CLINICAL REVIEW

Application Type	Pediatric Exclusivity Determination
Application Number(s)	sNDA 22-065/S-006
Priority or Standard	Priority
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Division / Office	DDOP/OODP
Reviewer Name(s)	Amir Shahlaee, MD
CDTL	Ke Liu, MD, PhD
Review Completion Date	9/9/2011
Established Name	Ixabepilone
(Proposed) Trade Name	Ixempra®
Therapeutic Class	Microtubule inhibitor
Applicant	Bristol-Myers Squibb
Formulation(s)	Intravenous Injection
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that the Pediatric Exclusivity be granted for ixabepilone (Ixempra®) and the information from the pediatric trials be included in the ixabepilone (Ixempra®) labeling.

This recommendation is based on the review findings that the applicant responded to the Pediatric Written Request (PWR) fairly and in a manner generally consistent with good scientific principles despite minor discrepancies from the terms of the PWR.

A dose-finding phase 1 trial (CTEP-5425) and a single-arm, 2-stage, phase 2 study (ADVL0524) were conducted according to the PWR. CTEP-5425 identified the maximum tolerated dose (MTD) and Dose Limiting Toxicities (DLT) of ixabepilone in pediatric patients with relapsed and refractory solid tumors. The activity of ixabepilone in patients with six solid tumors commonly seen in pediatric age groups was subsequently studied in ADVL0524. None of the patients enrolled on either study had an objective tumor response, defined as Complete response (CR) or Partial response (PR), to treatment with ixabepilone. These results led to early closure of ADVL0524 after the first stage.

The primary deficiency identified in this application was inadequate enrollment of patients ≤ 21 years old in 3 of the 6 cohorts of study ADVL0524. This deficiency, however, did not change the overall conclusion that ixabepilone did not have overall benefits in the treatment of pediatric populations with the specified solid tumors. Although study ADVL-0524 did not completely meet the minimum enrollment requirements, important information regarding the use of ixebepilone in pediatric population has been obtained from these study results which will be beneficial to physicians and should be made available to the healthcare community. This reviewer recommends that this information be included in the revised labeling.

1.2 Risk Benefit Assessment

The risk profile of ixabepilone in the pediatric population appears to be similar to that of the adult population. However, this submission provided evidence that ixabepilone has no efficacy in the pediatric patients with solid tumors. Therefore, the risks associated with ixabepilone use in this population are without benefit and not recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Ixabepilone

Proprietary Name: Ixempra®

Applicant: Bristol-Myers Squibb
P.O. Box 4000,
Princeton, NJ 08543 4000

Pharmacological Class: microtubule inhibitor

Proposed Indication: There is no proposed pediatric indication.

Proposed Dosage and Administration: There is no proposed dose or route of administration in pediatric patients.

2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant is not proposing an indication in pediatrics.

2.3 Availability of Proposed Active Ingredient in the United States

Ixempra is available in the following formulations:

Ixempra for injection, 15 mg supplied with diluent for Ixempra, 8 mL.

Ixempra for injection, 45 mg supplied with diluent for Ixempra, 23.5 mL.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Ixabepilone (Ixempra) is approved for the following indications in adults:

- in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane
- as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine

However, ixebepilone has no approved indication in the pediatric population.

Table 1 includes a brief overview of the regulatory history of the proposed pediatric development plan, Proposed Pediatric Study Request (PPSR), and the PWR (amended twice) issued for study of ixabepilone use in children with cancer.

Table 1 Summary of regulatory activity

October 24, 2001	Inquiry regarding possible PWR sent to the FDA. Submission included copy of NCI Phase 1 study
November 20, 2006	Request sent for study CTEP-5425 and ADVL0524 to be considered in the PPSR Concerns raised: 1. Children's Oncology Group (COG) does not collect laboratory results in Phase 2 studies although abnormalities are reported as AEs 2. AE coding is done by Common Terminology Criteria for Adverse Events (CTCAE), not Medical Dictionary for Regulatory Activities (MedDRA). 3. Safety data reported according to Adverse events expedited reporting system (AdEERS). 4. Both studies under NCI held IND # 59,699. 5. Applicant notified FDA that they do not issue queries on NCI/CTEP sponsored studies.
March 6, 2007	1st complete PPSR
March 29, 2007 (Minutes from March 23 teleconference)	1. FDA requests PK data on patients 1-2 years of age. BMS will discuss this request with the PI. 2. BMS agrees to submit information on concomitant use of CYP3A4 inducers as part of final study report. 3. BMS provides justification for planning to enroll leukemia patients on phase 1 study at NIH. Solid tumor cohort had already completed enrollment.

