cost-effective method for the protracted administration schedules which have shown greatest activity against pediatric tumors [46]. Due to irinotecan poor oral bioavailability, higher doses are required to reach similar levels of systemic exposure compared with intravenous administration. Combining oral irinotecan with prophylactic cephalosporins as described below has allowed for escalation of the MTD by 50% to 90 mg/m^2/dose x 5 days [44, 47] translating into similar levels of the active metabolite SN-38 when compared with intravenous administration. The tolerability, cost savings and convenience of administration make oral irinotecan an appropriate and attractive agent for use in the relapsed and refractory setting.

Pharmacokinetic data: Irinotecan is converted into its active metabolite SN-38 in the liver by carboxylesterase enzymes [48]. SN-38 is subsequently converted to SN-38 glucuronide by uridine diphosphate glucuronosyltranferases (UDG). Although the majority of irinotecan is metabolized into SN-38 under normal circumstances, a small minority is converted into two minor metabolites by cytochrome P450 isoenzyme CYP3A4. Predictably, inducers of the CYP3A4 isoenzyme have been shown to lead to increased clearance of irinotecan and reduced levels of SN-38 [49, 50]. Use of CYP3A4 inducers should be avoided due to concerns for decreased efficacy of irinotecan.

Toxicity data: The dose limiting toxicities of irinotecan administered intravenously on adult schedules of once every 1-3 weeks are myelosuppression and diarrhea. When irinotecan is administered on a protracted schedule as done in pediatrics, myelosuppression is substantially

reduced while diarrhea remains the dose-limiting toxicity [51-53]. The addition of cephalosporin prophylaxis to various treatment regimens of irinotecan has increased the tolerability of protracted irinotecan by significantly decreasing the incidence of diarrhea, allowing for the escalation of the maximum tolerated dose (MTD) [44, 45, 54]. The active metabolite SN-38 is thought to act locally in the gastrointestinal tract, directly injuring the intestinal mucosa and leading to a secretory diarrhea [55]. Cephalosporins ameliorate irinotecan-associate diarrhea by limiting conversion of the inactive glucuronidated SN-38 to active SN-38 by glucuronidase producing enteric bacteria. Pediatric regimens using cephalosporins have shown significant reduction in severe diarrhea when antibiotics are started a few days prior to irinotecan, and continued for three days past the fifth chemotherapy day. [44, 45, 54]

2.4 Rationale for Combining Eribulin and Irinotecan

While the planned testing of eribulin as a single agent in the pediatric population is necessary, nearly all pediatric cancers are treated with drug combinations, and searching for a suitable therapeutic partner for eribulin is the next logical step in development of this drug. We propose testing the combination of eribulin and oral irinotecan in a phase I trial designed to determine the recommended phase II dose of eribulin when combined with a previously established, well-tolerated regimen of oral irinotecan in adolescent and young adult cancer patients 13-30 years old. This age range was chosen because the likely clinical application for this drug pair will be in the treatment of pediatric-type sarcomas (e.g., Ewing sarcoma, osteosarcoma), which more often occur in adolescents and young adults. Further, the age and size of these patients will preclude the need for additional dose-finding studies for eribulin, as would be necessary if small children were included.

In adults, combination trials using eribulin with agents like carboplatin and cyclophosphamide are underway in non-small cell lung cancer, ovarian carcinoma, and breast cancer. These drug partners all are myelosuppressive. A more attractive partner may be one with non-overlapping dose-limiting toxicities like irinotecan. When given on a protracted 5-day schedule, irinotecan does not cause severe myelosuppression, making it attractive for combination with eribulin. Oral administration of irinotecan used alone and in combination therapy has been extensively tested in pediatrics in 5 clinical trials involving 158 patients, and provides a convenient and cost-effective method for the protracted administration schedules which have shown greatest activity against pediatric tumors. Importantly, the dose-limiting toxicity of protracted irinotecan is diarrhea, with only minimal myelosuppression. In addition, the combination of microtubule inhibitors and camptothecins is supra-additive, and is routinely used in COG studies which administer vincristine with 5-day cycles of irinotecan. Thus, this combination is attractive for study because of the potential for therapeutic synergy and the likelihood that both agents may be able to be administered at full dosage.

2.5 Correlative Studies Background

The pharmacokinetics of eribulin and irinotecan are well characterized. Our objective in this study is to collect pharmacokinetic data to understand exposure-toxicity and potentially exposure-efficacy relationships that can manifest in these patients. Notably, the pharmacokinetics of eribulin has not been determined in younger patients and may potentially be

different than in adults. Such differences have been observed with other anticancer drugs including topotecan, which is metabolized minimally and irinotecan, which is extensively metabolized [40, 56-61]. Comparatively, pediatric patients had similar irinotecan pharmacokinetics as adults but greater interpatient variability, which could be attributed to age. Such clearance differences would lead to higher exposure in pediatric populations and thus an overall lower dosage required for treatment. As the proposed population is likely to include patients with potentially high and low clearance characteristics, it is important to obtain pharmacokinetic evidence that may potentially provide evidence for differential dosing requirements based on age.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must ≥13 and ≤30 years of age at the time of study entry.

3.1.2 Patients must have a histologically confirmed solid tumor malignancy at either original diagnosis or relapse for which no curative therapy exists, and which has either recurred or progressed after at least one prior systemic therapy. Patients with primary brain tumors, or those with brain metastases at time of potential enrollment, are excluded. Additionally, patients with GIST, alveolar soft part sarcoma, or dematofibrosarcoma protuberans are excluded.

3.1.3 Patients must have either measurable or evaluable disease, as defined in Section 11.1.2.

3.1.4 Performance Level: ECOG performance status ≤ 2 (Karnofsky ≥60%, see Appendix A).
Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purposes of assessing the performance score.

3.1.5 Prior Therapy: No limit is placed on the number of prior therapies. Prior treatment with irinotecan or eribulin is allowed, although patients must not have received co-administration of eribulin and irinotecan and must not have had disease progression while receiving either eribulin or irinotecan.
Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within three weeks of start date of this protocol chemotherapy; six weeks is required after administration of nitrosourea agents.
b. Hematopoietic growth factors: At least 7 days since the completion of therapy with a growth factor or at least 14 days for a long-acting growth factor (e.g. pegfilgrastim)
c. Biologic (anti-neoplastic agent): At least 7 days or 3 half-lives since the completion of therapy with a biologic agent, whichever is longer. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are expected to occur. The duration of this interval must be discussed with the PI of the study.
d. Immunotherapy: At least 6 weeks since the completion of any type of immunotherapy (e.g. tumor vaccines).

e. Monoclonal antibodies: At least 3 half-lives must have elapsed since prior therapy that included a monoclonal antibody.
f. Radiotherapy: ≥ 2 weeks for local palliative XRT (small port); ≥ 6 months must have elapsed if prior TBI, craniospinal XRT; ≥ 3 months must have elapsed if ≥ 50% radiation of pelvis; ≥ 6 weeks must have elapsed if therapeutic doses of MIBG or other substantial BM irradiation was given.
g. Stem Cell Transplant or Rescue without TBI: Allogeneic and autologous HSCT will be allowed, if there is no evidence of active graft vs. host disease and ≥ 2 months must have elapsed since infusion. Patients must not be on systemic immunosuppression.

3.1.6 Organ Function Requirements: Patients must have normal organ and marrow function as defined below.

– Absolute neutrophil count	≥ 1,000/mcL
– Platelets	≥ 100,000/mcL (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to enrollment)
– Hemoglobin	≥ 8.0 g/dl (may receive RBC transfusions).
– Total bilirubin	≤ 1.5 × institutional upper limit of normal for age
– AST(SGOT)/ALT(SGPT)	≤ 2.5 × institutional upper limit of normal
– Albumin	≥ 2 g/dl
– Creatinine	within normal institutional limits for age OR creatinine clearance ≥ 70 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
- EKG	QTc ≤ 480 msec (CTCAE Grade 2)

3.1.7 Contraception: Because chemotherapeutic agents may be teratogenic, males and females of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for 4 months after the last dose of study chemotherapy.

3.1.8 Informed Consent: All patients ≥ 18 years must sign a written informed consent. Patients < 18 years old must provide assent, and the parent or legal guardian must sign the written informed consent.

3.2 Exclusion Criteria

3.2.1 Pregnancy or Breast-Feeding: Patients who are pregnant or breast-feeding are not eligible for this study due to the potential for fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in female patients who are post-menarchal.

3.2.2 Major surgery within 14 days prior to start of treatment. No time limitations after minor surgery (eg: core biopsy or central line placement)

3.2.3 Current evidence of GIST, alveolar soft part sarcoma, or dermatofibrosarcoma
3.2.4 Concomitant Medications:
a. Growth factor(s): Growth factors that support platelet or white cell number or function must not have been administered within the 7 days prior to enrollment (14 days if pegfilgrastim).
b. Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for the 7 days prior to enrollment are not eligible.
c. Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
d. Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.
e. Enzyme-inducing anticonvulsants or other medications: Patients who are currently receiving the enzyme inducing anticonvulsants: phenytoin, phenobarbital, carbamazepine, oxcarbazepine are not eligible. Patients who are currently taking rifampin, voriconazole, itraconazole, ketoconazole, aprepitant, or St. John's Wort are not eligible. See Appendix B for more details
f. Anticoagulants: Use of warfarin is not allowed while on study. Patients already on warfarin should use alternative anticoagulants while on this study. Warfarin must not have been administered within 7 days of starting protocol therapy.
g. Medications that prolong the QTc: Patients receiving medications listed in Appendix C are not eligible.
3.2.5 Infection: Patients who have an uncontrolled infection, or who are currently receiving treatment for *C difficile* infection.
3.2.6 Patients with a history of allergic reactions attributed to eribulin or irinotecan.
3.2.7 Patients with documented allergy to cephalosporins.
3.2.8 Patients with CNS tumors or known brain metastases.
3.2.9 Patients with known metastatic tumor in the bone marrow.
3.2.10 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study.
3.2.11 Uncontrolled intercurrent illness that would limit compliance with study requirements.
3.2.12 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with eribulin and irinotecan. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.3 Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Enrollment Guidelines

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be pre-screened by the investigators, study personnel, or the Principal Investigator by conducting a brief medical chart review to determine key eligibility criteria.

