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A phase 1 study of eribulin mesylate (E7389), a novel microtubule targeting chemotherapeutic agent, in children with refractory or recurrent solid tumors: a Children's Oncology Group Phase 1 Consortium study (ADVL1314)

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Abstract

BACKGROUND—Eribulin mesylate is a novel anti-cancer agent that inhibits microtubule growth, without effects on shortening, and promotes non-productive tubulin aggregate formation. We performed a phase 1 trial to determine the dose-limiting toxicities (DLTs), maximum tolerated or recommended phase 2 dose (MTD/RP2D), and pharmacokinetics (PK) of eribulin in children with refractory or recurrent solid (excluding CNS) tumors.

METHODS—Eribulin was administered intravenously on days 1 and 8 in 21-day cycles. Three dose levels (1.1, 1.4 and 1.8 mg/m²/dose) were evaluated using the rolling six design with additional patients enrolled into a PK expansion cohort at the MTD. PK samples were obtained following the day 1, cycle 1 dose.

RESULTS—Twenty-three patients, ages 3-17 (median 14) years were enrolled; 20 were evaluable for toxicity. DLTs occurred in 0/6 and 1/6 subjects at the 1.1 and 1.4 mg/m²/dose, respectively. One subject at the 1.4 mg/m²/dose had grade 4 neutropenia and grade 3 fatigue. At the 1.8 mg/m²/dose 2/5 subjects experienced dose-limiting (grade 4) neutropenia. Grade 3/4 non-dose-limiting

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CONFLICT OF INTEREST STATEMENT:

ESS, RER, SB, XL, CGM, SD, JMR, EF, BJW and SMB declare that they have no COI to disclose. DD, RS, LR and GR are employees of Eisai, Inc.

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toxicities included lymphopenia and hypokalemia, while low-grade toxicities included anorexia and nausea. No episodes of grade > 2 QTc prolongation or peripheral neuropathy were reported. Eribulin pharmacokinetic parameters were highly variable; the median elimination half-life was 39.6 (range 24.2-96.4) hours. A partial response was observed in one patient (Ewing sarcoma).

CONCLUSIONS—Eribulin was well-tolerated in children with refractory or recurrent solid tumors with neutropenia identified as the primary DLT. The RP2D of eribulin is 1.4 mg/m²/dose on days 1 and 8 of a 21-day cycle.

Keywords

Phase 1; children; eribulin; pharmacokinetics

INTRODUCTION

Microtubule-targeting agents (MTAs) are among the most commonly used and effective drugs in the treatment of pediatric malignancies¹. They exert their effects by binding to distinct sites on β -tubulin² and ultimately either inhibit (destabilize) or promote (stabilize) its polymerization with α -tubulin³. Vinca alkaloids (vincristine, vinblastine, vindesine and vinorelbine), bind to the vinca domain located adjacent to the GTP binding site on β -tubulin and destabilize the microtubule structure⁴. The role of vincristine in multi-modal chemotherapy regimens is unparalleled in pediatric oncology practice with US Food and Drug Administration (FDA) approvals for the treatment of pediatric leukemia, lymphoma, Wilms tumor, neuroblastoma, rhabdomyosarcoma and other soft tissue sarcomas⁵. Despite its widespread antitumor activity, peripheral neuropathy and tumor resistance are inherent limitations to its use. Vincristine-related neuropathy has led to a largely empiric dosing cap⁶. As a result, patients, particularly older children and adolescents, may receive a suboptimal dose contributing to an inferior outcome for diseases where vincristine plays an important role in frontline therapy⁷.

Microtubule stabilizing agents such as the taxanes (paclitaxel and docetaxel) and the epothilone ixabepilone, which after binding to β -tubulin cause the creation of stable, non-functional tubule bundles, are active against a broad range of adult malignancies^{8,9}. In addition, ixabepilone is active in paclitaxel resistant tumors¹⁰. However, the anti-tumor activity of these microtubule stabilizing agents in children has been disappointing¹¹⁻¹³. The ineffectiveness of these agents in pediatric malignancies has several potential explanations including the distinct histological origins of childhood cancer compared to carcinomas in adults, possible age-specific mechanisms of taxane and epothilone resistance and the inability of these drugs to bind to certain β -tubulin isotypes that may be of particular importance in pediatric cancers¹⁴.