	4. FDA notes that for the written request all patients should be ≤21 years of age. 5. The 10 plus 10 design of the phase 2 study applies to all solid tumor cohorts. 6. Age distribution of patients enrolled should be consistent with disease being studied. 7. FDA requests additional PK data for PK/PD analysis. Sponsor notes that COG does not collect PK data on phase 2 studies. 8. AE capture will be as per standard CTEP procedures. 9. FDA requested baseline labs to be collected in addition to abnormal labs. 10. Dose modifications and reasons for them should be captured. 11. Requested pre-clinical data outside the context of WR.
April 5, 2007	1. Discussion held between BMS and COG/NIH PI regarding obtaining additional PK data. 2. NIH study to be amended for enrollment of additional leukemia patients and lower age limit lowered to 12 months. 3. ADVL0524 should capture all baseline laboratory values and not only the abnormal ones. 4. Preclinical (xenograft) data provided. 5. No CYP3A4 inducers used as concomitant medications in CTEP5425.
June 22, 2007	WR issued
July 24, 2007	Xenograft data submitted
October 16, 2007	Ixabepilone approved for breast cancer indication
November 14, 2007	CMC amendment
December 12, 2007	Request for first amendment 1. enroll 2 instead of 3 patients ≤5

	years old at MTD 2. Request to remove PK and PD data from phase 2 requirements as no patients met their objective response requirements
February 29, 2008	Response to FDA inquiry of February 14, 2008: 61 eligible patients were enrolled in Stage 1 of ADVL0524. Median age (range) at entry was 13 yrs (3-36 yrs), 53 patients were ≤ 21 yrs of age.
March 4, 2008	Data from February 29, 2008 presented with breakdown by tumor categories.
April 22, 2008	1st Amendment to WR issued 1. PK data collection requirement for ADVL0524 removed 2. Only 2 patients ≤5 years must be treated at MTD on CTEP-5425.
September 14, 2009	Inquiry by FDA regarding status of studies and age groups enrolled.
September 18, 2009	Response to inquiry: 1. NGF level analysis not performed as limited neurotoxicity seen in CTEP-5425 2. Continuing plans to accrue 6-12 leukemia patients to CTEP-5425. 3. Full data on ADVL0524 not released by COG. However only 9 patients enrolled on Ewings/PNET arm.
June 15, 2010	Request for amendment #2: 1. Unable to perform NGF level and endogenous tubulin level assessments on CTEP-5425. 2. Unable to perform TTP analysis as no objective response on study CTEP-5425. 3. Two patients enrolled to leukemia cohort ineligible. Unable to recruit additional patients. 4. Automated volumetric measurement of pulmonary lesions was not performed on ADVL0524.
October 25, 2010	2nd Amendment to WR issued

	1. NGF and endogenous tubulin levels do not need to be measured 2. Volumetric lung metastasis measurement does not need to be performed.

Reviewer's note: All patients enrolled on CTEP-5425 and 43 of patients enrolled on ADVL0524 had been enrolled by November 20, 2006 when the PPSR was first submitted.

2.6 Other Relevant Background Information

The applicant is not seeking approval of ixabepilone for any pediatric indications.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains the debarment certificate. Complete data sets were provided for study CTEP-5425. However, the datasets for study ADVL0524 provided less information as they were based on COG criteria. Case report forms (CRFs) were provided for study ADVL0524 for all deaths within 30 days and discontinuations due to adverse events. Study CTEP-5425 had no deaths within 30 days or discontinuations due to adverse events. Overall quality and integrity of the submission is fair.