Registration of all participants must occur before any study-related procedures. Staff will be available to register participants Monday thru Friday, from 8:00 AM to 5:00 PM Mountain Standard Time. In emergency situations, where a patient must be registered during holidays or off-hours, you may call the research coordinator at 303-358-2638. You may not register a participant if a slot has not been reserved.

Please follow these steps to register a participant:

1. Obtain written informed consent/assent prior to any study related procedures.
2. Complete the eligibility checklist. The local investigator must sign the checklist confirming that eligibility has been reviewed.
3. Send the signed eligibility checklist along with supporting source documents, including the consent/assent, to the research coordinator at Children's Hospital Colorado (CHCO). You may send all the documents via fax or email. Please fax to 720-777-7289 or email the CHCO coordinator listed in the front of the protocol.
4. An investigator at CHCO will review and confirm eligibility. The eligibility will be signed by the investigator and returned to the site. An email or registration confirmation will be sent to the overall study PI, local investigator and local study coordinator. Patients will receive eribulin at the assigned dose level throughout their treatment unless dose modifications occur as outlined in Section 6.0.
5. The participant will be assigned a participant number that includes the site number followed by the sequential order of participants enrolled local; site #_sequential number (e.g., 01_01, then 01_02 for site number 01)

4.2 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the the appropriate participating site and the University of Colorado. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee (DSMC) and the participating sites IRB of record of any significant adverse events that are serious and/or unexpected, as per standard operating procedure for those entities. In addition, the DSMC will review all adverse events at routine intervals as per standard operating procedures

5. TREATMENT PLAN

5.1 Enrollment and Screening Process

Any testing done specifically for research purposes related to this study should be performed only after written informed consent is obtained.

5.2 Agent Administration

Treatment may be administered either in the inpatient or outpatient setting. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

There will be no intra-patient dose escalations.

Dose Escalation Schedule		
Dose Level	**Dose**	
	Irinotecan (mg/m^2/day)	**Eribulin (mg/m^2/dose)**
Level 0	90	0.8
STARTING DOSE: Level 1	**90**	**1.1**
Level 2	90	1.4

Therapy Delivery Map – Cycle # ____	_____ Patient name	_____ DOB

DRUG	ROUTE	DOSAGE	DAYS	Observations
Eribulin	IV over 2-5 min	See dose escalation scheme	1, 8	a. History b. Physical Exam (Ht/Wt/VS/ performance status) c. CMP d. CBC e. Pharmacokinetics[1]
Irinotecan	PO	90 mg/m^2/dose	1-5 (On day 1, irinotecan is given at least 15 minutes after eribulin)	
Cefixime	PO	400 mg/day	-1 through 8	

Ht _____ Wt _____ BSA _____ Dose level = _____

Assigned Eribulin dose is ____ mg/m^2 = _____ mg

Date Due	Date Given	Day	Eribulin	Irinotecan	Cefixime	Studies
		-1 (20*)			_____mg	
		0 (21*)			_____mg	
		1	_____mg	_____mg	_____mg	a, b, c, d, e[1]
		2		_____mg	_____mg	
		3		_____mg	_____mg	
		4		_____mg	_____mg	e (optional)[2]
		5		_____mg	_____mg	
		6			_____mg	
		7			_____mg	
		8	_____mg		_____mg	b, c[3], d[4], e[1]
		15				c[3], d[4]
		20			_____mg	
		21			_____mg	

[1]Blood samples for pharmacokinetic testing will be obtained pre-dose, 0.25, 1, 1.5, 2, 4, and 5 hours after the administration of eribulin on day 1 and prior to day 8 dose with regularly obtained labs (see Appendix g for Pharmacokinetic Study Form). **These samples will only be collected in the first treatment cycle.**
[2] An optional single pharmacokinetic sample may be collected anytime between 24-96 hours if labs are being obtained at UK for other purposes.
[3]CMP must be drawn weekly during cycle 1, and then may be drawn only at the start of subsequent cycles
[4]CBC with differential should be drawn **twice weekly during the first cycle**, and then must be drawn at least weekly during subsequent cycles

On day 1 in which eribulin and oral irinotecan are administered concurrently, the eribulin should precede irinotecan by at least 15 minutes.

Subsequent cycles should start after day 21 as soon as the ANC ≥ 1,000/µL and platelets≥ 100,000/µL, and eligibility criteria are met for renal and hepatic function (Section 3.1). This start date could vary by 3 days.

5.2.1 Administration of Eribulin

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

5.2.2 Administration of Oral Irinotecan

For oral use, the appropriate volume of irinotecan solution (20 mg/ml) is drawn up undiluted into a plastic oral syringe. Each dose is to be mixed with juice (crangrape, cranapple, cranberry, or other "cran" juice) immediately before administration. The oral syringes containing undiluted irinotecan are stable for 21days when stored in a refrigerator. Irinotecan has a very unpleasant flavor, and so the juice will be used to mask the drug taste (Appendix D). See protocol for premedication and supportive care measures.

If emesis occurs within 20 minutes of taking a dose of irinotecan, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Instructions for administration of oral irinotecan are included in Appendix D and a copy of Appendix B, outlining potential drug interactions with irinotecan, should be given to the patient.

5.3 Supportive Care

5.3.1 Antiemetics

Premedication with a 5-HT_3 antagonist is recommended 30 minutes prior to daily irinotecan doses. Aprepitant and/or steroids should not be used as antiemetics on this study due to effects on CYP3A4 and potential interference with irinotecan metabolism.

5.3.2 Growth Factors

Patients should not receive growth factors, including GMCSF, GCSF, or pegylated GCSF unless indicated in the Dose Modification section, 6.1.

5.3.3 Concomitant Medications

Eribulin has been associated with prolonged QTc, so medications that prolong QTc should be avoided when possible. A list of medications that prolong QTc is provided in Appendix C.

5.3.4 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, and general supportive case are to be used as necessary.

5.3.5 Prophylaxis for Irinotecan-Associated Diarrhea

Cefixime or an available equivalent antibiotic will be used to reduce irinotecan-associated diarrhea as previously mentioned [44, 45]. Antibiotic treatment should start at least two days prior to the start of irinotecan. This antibiotic therapy should continue until 3 days after the last dose of irinotecan.

5.3.6 Concomitant Medications for Diarrhea and Abdominal Cramping

Patients and their families will be instructed to contact their physician if diarrhea occurs. Any patient who develops diarrhea or abdominal cramping within the first 4 hours after oral administration of irinotecan should receive atropine intravenously at a dose of 0.01 mg/kg (maximum 0.4 mg). This so-called "early onset diarrhea" is often presaged by cholinergic manifestations such as diaphoresis and abdominal cramping. Because patients are treated with irinotecan over multiple days, it may be difficult to distinguish immediate from delayed diarrhea. Patients with presumed immediate diarrhea who do not improve with atropine, or patients who develop diarrhea more than 4 hours after receiving irinotecan, should be given treatment with oral loperamide for late onset diarrhea as outlined below.

All patients will receive a copy of instructions for the use of loperamide if/when diarrhea occurs (Appendix D). Each family will be provided with this antidiarrheal medicine with instructions to start at the first episode of poorly formed or loose stools, or at the earliest onset of bowel movements more frequent than normally expected for the patient.

Loperamide (1 mg/5 ml or 1 caplet = 2 mg) dosing guidelines for diarrhea:
Weight ≥ 43 kg (≥ 95 pounds): Take 4 teaspoonfuls or 2 caplets after the first loose stool, followed by two teaspoonfuls or one caplet every two hours as needed.
Weight 20 kg to 43 kg (≤94 pounds): Take 2 teaspoonfuls or 1 caplet after the first loose stool, followed by one teaspoonful or one-half caplet every 2 hours as needed.

Because patients will be receiving prolonged exposure to antibiotics (i.e., cefixime), patients having significant diarrhea should have stool samples evaluated for *C difficile* toxin, as this is a potentially treatable cause of diarrhea. If patients have fever with diarrhea, or bloody diarrhea, evaluation of stools for bacterial culture should also be performed.

If there is failure of loperamide to control diarrhea after 24 hours of use, patients may receive octreotide (Sandostatin™) at the dose of 10 micrograms/kg/dose subcutaneously every 12 hours x 3 days.

5.4 Criteria for Starting Subsequent Cycles of Therapy

A cycle may be repeated if:

- The patient has no evidence of disease progression as assessed clinically and/or with imaging studies

- The patient meets eligibility criteria for hematopoietic, renal, and liver function (Section 3.1)
- The patient has not met any criteria for removal from protocol therapy as described in Section 5.9

Patients who experience dose-limiting toxicity but do not have evidence of progressive disease may be eligible for additional protocol therapy as described in Section 6.0.

5.5 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as any of the following events, detailed in Sections 5.5.2 and 5.5.3 that are possibly, probably or definitely attributable to protocol therapy. Decisions regarding the estimation of the recommended phase II dose and assigning treatment dosages to subsequent patients will be made on observations occurring in the first cycle of therapy.

5.5.1 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.02 (CTCAE) http://ctep.cancer.gov/reporting/ctc.html.

Any suspected or confirmed dose-limiting toxicity should be reported within 24 hours to the coordinating center and Principal Investigators at both centers.

5.5.2 Non-Hematological Dose-Limiting Toxicity

Non-hematological dose-limiting toxicity is defined as any Grade 3 or Grade 4 non-hematological toxicity that is possibly, probably or definitely attributable to the investigational drugs with the specific exclusion of:

- Grade 3 nausea, vomiting or dehydration
- Grade 3 diarrhea $\leq$ 3 days
- Grade 3 diarrhea regardless of duration if patient did not receive appropriate supportive care (cefixime, loperamide, or atropine as outlined in Section 5.3)
- Grade 3 transaminase (AST/ALT) elevation that returns to grade $\leq$ 1 or baseline prior to the time for the next treatment cycle
- Grade 3 GGT
- Grade 3 fatigue $\leq$ 3 days
- Grade 3 fever, febrile neutropenia, or infection
- Grade 3 electrolyte abnormalities (Na, K, Cl, CO2, Ca, Mg, Phosphate) that improve to $\leq$ grade 2 within 7 days, with or without supplements

Allergic reactions that necessitate discontinuation of the study drugs will **not** be considered a dose-limiting toxicity.