Eribulin mesylate (E7389) is a novel anti-mitotic agent that is a synthetic analog of halichondrin B (HalB), a natural product isolated from the marine sponge *Halichondria okada*¹⁵. Like other anti-mitotic agents, eribulin inhibits cancer cell proliferation primarily via induction of irreversible cell cycle arrest at G2/M through disruption of the mitotic spindles and initiation of apoptosis. However, eribulin is mechanistically unique. Like vinca alkaloids, eribulin is a microtubule destabilizing agent, but unlike all known MTAs, eribulin

only inhibits microtubule growth while having no effect on microtubule shortening. In addition, eribulin can promote the formation of non-productive tubulin aggregates reducing the pool of microtubule building blocks¹⁶. Eribulin is metabolized primarily by CYP3A4 and is a substrate for the P-glycoprotein (P-gp) drug efflux pump; however, it maintains full *in vitro* activity against cancer cells that are taxane-resistant due to β -tubulin mutations¹⁷. It has been extensively studied in adult human subjects and is FDA approved for breast cancer¹⁸ and liposarcoma¹⁹ at a dose of 1.4 mg/m² administered intravenously on days 1 and 8 of a 21-day cycle²⁰.

In adults treated with eribulin, the dose limiting toxicities (DLTs) were neutropenia and febrile neutropenia. Other grade 3 toxicity related to eribulin included fatigue, muscle weakness, sensory neuropathy, hyperglycemia, hypophosphatemia, nausea and vomiting²¹. In adults receiving eribulin doses of 0.25 to 4.0 mg/m², the pharmacokinetic parameters were dose proportional, with an elimination half-life of approximately 40 hours, volume of distribution of 43 -114 L/m² and mean clearance of 1.16 L/hr/m² to 2.42 L/hr/m². The human plasma protein binding of eribulin at concentrations of 100 ng/mL to 1,000 ng/mL ranged from 49% to 65%. No accumulation of eribulin was observed with weekly administration²².

Evaluation by the Pediatric Preclinical Testing Program showed that eribulin had potent *in vitro* cytotoxic activity against most pediatric tumor cell lines with a median IC₅₀ of 0.27 nM. Further *in vivo* testing against acute lymphoblastic leukemia (ALL) and solid tumor xenografts demonstrated a complete response in 7 of 7 ALL models and an objective response in 16 of 30 solid tumor models. Complete responses were observed in Wilms tumor, Ewing sarcoma, rhabdomyosarcoma, glioblastoma, and osteosarcoma models²³.

Based on the pre-clinical and clinical activity in adult malignancies and pre-clinical activity in pediatric malignancies, we initiated a phase 1 clinical trial of eribulin in children with refractory solid tumors. The primary objectives of this trial were to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), define and describe the toxicities and describe the pharmacokinetics of eribulin in children.

MATERIALS AND METHODS

Patient Eligibility

Patients > six months and < 18 years of age with measurable or evaluable recurrent or refractory solid tumors, including lymphomas, were eligible. Histologic verification of malignancy from the time of the original diagnosis or relapse was required. Performance score (Lansky or Karnofsky) of 50 was required. Subjects were required to have recovered from the acute toxic effects of prior therapy and be at least 21 days from prior myelosuppressive therapy, 14 days from growth factor support and 42 days from prior immunotherapy. Three half-lives must have elapsed since prior monoclonal antibody administration, 84 days since a stem cell transplant and at least 150 days since total body, craniospinal or hemi-pelvic irradiation. Other eligibility criteria included adequate bone marrow function (peripheral absolute neutrophil count $\geq 1,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$ (transfusion independent) and hemoglobin $\geq 8 \text{ g/dL}$); adequate renal function