3.2 Compliance with Good Clinical Practices

The studies used as the basis for this pediatric exclusivity determination were sponsored by the National Cancer Institute's Cancer Therapeutics Evaluation Program (CTEP) under IND 59,699 and in accordance with CTEP standard operating procedures (submitted to the FDA and updated annually). CTEP standard operating procedures are in compliance with Good Clinical Practice (GCP), as required by the International Conference on Harmonization (ICH) E6 Guideline for GCP.

3.3 Financial Disclosures

Financial disclosures for studies CTEP-5425 and ADVL0524 were provided as part of this submission. There were no clinical investigators with disclosable financial interests in either study. Financial information, however, was missing on some sub-investigators at certain COG centers that participated in this study. The applicant has provided documentation of their attempts to locate these sub-investigators and obtain financial disclosure paperwork from them. The documentation provided by the applicant meets the requirement of demonstrating "due diligence" per 21 CFR 54.

Reviewer's note: Study CTEP-5425 is not a "covered clinical study" under 21 CFR 54 and financial disclosures were not required for this study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology in Pediatric Patients

4.4.1 Mechanism of Action

Ixabepilone is a semi-synthetic analog of epothilone B. Ixabepilone binds directly to β-tubulin subunits on microtubules, leading to suppression of microtubule dynamics. Ixabepilone suppresses the dynamic instability of αβ-II and αβ-III microtubules. Ixabepilone possesses low *in vitro* susceptibility to multiple tumor resistance mechanisms including efflux transporters, such as MRP-1 and P-glycoprotein (P-gp). Ixabepilone blocks cells in the mitotic phase of the cell division cycle, leading to cell death.

Reviewer's note: The sponsor has not submitted any data suggesting an alternative mechanism of action in pediatrics.

4.4.2 Pharmacodynamics

No new pharmacodynamic data were submitted as part of this application.

4.4.3 Pharmacokinetics

The applicant performed a pediatric population pharmacokinetic analysis (PPK) to accurately characterize ixabepilone pharmacokinetics (PK), and to determine the effects of covariates (age, gender, body weight and body surface area (BSA)) on ixabepilone PK in pediatric cancer patients. Subsequently, the pediatric PK parameters were compared with those from adult patients with the same dosing schedule enrolled in previous clinical trials.

The pediatric PPK analysis for ixabepilone was conducted with 294 plasma concentration values from 16 pediatric cancer subjects aged 2 to 18 years (median 12 years) enrolled in protocol CTEP-5425.

The adult PK parameters were obtained from a previous adult PPK model, in which the dataset included 12 ixabepilone monotherapy studies (2 Phase 1 and 10 disease specific Phase 2 studies), of which there were 5 clinical studies in which the ixabepilone dosing schedule was QD×5, every 21 days (CA163011, CA163012, CA163014, CA163036 and CA163051).
The pediatric PPK model showed that ixabepilone concentration-time data were well described by a linear, two-compartment, zero-order IV infusion model with first-order elimination. The model established a statistically significant relationship between clearance (CL) and BSA ($p<0.001$), where CL increases with an increase in BSA. This further supports the current body surface area based dosing of ixabepilone. No other covariates were statistically significant, after adjusting for the effect of BSA on CL.

The pharmacokinetics of ixabepilone in the pediatric patients were compared to those from 130 adult patients enrolled in clinical trials with the same dosing schedule. The median BSA normalized clearance of ixabepilone in pediatric patients (17 L/h/m^2) was similar to that in adult patients (20 L/h/m^2).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The studies submitted in support of NDA 22-065 S-006 are shown in Table 2.