Patients who develop ≥ Grade 3 QTc prolongation (≥ 501 msec) at any time must be removed from protocol therapy.

5.5.3 Hematological Dose-Limiting Toxicity

Hematologic DLT will be defined as any of the following:

- Greater than 7 days duration of either grade 4 neutropenia or grade 4 thrombocytopenia of > 7 days duration
- Grade 3 or 4 thrombocytopenia that requires platelet transfusions on greater than 2 occasions during a cycle.
- Failure to recover blood counts to eligibility criteria that cause a delay of ≥ 14 days between treatment cycles.

5.6 Dose Escalating Criteria

A 3 + 3 design will be used to determine dose assignment for patients, as described in Section 13.2. Specifically, the following rules will apply for dose escalation:

A. Evaluate 3 patients at $dose_k$:
   1. If 0 of 3 patients have DLT, then
      i. If first cohort, increase dose to $dose_{k+1}$ and go to A.
      ii. Otherwise, go to B.
   2. If 1 of 3 patients has DLT, then go to B.
   3. If more than 1 patient has DLT
      i. If lowest dose, then go to C.
      ii. Otherwise, decrease dose to $dose_{k-1}$ and go to A.

B. Evaluate 3 additional patients at $dose_k$:
   1. If 0 or 1 of 6 patients has DLT, then increase dose to $dose_{k+1}$ and go to A.
   2. If 2 or more patients have DLT, then
      i. If lowest dose, then go to C.
      ii. Otherwise, decrease dose to $dose_{k-1}$ and go to A.

C. Discontinue dose escalation/de-escalation.

Accrual will continue until the recommended phase II dose for a Phase II study (RP2D) is established and at least 6 patients have been treated at this dose. The RP2D is the highest dose level at which no more than 1 of 6 patients experiences first-cycle DLT. Doses higher than dose level 2 will not be studied in this trial. Once the RP2D is identified, an additional 10 patients will be enrolled at this dose level.

5.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 17 cycles until one of the following criteria applies:

- Disease progression

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.8 Duration of Follow-Up

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. All patients will be followed for at least 30 days after removal from study or until death, whichever occurs first.

5.9 Criteria for Removal from Protocol Therapy

a. Clinical or radiographic progressive disease (See Section 11).
b. Adverse events requiring removal from study (See Sections 6.1 and 6.2).
c. Refusal of further protocol therapy by patient/parent/guardian.
d. Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e. Completion of 17 cycles of therapy.
f. Determination that it is not in the patient's best interest by the treating physician.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported. Follow-up data will be required unless consent is withdrawn.

5.10 Off-Study Criteria

Patients will be considered off-study if any of the following events occur:

a. Thirty days has expired after the last dose of protocol therapy.
b. Death
c. Lost to follow-up
d. Withdrawal of consent for any further data submission.
e. Entry onto another antineoplastic therapeutic study.
f. Onset of new treatment regimen

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose modifications will involve eribulin but not irinotecan, given that the study question is to identify the recommended phase II dose of eribulin that can be safely administered with fixed-dose irinotecan.

Doses which have been reduced for toxicity will not be re-escalated.

6.1 Dose Modifications for Hematological Toxicity

Patients who experience dose-limiting toxicity at dose levels 1 or 2 but do not have evidence of disease progression may continue to receive therapy modified as described below.

Patients who experience Grade 3 febrile neutropenia may receive additional cycles of therapy at the same eribulin dose with the optional use of filgrastim/pegfilgrastim support.

Patients who experience DLT at dose level 0 will not receive further therapy on study.

6.1.1 Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the same dose of irinotecan with eribulin reduced to the next lowest dose level.

6.1.2 Patients who have dose-limiting neutropenia (Grade 4 neutropenia of > 7 days duration or delay in the start of the next cycle for ≥ 14 days due to neutropenia) with no other dose-limiting toxicity should receive the same dose in the next cycle with filgrastim or pegfilgrastim support at standard doses. [Note: Patients MUST NOT receive prophylactic filgrastim or pegfilgrastim in the first cycle of therapy.] If dose-limiting neutropenia recurs after growth factor is added, then the eribulin dose should be decreased to the next lowest dose level and filgrastim/pegfilgrastim support used again.

6.1.3 Patients who experience Grade 4 febrile neutropenia may receive additional cycles of therapy at the same eribulin dose with the use of filgrastim/pegfilgrastim support.

6.2 Dose Modifications for Non-Hematological Toxicity

Patients who experience Grade 3 prolonged QTc (≥ 501 msec) will be removed from protocol therapy.

Patients who experience dose-limiting toxicity at dose levels 1 or 2 but do not have evidence of disease progression may continue to receive therapy modified as described below.

Patients who experience DLT at dose level 0 will not receive further therapy on study

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in section 5.5.2) that returns to eligibility criteria within 7 days after the planned start of the next treatment cycle may continue on study but should receive subsequent doses at the next lower dose level of eribulin. If non-hematologic Grade 3 or 4 toxicities other than those listed in Section 5.5.2 recur at a reduced dose, the patient must be removed from protocol therapy.

6.2.2 Patients who have any Grade 3 or 4 non-hematological toxicity that does not resolve to eligibility criteria by 7 days after the planned start of the next treatment cycle must be removed from protocol therapy.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Definitions

Adverse Event: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable or definite).

Serious Adverse Event: An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unanticipated Problems: Include adverse events which in the opinion of the principal investigator are both unexpected and probably or definitely related to the intervention / drug or device, any unforeseen development that potentially increases the likelihood of harm to participants or others in the future, information that indicates a change to the risks or potential benefits of the research or an actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, psychological events, drug errors).

Other Reportable Adverse Events: Include death unrelated to study treatment if occurring within 30 days of the last study treatment, death at least possibly related to study treatment at any time point, secondary malignancy, pregnancy, fetal death, and neonatal death.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.2) and the characteristics of an observed AE (Section 7.3) will determine whether the event requires expedited reporting (via Medwatch Forms) **in addition** to routine reporting.

7.2 Expected Toxicities

7.2.1 Adverse Events List for Eribulin

Onset	Common: >20% of patients	Occasional: <20% of patients	Rare: <10% of patients
Immediate: hours to days	Nausea, vomiting		anaphylaxis
Prompt: days to weeks	Anorexia, weight loss, constipation, fatigue, pain, myelosuppression, increased LFTs, neuropathy,	Diarrhea, headache, increased creatinine, cough, dyspnea	Vertigo, hypertension, QT prolongation, venous thromboembolism, hand-foot syndrome, rash, abdominal pain, mucositis, edema, pancreatitis, electrolyte abnormality, hyperglycemia, anxiety, depression, insomnia, dizziness, dysgeusia , pharyngolargyngeal pain, conjunctivitis,
Delayed: weeks to months	Alopecia		

7.2.2 Adverse Events List for Irinotecan

Onset	Common: >20% of patients	Occasional: <20% of patients	Rare: <5% of patients
Immediate: hours to days	Nausea, vomiting, anorexia, fever, asthenia, cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea)	Constipation, headache, diarrhea	Anaphylaxis, dehydration with dizziness and hypotension, bradycardia, dyspnea and cough, disorientation/confusion, somnolence, pain at infusion site
Prompt: days to weeks	Diarrhea, neutropenia, alopecia, eosinophilia, elevations in transaminases, alkaline phosphatase, bilirubin, mucositis, infection	Anemia, rash, dyspepsia, thrombocytopenia	Colitis, renal failure (secondary to severe dehydration), thromboembolic events, ileus
Delayed: weeks to months			Pneumonitis
Unknown frequency and timing	Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk.		

For a comprehensive list of adverse events please refer to the package insert.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** Adverse events that occur while the patient is on study will need to be recorded. Please see below for specific reporting requirements. Each investigative site will be responsible for maintaining an AE log that captures all AEs and SAEs. All Adverse Events will be recorded as "related" or "not related" in the AE log. Each site will also need to report all SAEs that occur at that institution to their respective IRB as per their IRB policy in addition to the protocol requirements. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - 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.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the study PI's and coordinating center (CHCO) any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the standardized SAE form.

Note: If subject is in Long Term Follow Up, death is reported at continuing review.

Note: Abnormal laboratory values are not considered medical events, unless determined to be causative of SAE by the investigator or grade 5.

7.4.2 The following table outlines the required forms and reporting structure for clinical trials.

Expedited reporting to DSMC	Expedited reporting to FDA	Non-expedited AE	Form	IRB
All SAEs (severity of adverse event is Grade 3, 4 or 5)	Suspected AE that is serious and unanticipated (not listed in IB or consent)	CRF and DSMC reporting only	Voluntary Medwatch 3500 for serious and unanticipated CRF for all AEs, including SAEs	Yes if it meets the IRB reporting requirements: If reportable event, please send copy of IRB report to CHCO

7.5 Routine Adverse Event Reporting

All Adverse Events (Grades 1-5) **must** be recorded on case report forms and reported to the overall PI in routine study data submissions. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.** All Adverse Events will be recorded as "related" or "not related" in the AE log. Depending on the grade of each AE, it will need to be reported to CHCO within 5 calendar days or 24 hours. Please refer to the table below for AE reporting time lines.

Attribution	When to report AEs to CHCO			
	Gr. 1 and 2 AE Expected and Unexpected	**Gr. 3 AE Expected and Unexpected**	**Gr. 4 AE Expected and Unexpected**	**Gr. 5 AE Expected and Unexpected**
Unrelated Unlikely	Record in AE Log	5 calendar days	5 calendar days	24 hours
Possible Probable Definite	Record in AE Log	5 calendar days	5 calendar days	24 hours

8. PHARMACEUTICAL INFORMATION

A list of the 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 **<u>Eribulin mesylate</u>** [11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-i]furo[2",3":5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one, 2-[(2S)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2R,3R,3aS,7R,8aS,9S,10aR,11S,12R,13aR,13bS,15S,18S,21S,24S,26R,28R,29aS)-, methanesulfonate (salt), Halavan™®]

8.1.1 <u>Dosage and Route of Delivery:</u> Since this a Phase I study, dosage will be defined by the dose escalation scheme. To administer the drug, it will be aseptically withdrawn from the single-use vial and administer undiluted or diluted in 0.9% Sodium Chloride Injection, USP intravenously over 2 to 5 minutes.