(age-adjusted normal serum creatinine or glomerular filtration rate ≥ 70 ml/min/1.73m²); adequate liver function (total bilirubin $1.5\times$ institutional upper limit of normal for age, ALT ≤ 110 U/L AST ≤ 125 U/L and albumin ≥ 2 g/dL); and adequate cardiac function (shortening fraction $\geq 27\%$ or ejection fraction $\geq 50\%$ and QTc ≤ 480 msec). A separate cohort was included for children 6 to 12 months of age, with age-specific organ function criteria, definitions of toxicity, and modification of required blood sampling for research studies (however, this cohort failed to enroll any patients and was subsequently closed for lack of accrual). Secondary to eribulin being a strong P-gp substrate with poor central nervous system (CNS) penetration being noted in pre-clinical studies²⁴, patients with central nervous system (CNS) tumors or tumors with CNS metastases were excluded; as were patients with bone marrow metastasis, uncontrolled infections, viral hepatitis or patients with grade 1 peripheral sensory or motor neuropathy graded according to the modified ("Balis") Pediatric Scale of Peripheral Neuropathies²⁵. This trial was approved by the National Cancer Institute Central Institutional Review Board (CIRB). Written informed consent and assent, as appropriate, were obtained in accordance with federal and institutional guidelines.

Drug administration

Eribulin mesylate (HAVALEN™, Eisai, Inc., Woodcliff Lake, NJ) was supplied as a clear, colorless, sterile solution at a concentration of 0.5 mg/dL in a single use vial. The drug was administered undiluted or diluted in 0.9% sodium chloride to a final concentration between 0.005 mg/mL and 0.2 mg/mL and administered intravenously over 2-15 minutes. The starting dose of eribulin was 1.1 mg/m²/dose, approximately 80% of the adult recommended dose of 1.4 mg/m². Dose escalations to 1.4 mg/m², 1.8 mg/m² and 2.2 mg/m² or de-escalation to 0.8 mg/m²/dose, if dose limiting toxicity was observed at the starting dose level, were planned.

Eribulin was administered on days 1 and 8 of each 21-day cycle with certain exceptions. Patients who had grade 4 neutropenia or platelets $< 75,000/\text{mm}^3$ on day 8 had their eribulin dose for that day withheld. If the toxicity resolved to an ANC $\geq 750/\text{mm}^3$ and platelets $\geq 75,000/\text{mm}^3$ (transfusion independent) by day 11, the full dose was administered. If the toxicity did not resolve to an ANC $\geq 750/\text{mm}^3$ and platelets $\geq 75,000/\text{mm}^3$ by day 11, the day 11 dose was omitted and a DLT was recorded (and considered to have occurred "early"). Patients who had grade 3 or 4 non-hematologic toxicities attributable to eribulin on or prior to the day 8 dose were considered to have had a DLT. If the toxicity resolved to meet eligibility or grade ≤ 2 (if not part of the eligibility criteria) by day 8, the dose of eribulin was administered at the next lower dose level. If toxicities had not resolved to administration criteria by day 8 but had resolved by day 11, the dose was administered on day 11 at the next lower dose level. If toxicities had not resolved by day 11, the dose was omitted.

Study design

This dose escalation study utilized a rolling-six design²⁶. Briefly, up to six patients were enrolled concurrently at the starting dose. Enrollment to subsequent dose levels was determined by the number of enrolled patients, the number with DLTs and the number at risk for a DLT.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.0 (<http://ctep.cancer.gov>). Early DLTs (prior to administration of the day 8 eribulin dose) were described previously (in “Drug administration” section). Other hematologic DLTs were defined as grade 4 neutropenia for > 7 days; grade 4 thrombocytopenia on two separate days, or requiring a platelet transfusion on two separate days, within a 7-day period; or myelosuppression that caused a delay of > 14 days between treatment cycles. Non-hematologic DLTs were defined as grade 3 or 4 non-hematologic toxicity attributable to eribulin with the exclusion of grade 3 nausea and vomiting of fewer than 3 days duration, grade 3 transaminase elevation that returned to grade 1 or baseline prior to the time for the next treatment cycle, grade 3 fever or infection, or grade 3 electrolyte abnormalities responsive to oral supplementation. Non-hematologic toxicity that caused a delay of 14 days between treatment cycles was also considered a DLT. For patients < 12 months of age, any grade 2 non-hematologic toxicity attributable to the study drug was considered a DLT.

Any patient who experienced a DLT at any time during the protocol therapy was evaluable for adverse events. Patients without DLTs who received 100% of the total prescribed cycle dose (i.e. received both dose on day 1 and day 8 or 11) per protocol guidelines and had the appropriate toxicity monitoring studies performed were also evaluable for toxicity assessment and the primary study objective. The MTD was the maximum dose at which fewer than one-third of patients experienced a DLT during cycle 1 of therapy.