Table 2 Listing of pediatric studies with ixabepilone submitted

Study	Objectives	Design	Test product and treatment regimen	Patient population	Number of patients enrolled
CTEP-5425	Determine the maximum tolerated dose (MTD), toxicity profile, dose-limiting toxicities (DLTs), pharmacokinetic (PK), and preliminary antitumor activity in pediatric patients	Phase 1, single-center, open-label, dose-escalation study of ixabepilone	Ixabepilone 3, 4.5, 6, 8, or 10 mg/m^2/day administered IV over 1 hour daily for 5 consecutive days, every 21 days	Subjects (≥ 2 years and ≤ 18 years of age) with a histologically confirmed, measurable or evaluable solid tumor refractory to standard treatment	21 enrolled 21 treated 3 mg/m^2/day (N=3) 4.5 mg/m^2/day (N=4) 6 mg/m^2/day (N=3) 8 mg/m^2/day (N=8) 10 mg/m^2/day (N=3)
ADVL0524	Determine the tumor objective response rate, time to progression, and toxicity profile of ixabepilone in children and young adults	Phase 2, open-label study of ixabepilone, 2-stage design	Ixabepilone, 8 mg/m^2/day (maximum 16 mg/day), administered IV over 1 hour daily for 5 consecutive days, every 21 days	Children and young adults with histologically confirmed malignancy at initial diagnosis or recurrence; target tumor types were embryonal or alveolar rhabdomyosarcoma, osteosarcoma, Ewing sarcoma/PNET, synovial sarcoma or MPNST, Wilms tumor, or neuroblastoma	61 enrolled 59 treated Rhabdomyosarcoma Osteosarcoma Ewing/PNET Synovial/MPNST Wilms Neuroblastoma

5.2 Review Strategy

The main focus of this review is to evaluate whether the applicant has successfully fulfilled the requirement set forth in the issued PWR (amended twice) for the eligibility determination on the pediatric exclusivity. To that end, the two studies submitted in this supplement, CTEP-5425 and ADVL0524 were fully reviewed. To perform this review, the entire submission, previous meeting minutes, the PPSR, the PWR, and published literature were reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study CTEP-5425

Study CTEP-5425 was the first phase 1, dose-escalation study to be performed in pediatrics. This study corresponds to study #1 on the pediatric written request.

Study Title:

"Phase I Trial and Pharmacokinetic Study of BMS-247550 (NSC 710428, ixabepilone), an Epothilone B Analog, in Pediatric Patients with Refractory Solid Tumors and Leukemias"

Study milestones and amendments:

September 1, 2001: Original Protocol

November 7, 2001: Study Initiation Date (First patient, First visit):

February 20, 2003: Amendment #1

1. The Pharmaceutical Information Section was updated to include information regarding the 15 mg and 30 mg vials in which BMS-247550 may be supplied, stored, reconstituted and prepared for patient administration; pertinent information was added regarding drug administration to the Route of Administration Section
2. A statement was added to include side effects that were reported on BMS-247550 trials, but the relationship to BMS-247550 was still undetermined
3. Incompatibilities for infusion were updated to include all components (and their catalog numbers) that can be used for the administration of BMS-247550
4. An additional Nerve Growth Factor sample at the end of therapy was added
5. The following administrative changes were made throughout the protocol: the date and amendment status were updated and the protocol and CTEP numbers

were added to the header; study personnel responsibilities were changed and name/contact information was updated to reflect these changes

November 28, 2003: Amendment #2

The reported AEs and potential risks list in the protocol and informed consent was updated

August 6, 2004: Amendment #3

1. The protocol title page, Sections 1.1.1, 1.2.3, and 8.1.1 were updated to include the generic name of BMS-247550, ixabepilone
2. New information was included regarding pharmaceutical supply, preparation and administration, storage, and stability
3. The reported AE and potential risks section was revised to include pleural effusion, and thrombosis and embolism as AEs
4. The agent specific AE list was revised to include tearing (watery eyes)

April 22, 2005: Amendment #4

1. Text was updated to clarify that all AEs were to be reported in Clinical Data Update System (CDUS) including the AEs reported in Adverse Event Expedited Reports (AdEERS)
2. As requested, the definition of expected and unexpected AEs was revised; and a statement was added describing the electronic reporting for expedited AE reporting
3. The CTEP AdEERS Table and bullet statements replaced the prior requirements
4. The Comprehensive Adverse Events and Potential Risks List (CAEPR) list was added and replaced the prior list of known toxicities and was updated to include toxicities that were not previously in the protocol or informed consent document