8.1.2 <u>Adjustment of Dosing:</u> This is defined in section 6.1 and 6.2 of the protocol

8.1.3 <u>Source and pharmacology:</u> Eribulin mesylate is a non-taxane microtubule dynamics inhibitor. Eribulin mesylate is a synthetic analogue of halichondrin B, a product isolated from the marine sponge Halichondria okadai.

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

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/m^2 to 114 L/m^2 and mean clearance of 1.16 L/hr/m^2 to 2.42 L/hr/m^2 over the dose range of 0.25 mg/m^2 to 4.0 mg/m^2. 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.

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 the dose in feces and urine, respectively.

8.1.4 Formulation & Stability: Eribulin mesylate injection, 1 mg/2 mL, in a single-use vial. One vial per carton. 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.

8.1.5 Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol. The FDA-approved dose of Eribulin as a single agent in adults is 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

8.1.6 Toxicity: In Phase 3 studies, the most common treatment-emergent adverse events noted are described. Over half of patients experienced neutropenia or leukopenia, and 20% had anemia. One third of patients complained of asthenia or fatigue. Nausea was observed in 22% and diarrhea in only 14%. Peripheral neuropathy was observed in 27%. One third of patients experienced alopecia. Of the almost 2000 patients exposed in completed clinical studies as of May 2013, 367 patients had related serious adverse events. The most frequent treatment-related SAEs were febrile neutropenia (3.3%), neutropenia (1.9%), and pyrexia (1.2%).

8.1.7 Supplier: Eribulin is commercially available by Eisai. See package insert or IB for more detailed information.

8.2 Irinotecan [CPT-11,Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348

8.2.1 Dosage and Route of delivery: Irinotecan will be given orally daily for days 1-5 of each 21 day cycle. The dose will be 90 mg/m^2/dose. On day 1 of each cycle, it

will be given at least 15 minutes after the eribulin. For oral use, the appropriate volume of irinotecan solution (20 mg/ml) is drawn up undiluted into a plastic oral syringe. Each dose is to be mixed with juice (crangrape, cranapple, cranberry, or other "cran" juice) immediately before administration. The oral syringes containing undiluted irinotecan are stable for 21days when stored in a refrigerator. Irinotecan has a very unpleasant flavor, and so the juice will be used to mask the drug taste (Appendix D). See protocol for premedication and supportive care measures.

If emesis occurs within 20 minutes of taking a dose of irinotecan, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Instructions for administration of oral irinotecan are included in Appendix D and a copy of Appendix B, outlining potential drug interactions with irinotecan, should be given to the patient.

8.2.2 Adjustment of Dosing: This is defined in section 6.1 and 6.2 of the protocol

8.2.3 Source and pharmacology: Irinotecan is a semisynthetic water-soluble analog of camptothecin (a plant alkaloid isolated from Camptotheca acuminata). Irinotecan is a prodrug that requires conversion, by the carboxylesterase enzyme to the topoisomerase-I inhibitor, SN-38 in order to exert anti-tumor activity. SN-38 is approximately 1000 times more potent than irinotecan. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Renal excretion is a minor route of elimination of irinotecan. The majority of the drug is metabolized in the liver. SN- 38 is conjugated to glucuronic acid and this metabolite has no anti-tumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) which presumably leads to mucosal injury. In addition, APC and NPC are oxidative metabolites of irinotecan dependent on the CYP3A4 isoenzyme. After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. Irinotecan is 30% to 68% bound to albumin and SN-38 is approximately 95% bound to albumin.

8.2.4 Formulation & Stability: Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium

hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40mg (2ml) and 100mg (5ml). Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

8.2.5 Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

For oral use, the appropriate volume of irinotecan solution (20 mg/ml) is drawn up undiluted into a plastic oral syringe. Each dose is to be mixed with juice (crangrape, cranapple, cranberry, or other "cran" juice) immediately before administration. The oral syringes containing undiluted irinotecan are stable for 21days when stored in a refrigerator. Irinotecan has a very unpleasant flavor, and so the juice will be used to mask the drug taste (Appendix D). See protocol for premedication and supportive care measures.

Cefixime or an available equivalent antibiotic will be used as diarrheal prophylaxis. Initiation of antibiotic treatment at least two days prior to the start of irinotecan is recommended. This antibiotic therapy should continue until 2 days after the last dose of irinotecan.

Premedication with a 5-HT_3 antagonist, like ondansetron is recommended 30 minutes prior to daily irinotecan doses. Aprepitant is an inducer, a moderate inhibitor, and substrate of CYP3A4 and should not be used as an anti-emetic.

If emesis occurs within 20 minutes of taking a dose of irinotecan, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Instructions for administration of oral irinotecan are included in Appendix C.

8.2.6 Supplier: Irinotecan is commercially available. See package insert for more detailed information.

8.3 Cefixime [Suprax®]

8.3.1 Source and pharmacology: Cefixime is a third generation cephalosporin antibiotic for oral administration that inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins and interfering with the final transpeptidation step of peptidoglycan synthesis. Its spectrum of activity is similar to other third generation agents, including Enterobacteriaceae, and β-lactamase producing H. influenzae and N. gonorreae, and Staph. aureus. It is excreted primarily by the kidney. It has a serum half-life of approximately 3-4 hours.

8.3.2 Formulation & Stability: Cefixime is available in scored 200 mg and 400 mg film coated tablets, and in a powder for oral suspension, which when reconstituted, provides 100mg/5ml. The powder for oral suspension is strawberry flavored and

contains sodium benzoate, sucrose, and xanthan gum.

8.3.3 Guidelines for Administration: Given orally at 400 mg daily.

8.3.4 Supplier: Commercially available.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

The plasma concentrations of eribulin as well as irinotecan, SN-38 and SN-38 glucuronide will be measured to assess drug disposition and pharmacokinetic parameters in each patient.

9.1.1 *Pharmacokinetics*

9.1.1.1 Collection of Specimen(s). Blood plasma samples for pharmacokinetics will be collected during cycle 1 on day 1 at pre-dose and at 15 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, and 5 hours after the start of the eribulin infusion and a pre-dose sample on day 8. These samples will be required for all patients. An optional sample between 24-96 hours may also be collected after the start of the eribulin infusion, from patients that are available for blood draw. Whole blood samples will be collected from the central line or a peripheral IV provided a flush of at least 10 ml of normal saline has been administered. At each time point, 7 ml of venous blood will be withdrawn into sodium heparinized collection tube. Please refer to Pharmacokinetic Study Form in Appendix G

9.1.1.2 Handling of Specimens(s). After collection, blood and anti-coagulant will be mixed by inverting the tube 8–10 times. Blood samples will be placed on ice immediately and centrifuged within 5 min at 7200 g at 4°C for 2 min. Plasma will be transferred into amber plastic tubes and stored on dry ice prior to transferring at −80°C until analysis. Plasma concentrations of free-base eribulin will be quantified using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method as previously described [62]. Irinotecan, SN-38 and SN-38 glucuronide concentrations will be quantified using a validated HPLC method with fluorescence detection as previously described [63, 64].

9.1.1.3 Shipping of Specimen(s). Samples will be collected by study personnel in Dr. Leggas' lab for storage, processing and analysis. Please see Appendix G for additional information.

9.1.1.4 Site(s) Performing Correlative Study. University of Kentucky and Children's Hospital Colorado

10. STUDY CALENDAR

Evaluations/Material and Data to be Collected
Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section

3.0) must be no older than seven (7) days at the start of chemotherapy. The start of chemotherapy is defined as the initiation of treatment with irinotecan and eribulin. The start of protocol therapy is defined as the initiation of cefixime. Laboratory tests need not be repeated if chemotherapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are >7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating chemotherapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient must be re-screened to receive protocol-prescribed chemotherapy.

Imaging studies must be obtained within 14 days prior to start of chemotherapy (repeat the tumor imaging if necessary). For patients whose disease is evaluated with bone marrow studies, the bone marrow aspirates and biopsies are required within 14 days prior to start of chemotherapy.

Studies to be obtained	**Pre-Study**	**During Cycle 1**	**Prior to Subsequent Cycles^**	**Off Treatment**	**Off study[#]**
History	X	X	X	X	X
Physical Exam with vital signs	X	Weekly	X	X	X
Height, Weight, BSA	X	X	X		X
Performance Status	X		X		X
CBC, differential, platelets	X	Twice weekly	Weekly	X	X
Complete metabolic profile	X	Weekly	X	X	X
Pregnancy test (only females of childbearing potential)	X		X		
12-lead EKG	X	X**	X**		
Disease Evaluation	X	End of cycle 2[$]	End of cycle 4 then every 3 cycles	X	
Patient Diary*		X	X		
Pharmacokinetics (as per Section 9.1 and Appendix G)		X			

*Patients will be given the diary from Appendix F to fill out with each cycle of treatment. They will return this prior to starting the next cycle

[#]Every effort will be made to follow patients for at least 30 days after the last dose of medication, in order to monitor patients for resolution or late development of adverse events

^ Labs should be done within 48 hours of initiation of the subsequent cycle of chemotherapy

[$] Disease evaluation should be done between days 15-21 of cycle 2

**EKG will be performed prior to Day 8 eribulin during cycle 1, and prior to day 1 eribulin of cycle 2

11. MEASUREMENT OF EFFECT

Although not the primary endpoint of this trial, tumor response will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated after cycles 2 and 4, and then every third cycle as long as clinically stable.

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [65]. Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

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

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

11.1.2 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) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or 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 may only be considered measurable if there is documentation of residual viable disease after irradiation, or if there is unequivocal progression at that site following irradiation.

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.