Tumor response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1²⁷.

Study evaluations

Patient history, physical examination and laboratory studies were obtained before treatment and then weekly throughout the first cycle of therapy and before subsequent courses thereafter. Complete blood counts (CBCs) were obtained at least twice weekly during the first cycle and weekly thereafter. Disease evaluations were obtained at baseline, at the end of cycle 1 and after every other cycle $\times$ 2 and subsequently after every third cycle. During cycle 1, 12-lead electrocardiograms (EKGs) were obtained within 15-30 minutes pre-infusion and within 15 minutes after the end of the eribulin infusion on days 1 and 8 or 11.

Pharmacokinetic studies

Blood samples (3 mL) for eribulin mesylate pharmacokinetic studies were collected at a site distant from the infusion site and placed into pre-chilled sodium heparin vacutainer tubes prior to the day 1 dose and then 10 ($\pm$ 5) min, 30 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 24 hrs, 48 hrs and 72 after the infusion. A PK sample was also collected at either 96 or 120 hours after the end of the day 1 infusion, just prior to the day 8 or 11 dose and 10 ($\pm$ 5) minutes after the day 8 or 11 dose. Serum was separated by centrifugation at $2,500 \times g$ relative centrifugal force (RCF) for 15 minutes at 4°C, transferred into polypropylene tubes and stored at -70°C until shipment on dry ice.

Pharmacokinetic analysis for eribulin mesylate in plasma samples was conducted by Eisai, Inc. using a validated HPLC assay with MS/MS detection. Eribulin pharmacokinetic parameters were estimated using Phoenix[®] WinNonlin[®] Version 6.4 (Certara Corporation,

Princeton, NJ). For non-compartmental analyses, the apparent terminal elimination rate constants (k_z) were determined by linear least-squares regression through the last 5 points in the plasma-concentration profile. The apparent elimination half-life ($t_{1/2}$) was calculated as $0.693/k_z$. Areas under the plasma concentration-time curves (AUC) were determined using the linear trapezoidal rule from time zero to the time of the last detectable sample (C_{last}). Areas under the plasma concentration-time curves through infinite time ($AUC_{0-\infty}$) were calculated by adding the value C_{last}/k_z to AUC_{last} . The clearance (CL) of eribulin was calculated as $dose/AUC_{0-\infty}$. Comparative analyses were performed using the Wilcoxon Rank Sum Test.

RESULTS

Patient Characteristics

From August 11, 2014 to December 14, 2016 twenty-three patients were enrolled onto the study, all of whom were eligible (Table 1). Twenty-two patients were dosed with eribulin. Subjects had a median age of 14 years (range 3-17 years) and had 12 distinct solid tumor diagnoses. All patients had received prior multi-agent chemotherapy (median, 2 regimens; range, 1-5 regimens) and thirteen had prior radiation therapy.

Toxicities

Twenty subjects were evaluable for toxicity assessment; two were not evaluable for toxicity because the required study observations were not obtained, and one did not receive eribulin and was not therefore not evaluable for either toxicity or disease response. Seventeen children received eribulin at one of three dose levels as part of the escalation cohort, while an additional three children received eribulin in the PK expansion cohort. During the dose escalation component of the trial, three subjects experienced a first cycle DLT (Table 2), with a single additional subject experiencing a DLT during cycle 2. Cycle 1 DLTs (Table 2) included a single subject at the 1.4 mg/m^2 dose level with grade 3 fatigue and grade 4 neutropenia for > 7 days, and two subjects at the 1.8 mg/m^2 dose level with grade 4 neutropenia for > 7 days. Common grade 3/4 non-DLT cycle 1 toxicities related to eribulin (Table 3 and 4) included decreased white blood cell count ($n = 12$), decreased lymphocyte count ($n = 10$) and hypokalemia ($n = 2$). Low grade (grade 2) toxicities included anorexia ($n = 5$), nausea ($n = 3$), headache ($n = 3$) and fatigue ($n = 1$). The eribulin MTD and RP2D was $1.4 \text{ mg/m}^2/\text{dose}$ administered on days 1 and 8 of a 21-day cycle.