May 31, 2007: Amendment #5

1. Updated background sections regarding ongoing pediatric and adult studies of BMS-247550
2. Expanded the study at the MTD to treat a cohort of patients with refractory leukemia in order to define the tolerability of the solid tumor MTD of BMS-247550 in this patient population
3. Modified the eligibility criteria, exclusion criteria, and evaluation for patients enrolled on the expanded leukemia cohort
4. Modified the definition of DLT in the expanded leukemia cohort
5. Modified pharmacodynamic studies of BMS-247550 in patients with leukemia
6. A new consent document was written for patients enrolled in the expanded leukemia cohort

November 14, 2007: Amendment #6

1. Metronidazole was removed from the list of prohibited CYP3A4 inhibitors
2. Clarified that the intake of clotrimazole troches did not preclude from trial participation, as there is limited systemic absorption of clotrimazole following oral intake

December 4, 2007: Last patient, last visit (Study Completion Date)

April 21, 2009: Amendment #7

1. The Children's National Medical Center was added as a participating Institution; and the responsible investigators were included
2. Concomitant medication restrictions were added to the Exclusion Criteria section to clearly define the medications that were restricted
3. The storage, tracking, and handling or research specimens section was revised to reflect that there were no plans to store samples for future use
4. Multi-institutional guidelines were added to the protocol to outline guidelines for participating institutions for IRB approval, amendments and consents, patient registration, data collection and toxicity reporting, auditing and data and safety monitoring plans
5. The following statement was added: Unacceptable toxicities that have not resolved at the time of "off treatment" or "off study" must be followed until stabilization or resolution
6. Added for deaths in patients treated at the Children's National Medical Center or NCI that occur within 30 days of investigational agent must be reported to the IRB

April 1, 2010: Study terminated

Reviewer's note:
1. A reliable assay to measure the relative amounts of endogenous tubulin in PBMC that exists in the polymerized versus the unpolymerized state could not be established. Therefore, this pharmacodynamic assessment was not performed.
2. Although samples were collected, due to the minimal neurotoxicity, the investigator determined that NGF assessment was not warranted. Therefore, no NGF data was available for this study.
3. Two subjects were enrolled into the expanded leukemia cohort; however, due to issues with eligibility for 1 subject and rapid disease progression for the second subject, neither subject was able to be treated until disease progression. Despite attempts to increase enrollment through extensive investigator outreach and revised eligibility criteria, enrollment of the leukemia cohort was unsuccessful and the study was terminated. Letters were provided from phase 1 Program Chairs for COG and POETIC clarifying lack of investigator interest in pursuing a study of ixabepilone in leukemia.
4. These changes were reported to the FDA and led to amendment #2 of the written request.
5. The primary reason behind Amendment #7 was to expand the number of investigators and increase the number of patients recruited to the leukemia cohort.

Study Objectives:

PRIMARY OBJECTIVES:

1. Determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of the epothilone B analog, BMS-247550 (ixabepilone), administered as a one hour infusion daily for five consecutive days (daily x 5), every 21 days in children with cancer.
2. Define the toxicity spectrum of BMS-247550 on the daily x 5 schedule in children with cancer.
3. Evaluate the plasma pharmacokinetics of BMS-247550.
4. Evaluate the pharmacodynamics of BMS-247550 using an assay that measures the relative amounts of endogenous tubulin in peripheral blood mononuclear cells (PBMC) that exists in the polymerized versus the unpolymerized state.
5. Measure nerve growth factor (NGF) levels before and after the start of treatment with BMS-247550 as a potential surrogate marker for the development of peripheral neuropathy.

SECONDARY OBJECTIVES:

1. Measure responses to BMS-247550
2. Compare the tolerance, toxicity profile, MTD, DLT, pharmacokinetics and pharmacodynamics of BMS-247550 in children treated on this study and adults

treated on the Medicine Branch, NCI phase I trial of BMS-247550, which uses the same trial design and study endpoints.