Evaluable Disease (also termed “non-measurable” or “non-target” disease). All other lesions (or sites of disease), including smaller pathologic lymph nodes are considered evaluable 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 also considered as evaluable (non-measurable).

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST 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 it can be documented 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.
Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the cycle of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered

in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [66-68]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [69].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' 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.

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.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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).

11.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

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

* See RECIST 1.1 manuscript for further details on 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: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Evaluable (non-measurable) Disease (*i.e.*, Non-Target Disease)

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

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

11.1.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

12. REGULATORY REQUIREMENTS/DATA COLLECTION

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.2 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the appropriate participating site and the Coordinating Site (CHCO). The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee (DSMC) and the participating sites IRB of record of any significant adverse events that are serious and/or unexpected, as per standard operating procedure for those entities. In addition, the DSMC will review all adverse events at routine intervals as outlined below.

12.3 Protocol Review and Amendments

This protocol, the proposed informed consent and assent forms along with any documents given to participants (e.g., drug diaries) must be submitted, reviewed and approved by a properly constituted IRB governing each study location. This process will occur following approval by the Coordinating Center IRB (COMIRB).
Any changes made to the protocol will be submitted as amendments and must be approved by the IRB that governs CHCO prior to implementation. The overall study PI and/or study coordinator will then distribute all amendments to the participating sites for submission to their local IRB. All sites must then send all approved documents to the overall study coordinator at CHCO.

12.4 Informed Consent

All participants must be provided a consent and assent form (if applicable) describing the study. All participants must be provided sufficient information to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally

authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.5 Study Documentation

The investigator must prepare and maintain adequate and accurate source documents designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

12.6 DATA AND SAFETY MONITORING

The overall PI Coordinating Center (CHCO) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan and complying with all reporting requirements to the local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center).

12.4.1. Monitoring Plan

As the lead investigator in this multi-site trial, the overall PI is responsible for organizing and conducting monthly teleconferences with all participating sites. The overall PI will also be responsible for including data from all of the participating sites within the overall trials six-month DSM report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six-month review to their local IRB of record at the time of continuing review.

Teleconferences will take place with each participating site only when there are active patients. This call will include the local investigator, local research coordinator, and overall PI and CHCO coordinator.

12.4.2 Subject Data Monitoring:

Monitoring and auditing of research subjects on study will be conducted remotely by the CHCO coordinator and overall study PI. Documentation that will be monitored is listed in the following section. Data will be monitored for completeness and adherence to protocol requirements.

12.7 Data and Safety Monitoring Committee (DSMC)

The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence. For all sub sites, please adhere to the tables in Section 7.4 for AE reporting timelines to CHCO. Once the AE is reported to CHCO, the primary coordinator will report AEs, as required to the DSMC and IRB for review.

The overall PI will provide a DSM report to the CU Cancer Center DSMC on a six monthly basis. The DSM report will include a protocol summary; current numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. Results and recommendations from the review of this six month report by the DSMC will then be submitted by CHCO to all participating sites so they may submit to their IRB of record at time of continuing review.

12.8 Data Collection

Data will be collected for this study and sent to CHCO for review via email or fax. Data will be collected by the CHCO coordinator and reviewed along with the overall PI.

Form / Source Documentation (SD)	**Submission Timeline**
Eligiblity Checklist	Complete prior to registration with CHCO

All source documentation that is submitted with the eligibility checklist must be de-identified. The only documents that will not be de-identified are the consent/assent forms and Patient Data Sheet. All other forms and source documents submitted will be identified only by the subject number.

12.8.1 Method

Instructions for submitting data are listed in Study-Specific Data Management Plans created by CRDM SRF staff.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

A phase I, dose-escalation trial is proposed to determine the recommended phase II dose (RP2D) of escalating doses of eribulin in combination with standard-dose oral irinotecan. Cohorts of 3 patients per dose level are proposed using a 3+3 design [70, 71]. The following rules will be incorporated for dose escalation/de-escalation and establishing the recommended Phase II dose using the occurrence of DLT during the first cycle of therapy that is possibly, probably, or definitely attributable to study therapy.

A. Evaluate 3 patients at $dose_k$:
    1. If 0 of 3 patients have DLT, then
        i. If first cohort, increase dose to $dose_{k+1}$ and go to A.
        ii. Otherwise, go to B.
    2. If 1 of 3 patients has DLT, then go to B.
    3. If more than 1 patient has DLT

i. If lowest dose, then go to C.
ii. Otherwise, decrease dose to $dose_{k-1}$ and go to A.

B. Evaluate 3 additional patients at $dose_k$:
   1. If 0 or 1 of 6 patients has DLT, then increase dose to $dose_{k+1}$ and go to A.
   2. If 2 or more patients have DLT, then
      i. If lowest dose, then go to C.
      ii. Otherwise, decrease dose to $dose_{k-1}$ and go to A.

C. Discontinue dose escalation/de-escalation.

The RP2D is defined as the highest dose level in which there is no more than 1 DLT in 6 patients. Ten additional patients will be enrolled at the RP2D level. Similar dose modifications as specified in Section 6 would be applied to these patients. Doses higher than dose level 2 will not be studied in this trial.

13.2 Sample Size/Accrual Rate

The primary goal of this Phase I trial is to determine the RP2D and assess safety of the combination regimen. A total of 6 -22 adolescent and young adult subjects will be accrued into the trial

It is anticipated that 0.5-1 subjects will be accrued per month so that study accrual will be completed within 36 months.

13.3 Stratification Factors

Not applicable for this trial

13.4 Analysis of Primary and Secondary Endpoints

All patients who received study drug will be included in the safety analysis of this combination regimen. Dose-limiting toxicity rate, adverse event data and corresponding toxicity grades during the days of treatment will be summarized in each dose level and in the overall patient population. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), and the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed.

Listings of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal. Safety data will be summarized for the overall patient group and by dose levels. Toxicities will be graded according to Common Toxicity Criteria (CTCAE) v4.02.

Estimates of antitumor effect based on RECIST 1.1 criteria will be estimated. Furthermore,

specific PD parameters will be assessed including SN-38 and SN-38 glucuronide. Descriptive statistics will be employed to summarize quantitative levels of PD parameters at each time point of follow-up while changes in PD from baseline will be calculated and compared using paired statistical tests. Pharmacokinetic modeling (two-compartment or non-compartmental models) will be employed to estimate several PK parameters (area under the concentration versus time curve, AUC, half-life, clearance, Cmax, etc). These analyses will be considered exploratory in this Phase I trial.

13.5 Data Management

The study statistician and staff from the Biostatistics Shared Resource Facility (BSRF) of the Markey Cancer Center worked closely with the study investigators and the Clinical Research and Data Management (CRDM SRF) at Markey in the development of eCRFs for the study. Specifically, the statisticians attended several meetings including the Protocol Initiation Meeting (PIM) to address all statistical considerations for this protocol including incorporation of dose-escalation plans for this Phase I trial, appropriate and accurate collection of primary and secondary study endpoints and inclusion of valid values and range checks for data fields. Red Cap, managed by staff at CHCO, will be the primary database repository of clinical data from all patients enrolled into this trial. Data will be accessed by the study statistician on a regularly-scheduled basis to perform statistical programming for conduct of data quality control, data management, generation of interim reports and statistical analysis. The BSRF has developed an automated mechanism for generating a trigger for assessment of dose limiting toxicities based on the dose escalation rules in sections section 5.0 above. In collaboration with the study team, procedures will be developed for timelines for data quality control, resolution of data queries, interim reporting and final data analysis.

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 INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Irinotecan interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Irinotecan interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is ***CYP isoenzyme 3A4***. **Irinotecan** is broken down by this enzyme in order to be cleared from your system.
- **Irinotecan** must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
    - You should notify your study doctor if you are prescribed: **phenytoin**, **phenobarbital**, **carbamazepine** or **ketoconazole** since these drugs are known to affect the levels of irinotecan in your body.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of CYP 3A4."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult. Read labels carefully! Acetaminophen is an ingredient in

many medicines for pain, flu, and cold.
- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking **Irinotecan.**

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the agent **irinotecan.** This clinical trial is sponsored by the NCI. **Irinotecan** interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Irinotecan** interacts with a specific liver enzyme called **CYP 3A4**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP 3A4**" ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX C MEDICATIONS THAT PROLONG QTc

Generic name	Brand name
Amiodarone	Cordarone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®
Flecainide	Tambocor®
Halofantrine	Halfan®

Generic name	Brand name
Haloperidol	Haldol®
Ibutilide	Corvert®
Mesoridazine	Serentil®
Methadone	Dolophine®
Moxifloxacin	Avelox®
Pentamidine	Pentam®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Procan®
Quinidine	Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

For the most current list of medications, please refer to the following website: www.torsades.org

APPENDIX D ORAL IRINOTECAN ADMINISTRATION GUIDELINES

- The hospital pharmacist will provide you with 5 doses of irinotecan, each in an oral syringe. Because irinotecan has an unpleasant taste, it is usually mixed with a small amount of juice **IMMEDIATELY BEFORE** giving the medicine to your child.

- The best juice to use is CranGrape Juice, although CranApple or cranberry juice is fine as well.

- **DO NOT** mix the irinotecan in orange juice, apple juice, milk or soda.

- Use a disposable cup to mix the irinotecan with juice. The amount of juice used is up to you. The more juice used, the more the flavor of the irinotecan will be masked. However, it is critical that your child drink **ALL** of the juice mixed with irinotecan. Most parents start by mixing the irinotecan in about one teaspoon (5 ml) of juice. Discard the cup when empty after the irinotecan + juice has been taken.

- Irinotecan should be mixed with juice only on the day the dose is given. The other doses should be stored in a **REFRIGERATOR**. Irinotecan will last for 21 days at a time, provided it has not been mixed with juice.

- Use of nausea medicines (Zofran, Kytril, or Anzemet) may be helpful, and these medicines are best given about 30-60 minutes before the irinotecan. Please discuss this with your doctor.

If you are unable to take the medicine, or vomits within 30 minutes of taking the medicine, please call your doctor for further instructions.