As a conservative approach, focused attention was given to cardiac electrophysiology during this study due to a minor increase in the QTc noted in adult subjects receiving eribulin²⁸. In twenty-two subjects who received at least one dose of eribulin and who had at least one set of pre- and post-dose EKGs, the baseline mean QTc was 419 msec (standard deviation (SD) 20 msec). After the first dose of eribulin, four subjects experienced grade 1 prolonged QTc (450-480 msec) and one had grade 2 prolonged QTc (481-500 msec). All subjects who experienced QTc prolongation subsequently had their QTc return to baseline.

Pharmacokinetics

The pharmacokinetics of eribulin mesylate were studied in 22 patients during cycle 1. The plasma concentration versus time profile for patients treated at the 1.4mg/m² dose level is illustrated in Figure 1 and summary statistics for parameter estimates across all dose levels are summarized in Table 5. There was heterogeneity in C_{max} and AUC values (Figure 1A and 1B and Table 5). Given the wide variability and small dose range, dose proportionality was difficult to accurately assess. However, in this population, there was no statistically significant difference in clearance with increasing dose levels ($p = 0.6350$). Overall, the median terminal half-life of eribulin was 39.6 hours. Eribulin plasma clearance values varied over a 10-fold range (0.41 – 4.78 L/hr/m²) with a median value of 1.75 L/hr/m². There was no difference in clearance (Figure 1C) between males (median = 1.88 [0.79 - 2.79] L/hr/m²) and females (median = 1.75 [0.41 – 4.78] L/hr/m²) ($p = 1.00$). Median clearance was 79% higher in children age <12 years ($n = 7$) (median = 2.45 [1.63 – 4.78] L/hr/m²) compared to those 12 years ($n = 15$) (median = 1.37 [0.41 – 2.79] L/hr/m²) ($p = 0.01$).

With the primary toxicity of eribulin in this population noted to be neutropenia, it was explored whether this might be related to individual differences in drug exposure. While subjects who experienced grade 4 neutropenia in cycle 1 ($n = 8$) had higher median exposures to eribulin than subjects who did not ($n = 12$), no parameter met statistical significance when examined by Wilcoxon/Kruskal-Wallis tests (AUC₀₋₂₄: 603 h●nM vs. 537 h●nM, $p = 0.35$; AUC_{0-∞}: 1903 h●nM vs. 899 h●nM, $p = 0.10$).

Response

Of the 22 subjects evaluable for response, one at dose level 1 (1.1 mg/m²/dose) (Ewing sarcoma) experienced a partial response and remained on protocol therapy for four cycles. In addition, three subjects had stable disease: one, at dose level 1, with alveolar soft part sarcoma (3 cycles), one, at dose level 2 (1.4 mg/m²/dose), with malignant peripheral nerve sheath tumor (8 cycles), and one, at dose level 3 (1.8 mg/m²/dose) with clear cell sarcoma (5 cycles).

DISCUSSION

This pediatric phase 1 trial demonstrates that eribulin mesylate was well tolerated in children with refractory or recurrent solid tumors and established a RP2D of 1.4 mg/m²/dose administered intravenously on days 1 and 8 of a 21-day cycle. This is the recommended dose in adult patients and, similar to the adult experience, the major DLT in children was neutropenia with common other significant toxicities including nausea and vomiting. Only minor prolongations in QTc that were not of clinical significance were observed. Any grade fatigue as an eribulin-related adverse event was less commonly reported in this study of children (30%) than has been reported in adults (~50%)^{18,19,29,30}. In addition, adult studies have consistently reported peripheral neuropathy in one-quarter of subjects; however, using pediatric specific neuropathy grading, there were no reports of peripheral neuropathy in children on this study^{19,29,30}. These data suggest that certain aspects of drug tolerance may be disparate in children when compared to adults. The decrease in non-hematological

toxicity compared to adults may, in part, be related to increased clearance of eribulin in children less than 12 years of age or potentially represents a pharmacodynamic difference.