OBJECTIVES IN THE EXPANDED LEUKEMIA COHORT

1. At the solid tumor MTD, assess the safety and tolerability of BMS-247550 in patients with refractory or relapsed leukemia.
2. Evaluate the plasma pharmacokinetics of BMS-247550 in patients with refractory or relapsed leukemia.
3. Evaluate the extent of tubulin polymerization in leukemic blasts at baseline and after treatment with BMS-247550 ex-vivo.
4. Compare the effects of tubulin polymerization in leukemic blasts with BMS-247550 versus paclitaxel ex-vivo with and without the presence of a potent P-glycoprotein (Pgp) inhibitor.
5. Evaluate the activity of known drug transporters in drug resistant leukemias in leukemic blasts.

Study Design:

This is a single-center, phase I, open label, trial of intravenous BMS-247550 in pediatric patients with advanced, refractory solid tumors including brain tumors. Patients will receive BMS-247550 intravenously over 60 minutes daily for 5 consecutive days (day 1-5), every 21 days (21 day treatment cycle). Treatment cycles can be repeated immediately upon completion of the previous 21 day cycle provided that the patient has recovered from the toxicities of the previous cycle and the criteria for removal of a patient from study have not been met. Treatment cycles can be extended to 28 days to allow for patients to recover from toxicity.
During cycle 1, detailed pharmacokinetics of BMS-247550 will be obtained after the first dose (day 1) and then peak and trough samples will be obtained after the second-fifth dose (days 2-5), and if feasible, 24 and 48 hours after the fifth dose (day 5) on day 6 and 7. This dose-finding study follows a 3x3 design and is designed to determine the maximum tolerated dose (MTD) and toxicity profile of BMS-247550 in pediatric patients with solid tumors. Once the MTD of BMS-247550 is reached, that dose level will be expanded to up to 12 patients in order to study the pharmacokinetics and pharmacodynamics of BMS-247550 in a broad age range of patients. The MTD is defined as the dose level immediately below the dose level at which ≥2 patients in a cohort (dose level) of 2 to 6 patients experienced a DLT. The cohort at the MTD should be expanded to as many as 12 patients in order to gain experience with the toxicities and pharmacokinetics of BMS-247550 over a broad age range of patients. An attempt should be made to treat at least 3 patients who are ≥12 yr of age and at least 3 patients who are <12 yr of age. In the expanded cohort at the MTD, <25% (≤3 patients out of 12) of patients should have experienced DLT.

A cohort of 6 additional patients with relapsed or refractory leukemia will be evaluated at the solid tumor MTD. In the expanded cohort of leukemia patients treated on 8 mg/m^2/dose daily x 5 days every 21 days will have no further dose escalation if tolerated. The solid tumor MTD will be considered the leukemia MTD and recommended phase II dose. BMS-247550 8 mg/m^2/dose daily x 5 days every 21 days will be declared intolerable for patients with leukemia if ≥ 33% of a cohort of at least 6 patients experience a DLT. If BMS-247550 at 8 mg/m^2/dose daily x 5 days every 21 days is declared intolerable in this population, an additional cohort of patients will be enrolled at 6 mg/m^2/dose daily x 5 days every 21 days.

Eligibility Criteria:

INCLUSION CRITERIA FOR PATIENTS WITH SOLID TUMORS

1. AGE: Patients must be ≥2 years and ≤18 years of age.

2. DIAGNOSIS: Histologically confirmed solid tumors, which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing's sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, and primary brain tumors. In patients with brain stem or optic gliomas the requirement for histological confirmation may be waived.

3. MEASURABLE/EVALUABLE DISEASE: Patients must have measurable or evaluable tumors.

4. PRIOR THERAPY:
    - The patient's cancer must have relapsed after or failed to respond to frontline curative therapy and there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities.
    - Patients must have had their last dose of radiation therapy at least four weeks prior to study entry, their last dose of chemotherapy at least 28 days prior to study entry (6 weeks for nitrosoureas), and their last dose of any investigational cancer therapy at least 30 days prior to study entry.
    - Patients must have recovered from the toxic effects of all prior therapy before entry onto this trial.
    - Patients with brain tumors must be on a stable or tapering dose of corticosteroids for 7 days prior to the baseline scan performed for the purpose of assessing response to therapy on this study.
    - Patients should be off colony stimulating factors such as Filgrastim (G-CSF), sargramostim (GM-CSF), and IL-11 (with the exception of erythropoietin) for at least 72 hours prior to study entry.