APPENDIX E PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Dear Patient or Parent:

You are receiving irinotecan. This drug can cause severe diarrhea. Before your FIRST chemotherapy treatment please be sure to:

1. BUY IMODIUM A-D. Make sure you have this medication at home before your first chemotherapy treatment. Imodium A-D is also called LOPERAMIDE and comes in 2 mg caplets and in liquid form at a concentration of 0.2mg/ml.

2. AFTER your chemotherapy has started, at the FIRST SIGN of diarrhea be sure to START taking Imodium A-D. DO NOT DELAY starting Immodium A-D if you notice your stools to be more loose, soft, or watery than usual. Do not skip doses. Give Immodium A-D as follows:
• > 43 kg (95 pounds) and more: 4 teaspoonfuls or 2 caplets after first loose stool followed by 2 teaspoonfuls or 1 caplet every two hours as needed.
• 20-43 kg (44-94 pounds): take 2 teaspoonfuls or 1 caplet after the first loose stool followed by one teaspoonful or one-half caplet every 2 hours as needed.

3. STOP taking IMODIUM when you HAVE NOT had any bowel movements for 12 hours.

4. Call your doctor if you still have diarrhea after taking Imodium for 24 hours, or if there is fever or vomiting, or if you have any questions.

5. Your diarrhea can also get a little better if you take the following steps IN ADDITION TO taking Imodium A-D:
- Drink plenty of water or Gatorade
- Drink broth or clear soup to replace salt
- Stay away from milk, dairy products, alcohol, hot or cold beverages, coffee, tea and drinks with Caffeine

6. Do not take medicines such as Miralax, Mylanta, Maalox, Senokot, or Colace

7. Eat foods that are easy to tolerate such as bananas, rice, apple sauce, chicken (white meat), white toast, and canned fruits

8. Please fill out the Irinotecan Administration Diary below during this treatment and give to your nurse or physician.

APPENDIX F ORAL IRINOTECAN ADMINISTRATION DIARY

Patient Name _____ Course #_____

Day of course	Date	Time Irinotecan Given	Time Cefixime Given	Number of stools	Consistency (F=Formed L=Loose W=watery)	Mark when Imodium A-D was started
-1*		------				
0*		------				
1						
2						
3						
4						
5						
6		------				
7		-----				
8		-----				
9		-----	-----			
10		-----	-----			
11		-----	-----			
12		------	-----			
13		-----	-----			
14		-----	-----			
15		-----	-----			
16		-----	-----			
17		-----	-----			
18		-----	-----			
19		-----	-----			
20		-----				
21		------				

***Course 1 only**

APPENDIX G PHARMACOKINETIC STUDY FORM

Study Date	_____	Patient ID	_____	DOB:	_____
*Gender	_____	*Race	_____	*Ethnicity	_____
BSA (m^2)	_____	Height (cm or ft:in)	_____	Weight (lb or kg)	_____

*This information is requested on a voluntary basis to account/explore potential differences in pharmacokinetics

Eribulin: Dose (mg/m2) _____

Start time: _____ Stop time: _____
Notes:_____

Irinotecan: Dose (mg/m2) _____

Administration time: _____
Notes:_____

Each sample for the PK study is to be 7 ml of whole blood collected into a sodium heparinized collection tube. All times listed in the table below are relative to the start of the eribulin IV dose. Each tube must be labeled with the patient's study ID number, time and date the sample was drawn. Data should be recorded on this Pharmacokinetic Study Form.

Blood sample collection

	Date of Collection	Time of Collection
Pre dose		
15 min after end of infusion		
1 hr after end of infusion		
1.5 hr after end of infusion		
2 hr after end of infusion		
4 hr after end of infusion		
5 hr after end of infusion		
24-96 hr after end of infusion (optional)		
Pre dose (day 8)		

Processing and shipping instructions for plasma samples

A sample processing and handling kit containing all the consumables, labels, and storage containers will be provided for a set of 5 patients. Upon receipt keep all materials including the shipping box. Refer to shipping instructions below.

Whole blood samples will be collected from the central line or a peripheral IV provided a flush of at least 10 ml of normal saline has been administered. At each time point, ~7 ml of venous blood will be withdrawn into two 4-mL sodium heparin collection tubes.

PK sample processing:

1) Immediately upon collection place blood sample (heparinized) tubes in wet ice and note the collection time on the sample collection timesheet.
2) Transfer blood sample into 4 clear siliconized microcentrifuge tubes. Centrifuge the blood samples for 2 min at 7200 g to separate plasma (top layer) from red blood cells.
3) Transfer plasma into two amber siliconized tubes, with a plastic transfer pipet. Discard red cells. Cap the tubes.
4) Complete information on the labels and affix onto each tube.
5) Store samples on dry ice and transfer into the provided storage container (81 or 100 slot box) before storing in the -80ºC freezer.

Shipping instructions:

1. Place the small storage box containing the plasma samples into the plastic biohazard specimen bag. Seal the bag and place it in the Styrofoam container with dry ice. Enclose the sample collection timesheets for each patient into a plastic Ziploc bag in the container. Place the Styrofoam container back in the shipping box. Seal the box with shipping tape. Affix 1) the biohazard, 2) the exempt human specimen and 3) the dry ice labels on the shipping box. Place the provided return-shipping label on the package for overnight delivery to the Leggas lab at the University of Kentucky.
2. Samples should only be shipped on **Monday-Wednesday** for overnight delivery.
3. Ship samples to:

   Dr. Mark Leggas
   College of Pharmacy
   University of Kentucky
   789 South Limestone, Room 323
   Lexington, KY 40536-0596
   E-mail: mark.leggas @uky.edu
   (859) 327-1341

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COMIRB
APPROVED
For Use
21-Apr-2017
20-Apr-2018

Study Title:	**A Phase I/Ib Study of Eribulin in Combination with Oral Irinotecan for Adolescent and Young Adult Patients with Relapsed or Refractory Solid Tumors**
Principal Investigator:	**Carrye Cost, MD, Tom Badgett, MD, PhD, Theodore Laetsch, MD**
COMIRB No:	**15-0659**
Version Date:	**March 22, 2017**

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

The word "you" refers to you or your child if the patient is under age 18. "We" means the doctors and other people on the research team.

Why is this study being done?

Currently there is no known effective treatment for your type of cancer. You are being asked to take part in this study because you have a solid tumor for which there is no known curative therapy. Your cancer is recurrent or refractory. Recurrent means that the cancer has come back after treatment. Refractory means that the cancer has not responded to standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

This study is designed to test the experimental combination of eribulin and oral irinotecan in the hope of finding a drug combination that is safe and effective against solid tumors that have come back or not responded to standard therapy. Both drugs have been approved to treat different types of cancer, although the drugs have not been studied together in combination. This is called a Phase I study because the main purpose is to evaluate the safety of the drug combination, and what dose of eribulin may be best to use for further studies. The purposes of this study are to find out what effects the combination of the investigational drug, eribulin and oral irinotecan has on your type of cancer and whether both drugs can be given safely together.

There are two parts to this study: the dose-escalation part, and the dose expansion part.

The first part of this study is called dose-escalation. This part of the study will determine the recommended dose of eribulin. The dose of oral Irinotecan will not change. The main goal of this part of the study will be to measure the safety and side effects of the combination. The dose of eribulin you receive is determined when you are enrolled in the study. Participants enrolled early in the study will receive a lower dose. Participants enrolled later in the study period may receive a

higher dose. The dose of oral irinotecan is not increased during this study. The irinotecan dose is typical for patients with your type of cancer. For each dose group, called a cohort, a number of scientists and doctors will carefully look at labs and other tests to make sure it is safe to enroll adolescents and young adults in the next higher dose group. The dose of eribulin will not be increased higher than the dose that has been proven safe in adults. During the study, blood samples will be taken to measure how much of the chemotherapy are in your blood at certain times.

The second part of this study is called the dose expansion phase. This phase will plan to enroll more adolescents and young adults with a fixed dose of study drug that has been determined from the dose-escalation part of the study. You will be given the same amount of eribulin and Irinotecan as the other patients that join during the dose expansion part of this study.

The goals of this study are:

- To determine the best dose of eribulin that can be safely given together with oral irinotecan to treat adolescents and young adults with relapsed or refractory solid tumors;
- To learn about the side effects (good and/or bad) of giving eribulin with oral irinotecan;
- To determine if tumors get smaller after treatment with eribulin and oral irinotecan;
- To measure the amount of eribulin in your blood after you receive these medications

Other people in this study

Between 6-22 patients will be enrolled on this study at Children's Hospital Colorado, the University of Kentucky, or the University of Texas Southwestern Medical Center.

What happens if I join this study?

Before you begin the study:

If you decide to participate in this study, you will sign this consent document and you will be given a copy of your signed consent before any of the procedures listed below are performed. Please refer to the Calendar of Events located at the back of this consent form for guidance while reviewing the procedures that will take place at the screening and at various times during participation in this study.

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your cancer. If you had some of them recently, they may not need to be repeated. This will be up to your study doctor. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study.

- Your medical history will be reviewed;
- You will have a physical exam including a measurement of your height and weight;
- Your vital signs will be recorded (blood pressure, heart rate and temperature);
- Your ability to perform daily tasks will be assessed;
- You will be asked about any medications that you are taking or have taken recently;

- Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT, MRI, or PET scans.
- An electrocardiogram (ECG) will be done to test the function of your heart;
- If you are able to become pregnant, you will be asked to provide a urine sample for a pregnancy test*. If you are pregnant, you will not be allowed to participate in this study.

*If there is ANY chance that you can get pregnant, you must either agree to practice abstinence from heterosexual intercourse or begin an effective method of birth control.

During the study:

Treatment Plan

If the exams, tests and procedures show that you are eligible to participate in this study, eribulin will be given as a 5-minute intravenous infusion on Days 1 and 8 of each cycle. Irinotecan will be given orally on Days 1 through 5 of each cycle. A cycle lasts 3 weeks (21 days).

You can receive up to 17 cycles of therapy (approximately 12 months or about 1 year) as long as you are benefitting from treatment, not having bad side effects and continue to meet the criteria to continue safely on this study. Although other participating subjects may receive a different dose of eribulin, your assigned dose will not change during your participation in this study unless you develop certain side effects that require lowering your dose of eribulin.