Pharmacokinetics were highly-variable over the dose range studied with a median terminal half-life of 39.6 hours. These data are fairly consistent with adult studies^{31,32}. We did find, that there is an age dependent difference in BSA corrected clearance when young children (12 years old) were compared to older children and adolescents. While our older child cohort had a clearance that was similar to adults (1.3-2.3 L/h/m^{2.31}), our subjects 12 years old had a somewhat higher clearance of 2.4 L/h/m². Possible confounders to this analysis include the uneven distribution of subjects by age cohort in each dose level, intrinsic to a phase 1 study, and the fact that since eribulin is a lipophilic drug, the lower clearance in older children could be affected by the higher percentage of body fat generally found in older children. However, this suggests that studies of increased dosing in younger patients to ensure similar drug exposure to older patients might be considered. While previous studies in adults have shown that the incidence of neutropenia increases with dose and maximum exposure^{31,32}, we showed only a trend towards statistical significance in the major exposure parameters between our subjects who experienced grade 4 neutropenia and those who did not.

In this population of heavily pre-treated patients, one subject with sarcoma achieved a partial response and three others received 3 or more cycles of therapy. While not powered to answer questions of efficacy, this study suggests eribulin may be of interest in pediatric patients with Ewing or soft tissue sarcomas. A study evaluating eribulin activity in adolescents with relapsed osteosarcoma [median age was 16 years (range 12-25)] was recently completed (Children's Oncology Group study AOST1322, NCT02097238). Eribulin was given at 1.4 mg/m²/dose on days 1 and 8 of a 21-day cycles and was well tolerated but failed to show activity in patients with recurrent osteosarcoma. No patient demonstrated objective response and all patients had progression prior to 4 months³³. Consistent with these data³³, 0/9 of our subjects with osteosarcoma achieved any observable benefit.

Recent *in vitro* investigations have shown that eribulin induces changes in tumor biology beyond its established role in microtubule targeting. In breast tumors, leiomyosarcoma and liposarcoma xenografts and cell lines, eribulin has been shown to modify gene expression, induce tumor cell differentiation and cause tumor vasculature remodeling, all leading to cancer regression³⁴⁻³⁶. This tumor vasculature remodeling is thought to explain recent data demonstrating tumor eribulin exposures of 20-30 times that seen concurrently in the plasma in xenograft mice³⁷. Furthermore, a set of 26 microRNAs was discovered to differentiate responders and non-responders in a recent EORTC phase 2 study of eribulin in adults with various soft tissue sarcomas³⁸. Together, these data suggest that eribulin mesylate may be a targeted agent and highly effective in a select subset of tumor types. Our study supports the continued exploration of the potential benefit of eribulin mesylate both alone and in combination therapy in children with cancer.

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Abbreviations

ALL	Acute lymphoblastic leukemia
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
BSA	Body surface area
CBC	Complete blood count
CIRB	National Cancer Institute Central Institutional Review Board
CNS	Central nervous system
CYP3A4	Cytochrome P450 3A4
DLT	Dose-limiting toxicity
EKG	Electrocardiogram
FDA	US Food and Drug Administration
IC₅₀	Half maximal inhibitory concentration
MTA	Microtubule-targeting agent
MTD	Maximum tolerated dose
P-gp	P-glycoprotein
PK	Pharmacokinetics
QTc	Corrected QT interval
RCF	Relative centrifugal force
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose

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FIGURE 1.

(A) The plasma concentration versus time profile for patients treated at the 1.4mg/m² dose level. (B) The graph of AUC_{0-∞} (h•nM) vs Dose (mg/m²) demonstrating substantial variability in AUC values even at given dose levels. (C) Box and whisker plots of clearance corrected for body surface area (L/h/m²) differentiated by age and gender show that while there was no difference in clearance between males and females, there was a statistically significant difference in clearance when comparing younger children to older children and adolescents.