Eribulin is given in the clinic and does not require hospitalization, although treatment can be given in the hospital if necessary. Oral irinotecan can be started in the clinic on the Day 1 and you will need to obtain the remaining days of oral irinotecan from an outside pharmacy. You will be given specific instructions from the research team on how to take the oral Irinotecan. You will also be given a medication diary to fill out at home each time this oral medication is taken and we will ask you to return this diary at the end of each course of treatment. Your study doctor will also prescribe an oral antibiotic to help reduce diarrhea caused by Irinotecan. This antibiotic should be taken 2 days before you receive the first dose of eribulin and Irinotecan and taken for 10 days with each cycle of chemotherapy. The study treatment plan is summarized in the table below:

Treatment Schema:

Day	-1	0	1	2	3	4	5	6	7	8	9-19	20	21
Eribulin			●							●			
Oral Irinotecan			●	●	●	●	●						
Cefixime (antibiotic)	●	●	●	●	●	●	●	●	●	●		●	●

Because eribulin is given intravenously, your physician may recommend that you have a “port” or some type of central venous line placed, if this has not already been done. These are special types of intravenous lines that are placed into a large vein in the chest by a surgeon during a short operation. The “port” or central line is used to administer chemotherapy drugs and also to withdraw small amounts of blood for testing during treatment. The risks associated with placement of these devices will be explained to you and you will be given a separate informed consent document to review and sign if placement of this device is necessary. If you do not have a central line, you will need to have a peripheral IV placed. There is a small amount of pain from the IV and a very small risk of minimal bleeding.

The dose of eribulin for the first patients enrolled on the study will be 80% of the dose given when used alone. Irinotecan will be given at the standard oral dose. Between 2 and 6 patients will receive the combination of eribulin at the starting dose. If the side effects are not too severe, the next group of patients will receive a higher dose of eribulin, but the dose of irinotecan will remain the same. If the side effects are too severe, the next group of patients will receive a lower dose of eribulin, but the dose of irinotecan will remain the same.

Your dose of eribulin and irinotecan will not be increased. If you have bad side effects, the dose of eribulin may be decreased. If you are a patient enrolled early in this study you may receive a lower dose of eribulin than those who are enrolled later. It is therefore possible that you may receive a dose that is less likely to have any effect on your tumor. If you are a patient enrolled in this study at a high dose level it is possible that you will receive a dose that is more likely to cause side effects. Dosing is done this way because we do not yet know the best doses of the two drugs in combination to use.

Pharmacokinetic Samples – **REQUIRED**
To see how much study drug is in your blood, about 7 ml of blood will be collected during the study at the following time points:

- Day 1: pre-dose;
- Day 1: 30 minutes, and 1, 1 ½, 2, 4, and 5 hours after the end of the eribulin infusion
- Day 8: pre-dose

If you want to participate in this study, you must agree to have these samples taken. The samples may be drawn from an existing IV or central line. They will be collected on days when you are already in clinic or the hospital having blood work done.

Pharmacokinetic Samples – **OPTIONAL**
There is an additional single blood draw for pharmacokinetics between day 2 and 4. This extra test is optional. If you do not agree to have this sample taken, you can still receive treatment as part of this study.

Consent to Use Sample for Pharmacokinetic Research

☐ Yes, I agree my samples can be used for Pharmacokinetic testing.
☐ No, I do not want my samples used for Pharmacokinetic testing.

By signing below, you indicate that you have read the information about “Pharmacokinetic Samples - Optional” and have indicated your choice.

_____	_____	_____
PRINT Participant’s Name	Date	Participant’s Signature (Ages 13-17)
_____	_____	_____
PRINT Parent’s Name	Date	Parent’s Signature

How long will I be on this study?
You can receive up to 17 course of treatment on this study. Each course is 21 days. It will take about 12 months to complete the 17 courses.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your study doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for 30 days after the last dose of study drug.

What are the possible discomforts or risks?

While receiving treatment with this drug combination, you may be at risk of side effects.

This is a Phase I study. A Phase I study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase I study, some patients may have very serious side effects and could die as a result of these side effects.

Everyone taking part in the study will be monitored carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medications to help lessen side effects. Many side effects go away soon after you stop taking the combination of eribulin and Irinotecan. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. We will tell you if we learn of any new information that may affect your health, welfare, or decision to stay in this study.

You should tell your study doctor immediately if you think you are developing any unusual side effects even if they are not listed here. Any delay in treating these side effects may prolong their course, make them more difficult to treat and in rare occasions may even be fatal.

You should not take any other medications, including non-prescription treatments such as aspirin, without the approval of your study doctor.

Possible Risks and side effects related to Eribulin include:

Common (in more than 20% of patients)	**Less Common (in more than 4-20% of patients)**
• Fewer red blood cells in the blood • Low numbers of white blood cells called lymphocytes and neutrophils/granulocytes that may make it easier to get infections which may be life threatening; • Nausea; • A feeling of extreme tiredness not relieved by sleep(fatigue); • Hair loss	• Watery eyes; • Abdominal pain; • Constipation; • Diarrhea; • Heartburn; • Vomiting; • Dry mouth; • Sores in mouth or in GI tract; • Swelling caused by fluid build-up in the tissues of the arms and legs; • Fever; • Infection; • Swelling and redness of skin if you are receiving radiation; • Low blood platelet count; • Bruising, bleeding; • Weight loss, • Loss of appetite (anorexia); • Dizziness; • Headache; • Changes in taste; • Feeling of "pins and needles" in arms and legs;

Common (in more than 20% of patients)	Less Common (in more than 4-20% of patients)
	• Muscle weakness; • Numbness, tingling or pain of the arms and legs; • Cough, shortness of breath, sore throat; • Increased blood level of liver tests (ALT, AST) which may mean there is damage to the liver; • Low levels of salts in the body (potassium) which may require you to take another medicine to correct salt level

Abnormal heartbeat and heart rhythm (such as QT prolongation, which can lead to heart rhythm disorder) were seen in the EKGs (heart tracing) in some subjects with heart disease or heart rhythm disorders during clinical trials. You should avoid taking medications that can interact with eribulin and make this potential side effect worse. Talk to your study doctor before starting any new medicine.

Some drugs, food and supplements that may interact with eribulin include:

Antibiotics:	Azithromycin, clarithromycin, erythromycin, moxifloxacin, sparfloxacin
Heart Medicines:	Amiodarone, diltiazem, disopyramide, dofetilide, dronedenarone, flecainide, procainamide, sotalol
Nausea Medicines:	Chlorpromazine, droperidol
Some Chemotherapies:	*Be sure to talk to your study doctor about this*
Many other drugs:	Chloroquine, halofantrine, haloperidol, ibutilide, methodone, pentamidine, pimozide, quinidine, terfenadine, thioridazine

The list above does not include everything that may interact with your chemotherapy. Talk to you study doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

Possible risks and side effects related to Irinotecan include:

Likely (happens to 21-100 children out of 100)	Less Likely (happens to 5 - 20 children out of 100)	Rare but serious (happens to < 5 children out of 100)
• Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light • Loss of body water • Nausea and Vomiting • Inflammation and/or sores in the mouth • Loss of appetite • Stomach pain	• Fewer red blood cells and platelets in the blood • Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which can cause excessive loss of water and salts from the body • Constipation • Pain at the injection site • Blood clots which may be in rare cases life threatening*	• Severe allergic reaction which can be life threatening with shortening of breath, low blood pressure and a rapid heart rate • Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such as sodium and potassium from the body and could lead to the kidneys failing which could be life threatening • Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain • Headache

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
• Fever • A feeling of weakness and tiredness • Temporary hair loss • Elevation of liver and bone enzymes in the blood and of bilirubin (yellow pigment formed in the liver) • An increase in a type of white blood cell called eosinophil. These are sometimes associated with allergic reactions • Decrease in number of red and white blood cells and platelets made in the bone marrow	• Rash • Inflammation and/or sores in the mouth, throat and/or esophagus • Headache • An upset stomach • Increase in liver and kidney levels	• Skin inflammation • Trembling • Blood in the urine • Mildly increased level of protein and glucose in the urine • Low amount of protein in the blood • Mouth sores • Sensation of warmth on face • Risk to the unborn child in pregnant patients** • Pain at infusion site • Disorientation/confusion • Dizziness and low blood pressure • A blockage of the bowel that prevents passage through the bowel • Slow heart beat

* This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

** Birth defects and other serious abnormalities in the unborn baby have been noted with irinotecan in animal studies at doses similar to or less than those used in humans. The timing and frequency of these effects is as yet unknown. These may include multiple birth defects and abnormalities of bone formation, small size of baby at birth and increased risk of death of the unborn baby. Irinotecan is excreted in rat milk but this is unknown for humans.

Possible risks and side effects related to Cefixime:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5-20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Belly pain • Nausea • vomiting • Indigestion	• Headache • Dizziness • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Low number of white blood cells in the blood • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Decrease in platelets which may make you bruise or bleed easily. • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain, • High blood tests of kidney and liver function • Hepatitis, yellowing of skin and whites of eyes • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be

Likely (happens to 21-100 children out of 100)	Less Likely (happens to 5-20 children out of 100)	Rare (happens to less than 5 children out of 100)
		breakdown of the skin

Serious Side Effects:
Any of the side effects listed in the tables above can become serious.

Imaging Studies:
You will have one or more of the following imaging studies, depending on which your doctor thinks is best to evaluate your tumor. You may have an MRI, CT, or FDG-PET scan. There are different risks associated with each of these scans and you doctor will discuss these risks with you.

CT scans:
As part of this study we will perform a CT scan of the area of your body where your tumor is and any additional areas that your doctor thinks are important to scan. CT is a way of taking detailed pictures inside your body by using X-rays. X-rays are a type of radiation.

You get some radiation from your environment. You get radiation from bricks and concrete, from some foods, and from radon gas, which is an invisible gas that seeps out of the ground. The amount of radiation that this CT scan will deliver to your body (give you) is about the same as you would get from living in your environment for up to **5 years**, depending on the area where the scan is focused. This is an estimate. The amount of radiation you get could be higher or lower, depending on the machine, the power setting, and your body weight. Exposure to radiation at high levels increases a risk of developing cancer. The risk of this procedure is not equal for everyone. The risk is much higher for unborn babies if the mother has this procedure. The risk is also much higher for young children and teenagers. The risk is much lower for people over the age of 30.

MRI:
In this study we will take Magnetic Resonance Images (MRI's) of your body. The MRI machine uses powerful magnetic waves to take pictures inside the body. The waves themselves are not harmful, but they can cause metal to heat up and electronics to stop working. You should NOT have an MRI if you have metal or electronic devices inside your body. Heart pacemakers and insulin pumps are examples of electronic devices.

The MRI machine is a small round tube. It might make you uncomfortable if you do not like tight spaces. The most common side effect of having an MRI is flashing lights in the eyes. This is caused by the magnetic waves and is not harmful. Some people also experience warmth and reddening of the skin. This usually goes away after a few minutes.

IV contrast:
As part of a CT or MRI scan, you may be given an intravenous injection of dye in order to help see the organs on the radiology images. You will feel a slight pin prick when the needle is inserted into your vein. You may have a warm, flushed sensation during the injection of the contrast materials and a metallic taste in your mouth that lasts for a few minutes. Some people may develop allergic symptoms (e.g., hives, itching, difficulty breathing), and in very rare cases, anaphylactic shock (low blood pressure, with loss of consciousness, severe loss of body fluid that can lead to shock or death). In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

Risks of an FDG-PET scan:
The risks with a PET scan are very minimal. The amount of radiation is low and the FDG degrades quickly so that no detectable radioactivity is present after several hours. Any remaining FDG in your body is removed from the body through urine. Family members are not at risk for exposure since greater than 90% of the radioactivity has left the body or decomposed before you have left the cancer clinic.

Electrocardiogram (ECG)
For an ECG, someone (study staff or clinic staff) will attach special stickers to your chest, legs and arms. Wires will be connected to these stickers to read the electrical activity of your heart. You will have to lie still for a few minutes. Removing the stickers might be a little uncomfortable and you may experience mild irritation, slight redness, and itching in this area.

Reproductive Risks:
Patients who agree to participate in this study should not become pregnant while on this study. This study and the drugs used in this study may be hazardous to an unborn child. Patients and their sexual partners should avoid sex and /or use an effective method(s) of contraception that is medically appropriate based on your study doctor's recommendation at that time.

If you become pregnant, you suspect pregnancy or if you have missed your period or it is late, or if you have a change in your usual menstrual cycle (e.g. heavy bleeding during your period or bleeding between periods), you should immediately contact your study doctor. In case of pregnancy, you or your partner's pregnancy and its outcome will be reported to the study sponsor.

If you become pregnant during this study, the study drug will be discontinued and you will be referred for obstetric care. The sponsor has not set aside any funds to pay for any aspects of obstetrics, child or related care and does not plan to pay for them.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the treatment combination of eribulin and oral irinotecan for adolescent and young adult patients with recurrent or refractory solid tumors. However, there is no guarantee that your health will improve if you chose to participate in this study. Also, there could be risks to being in this study. If there are risks, these are listed above in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your cancer. These other ways include:

- Getting treatment or care for your cancer without being in a study, such as other chemotherapy treatments;
- Being in another study with a different experimental medicine;
- Getting no treatment;
- Getting palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other difficulties caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel, and keep you as active and comfortable for as long as possible.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Private grants are sponsoring this research. The Morgan Adams Foundation and a K12 grant through the University of Colorado Denver are providing financial support and/or material for this study. The sponsor will only pay for research procedures, as explained on the following page in the 'Will I have to pay for anything?' section. They will not pay for treatment or procedures that are considered standard of care or part of your usual cancer care.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

There are some medical treatments that you would have to get for your cancer whether you are in this study or not. You will have to pay for these. The health care costs during your participation in this study that are considered part of the standard treatment of your disease will be billed to your insurance or other third-party payer. This includes routine blood tests, hospitalizations, radiology scans, and other procedures that will be done in this study, including the medications.

All the drugs being used on this study are commercially available agents. You will pay for the amount of drugs needed to complete this study. The cost is normally covered by your insurance company.

You and/or your insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment you receive during this study that you would normally receive for your condition. These are costs that are considered medically reasonable and necessary and will be part of the care you receive if you do not take part in this study. A co-payment/deductible from you may be required by your insurer or Medicare/Medicaid even if your insurer or Medicare/Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be substantial. We encourage you to meet with a Financial Counselor at Children's Hospital Colorado to review this information and what your expenses might be before you decide to participate. Patient Financial Services can be reached at 720.777.6422.

The required and optional pharmacokinetic research samples will be obtained and processed at no cost to you. Private grants are sponsoring these research procedures.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage .

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

Can I be removed from this study?

The study doctor may decide to stop your participation in the study without your permission if he or she thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

The study doctor may also withdraw you from the study and the study drug may be stopped without your consent for one or more of the following reasons:

- Staying in the study could be harmful for you;
- You need treatment not allowed by the study
- You are not able to complete the study procedures as required
- You become pregnant
- The study is stopped by sponsor, for reasons not related to you.

All information and samples collected from you before you stop the study may still be used by the sponsor to understand more about the study drug and/or your type of cancer.

If you are taken out of the study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study.

What happens if I am injured or hurt during the study?

Dr. Carrye Cost should be informed about any injury you experience while you take part in this study. Her phone number is 720.777.6775. A member of the research team can be paged 24 hours a day for emergencies. Please call 720.777.6740 at night and on weekends to have someone paged.

If you are hurt by this research, we will give you medical care. You will get medical treatment if you are injured as a result of taking part in this study. It is important for you to understand that the Children's Hospital Colorado does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Instead, you and/or your health plan will be charged for this treatment. There are no plans for the study to pay for medical treatment for injuries. Also, Children's Hospital Colorado will not pay for any wages you may lose if you are harmed by this study. However, signing this form does not mean that you are giving up any legal rights to try to get compensation for injury.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to be in this study, you may stop the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from us and this institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Carrye Cost at Children's Hospital Colorado and Dr. Tom Badgett at the University of Kentucky. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Cost at 720.777.6777. You will be given a copy of this form to keep. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver and the hospital(s) it works with have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- Children's Hospital Colorado (CHCO)

CHCO shares a medical record system with the Barbara Davis Center and PedsConnect; therefore it is also possible that our information could be viewed by healthcare professionals at these organizations.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

We cannot do this study without your permission to see, use, and give out your information. You do not have to give us this permission. If you do not, then you may not be in this study.

We will see, use, and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the University of Colorado Denver and its affiliate hospitals may not be covered by this promise.

We will do everything we can to keep your records a secret. It cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Primary Investigator, at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Dr. Carrye Cost
The Center for Cancer and Blood Disorders
Children's Hospital Colorado, Box B115
13123 East 16th Avenue
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information. By signing this form, you are also giving Dr. Cost permission to give your health information to these groups:

- Federal offices such as the Food and Drug Administration (FDA) and Office of Human Research Protection (OHRP),that protect research subjects like you;
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team;
- The laboratory that will store blood samples, University of Kentucky
- The Clinical Trials Office at the University of Colorado Cancer Center;
- Officials at the institution where the research is being conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all the rules for research;
- The National Cancer Institute, the National Institute of Health and/or the Department of Health and Human Services.

We might talk about this research study at meetings. We might also print the results of this research study in medical and scientific journals. We will always keep the names of research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study has been completed.

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make *all or some* **of the following health information about you collected in this study available to:** University of Kentucky, University of Texas Southwestern Medical Center.

Information about me that will be seen, collected, used and disclosed in this study:

- Portions of my previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, and procedure results.
- Research visits and research test records.
- Blood samples and the data with the samples.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver, and the hospitals involved in this study work to find the causes and cures of disease. The data, blood and specimens collected from you during this study are important to this study and to future research. If you join this study:

- The data, blood, or other specimens are given by you to the investigators for this research and so no longer belong to you.
- Both the investigators and any sponsor of this research may study your data and tissue, blood, or other specimens collected from you.
- If data, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or IRB approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

HIPAA Authorization for Optional Additional Study Procedures

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Consent and Authorization Form Approval

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:_____ Date: _____
Subject, (if over 18 years); OR Parent/Guardian

Print Name:_____

Relation to Subject: _____

Signature:_____ Date: _____
Subject (Ages 13-17) in addition to Parent Signature

Print Name:_____

Consent form reviewed by:_____ Date:_____

Print Name:_____

Investigator:_____ Date:_____
(Investigator must sign within 5 days)

Signature of Witness: _____ Date_____
(If applicable: required for subjects who are non-English speaking or with other limitations that require a witness signature)

☐ Witness to Signature

☐ Witness to consent process

Schedule and Description of Assessments

Studies to be obtained	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^	Off Treatment	Off study#
Complete History	X	X	X	X	X
Physical Exam with vital signs	X	Weekly	X	X	X
Height, Weight, BSA	X	X	X		X
Performance Status	X		X		X
CBC, differential, platelets	X	Twice weekly	Weekly	X	X
Complete metabolic profile	X	Weekly	X	X	X
Pregnancy test (only females of childbearing potential)	X		X		
12-lead EKG	X	X**	X**		
Disease Evaluation	X	End of cycle 2$	End of cycle 4 then every 3 cycles	X	
Patient Diary*		X	X		
Pharmacokinetics (as per Section 9.1 and Appendix F)		X&			

*Patients will be given the diary from Appendix F to fill out with each cycle of treatment. They will return this prior to starting the next cycle
#Every effort will be made to follow patients for at least 30 days after the last dose of medication, in order to monitor patients for resolution or late development of adverse events
^ Labs should be done within 48 hours of initiation of the subsequent cycle of chemotherapy
$ Disease evaluation should be done between days 15-21 of cycle 2
**EKG will be performed prior to Day 8 eribulin during cycle 1, and prior to day 1 eribulin of cycle 2
$Pharmacokinetics on Day 1 and 8 are required, whereas PKs on Day 4 are optional.

Areas shaded are research-related interventions.

Initials_____