TABLE 1

Patient Characteristics for eligible Patients (n=23)

Characteristic	Number (%)
Age (years)	
Median	14
Range	3 - 17
Sex	
Male	12 (52)
Female	11 (48)
Race	
White	16 (70)
Asian	1 (4)
American Indian or Alaska Native	0 (0)
Black or African American	3 (13)
Unknown	3 (13)
Ethnicity	
Non-Hispanic	19 (83)
Hispanic	4 (17)
Unknown	0 (0)
Diagnosis	
Ewing sarcoma	4 (17.4)
Hepatoblastoma	2 (8.7)
Malignant peripheral nerve sheath tumor	1 (4.3)
Nephroblastoma	1 (4.3)
Neuroblastoma	1 (4.3)
Osteosarcoma	9 (39.1)
Soft tissue sarcoma, non-rhabdomyosarcoma	5 (21.7)
Prior Therapy	
Chemotherapy Regimens (n=23)	
Median	2
Range	1 - 5
Radiation Therapy (n=13)	
Median	1
Range	1 - 2

TABLE 2
Summary of Dose Limiting Toxicities for the Dose Escalation Phase and Expanded PK Phase

Trial Phase	Dose Level	Number of Patients Entered	Number of Patients Evaluable	Number of pts with DLT	DLTs
Dose Escalation	1.1 mg/m ²	6	6	0	-
	1.4 mg/m ²	6	6	1	Fatigue and Early neutropenia *
	1.8 mg/m ²	5	5	2	Early neutropenia (n = 1) and Neutropenia (n = 1) *
PK	1.4 mg/m ²	6	3	0	-

DLT = dose limiting toxicity, PK = pharmacokinetic

* Absolute neutrophil count (ANC) < 500/mm³ at any point prior to or on Day 8 which did not resolve to an ANC > 750/mm³ by Day 11 (Early) or an ANC < 500/mm³ at any time if for > 7 days

All Hematologic toxicities related to protocol therapy observed in evaluable patients (n=20)

TABLE 3

Toxicity Type	# of patients in Cycle 1 (n=19)				# of patients in later Cycles (Total Cycles) (n=8)				# of patients in Follow-Up (n=13)			
	By Maximum Grade				By Maximum Grade				By Maximum Grade			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	6	7	2		4	2			1	3		
Lymphocyte count decreased	2	3	10				5		1	1	3	
Neutrophil count decreased		4	4	8		1		5			1	
Platelet count decreased	6	1			3				3			
White blood cell decreased	3	3	7	5		2	3	1	1	1		

Note: Attribution as related to eribulin for all toxicities listed was DEFINITE, POSSIBLE or PROBABLE only.

All Non-Hematologic toxicities[‡] related to protocol therapy observed in evaluable patients (n=20)**TABLE 4**

	# of patients in Cycle 1 (n=19)			# of patients in later Cycles (Total Cycles) (n=8)			# of patients in Follow-Up (n=13)		
	By Maximum Grade			By Maximum Grade			By Maximum Grade		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	2					1			
Alopecia	1			1					
Anorexia	5				1				
Aspartate aminotransferase increased	1				1				
Fatigue	1	1							
Headache	3								
Hypokalemia		2							
Nausea	3			1	1				
Proteinuria				1			1		
Weight loss				2					

Note: Attribution as related to eribulin for all toxicities listed was DEFINITE, POSSIBLE or PROBABLE only.

[‡] All listed toxicities occurred at Grade 2 in 10% of subjects

TABLE 5

Median (range) Pharmacokinetic Parameters

DOSE (mg/m ²)	Number patients	C _{max} (nM)	t _{1/2} (hr)	AUC ₀₋₂₄ (h●nM)	AUC _{0-∞} (h●nM)	CL (L/hr/m ²)
1.1	6	464 (411-611)	55.6 (29.6-96.4)	478 (323-792)	1220 (572-3053)	1.26 (0.48-2.60)
1.4	11	570 (171-1056)	38.0 (24.2-82.8)	594 (261-1284)	1004 (592-4377)	1.88 (0.43-3.12)
1.8	5	382 (264-1245)	40.5 (29.1-66.0)	507 (326-2843)	899 (516-5975)	2.71 (0.41-4.78)
All Patients	22	510 (171-1245)	39.6 (24.2-96.4)	568 (261-2843)	1045 (516-5975)	1.75 (0.41-4.78)

C_{max}: maximum concentration; t_{1/2}: terminal half-life; AUC₀₋₂₄: exposure as calculated by area under the concentration versus time curve between the start of the infusion and 24 hours post the end of the infusion; AUC_{0-∞}: exposure as calculated by area under the concentration versus time curve between the start of the infusion and theoretical infinity time post the end of the infusion based on collected values; CL: clearance.