5. PERFORMANCE STATUS: Patients >10 years must have a Karnofsky performance level ≥ 50, and children ≤10 years must have a Lansky performance level ≥50. Patients who are unable to walk because of paralysis or weakness, but who are up in a wheelchair will be considered ambulatory for the purpose of calculating the performance score.

6. HEMATOLOGIC FUNCTION: Patients must have adequate bone marrow function, defined as a peripheral absolute neutrophil count of ≥1,500/μL, and a platelet count ≥100,000/μL.

7. HEPATIC FUNCTION: Patients must have adequate liver function, defined as bilirubin <1.5 x the upper limit of normal, SGPT (ALT) and SGOT (AST) <2.5 x the upper limit of normal.

8. RENAL FUNCTION: Patients must have an age-adjusted normal serum creatinine (see Table 3) OR a creatinine clearance ≥60 mL/min/1.73 m^2.

Table 3 Age adjusted Creatinine levels in Pediatric Patients

Age (Years)	Maximum Serum Creatinine (mg/dl)
≤5	0.8
5< age ≤10	1.0
10< age ≤15	1.2
>15	1.5

9. INFORMED CONSENT: All patients or their legal guardians (if the patient is <18 years old) must sign a document of informed consent (screening protocol) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardians must sign the protocol specific informed consent to document their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (other than the studies which were performed to determine patient eligibility).

10. DURABLE POWER OF ATTORNEY (DPA): Patients who have brain tumors and who are 18 years of age will be offered the opportunity to assign a DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

11. BIRTH CONTROL: Subjects of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while they are being treated on this study.

INCLUSION CRITERIA FOR EXPANDED COHORT OF LEUKEMIA PATIENTS

1. AGE: Patients must be ≥ 12 months and ≤21 years of age.

2. DIAGNOSIS: Patients must have a diagnosis of relapsed or refractory leukemia.

3. DISEASE STATUS: Patients with refractory or second or greater relapsed leukemia must have greater than 25% blasts in the bone marrow (M3 bone marrow).
   Active extramedullary disease (except for leptomeningeal disease) may also be present.

4. THERAPEUTIC OPTIONS: Patients' current disease state must be one that has relapsed after or failed to respond to frontline curative therapy and there must not be other potentially curative treatment options available. Curative therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities.

5. PRIOR THERAPY: Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

   - Myelosuppressive chemotherapy or monoclonal antibody treatment: Patients must have had their last dose of chemotherapy at least two weeks prior to study entry. Patients with acute promyelocytic leukemias (APL) must be refractory to treatment with retinoic acid and arsenic trioxide.
   - Patients with Philadelphia (Ph) chromosome positive CML must be refractory to imatinab (Gleevac).
   - Patients must not have received treatment with a monocolonal antibody within 3 weeks of entry onto this study.
   - Hematopoietic growth factors: At least 7 days since the completion of therapy with a growth factor with the exception of erythropoietin.
   - Biologic (anti-neoplastic agent): At least 7 days since of the completion of therapy with a biologic agent. 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 known to occur. The duration of this interval must be discussed with the study chair.
   - Steroid Therapy: Must be on a stable or tapering dose of corticosteroids for 7 days prior to enrollment on this study.

- Radiation Therapy: ≥ 2 weeks for local palliative XRT; ≥3 months must have elapsed if prior to TBI, craniospinal XRT, or ≥ 50% of radiation of pelvis; ≥ 6weeks must have elapsed if other substantial bone marrow radiation.
- Stem Cell Transplant or Rescue: No evidence of acute graft vs. host disease and ≥ 2 months must have elapsed.

6. PERFORMANCE STATUS: Patients >10 years must have a Karnofsky performance level ≥50, and children ≤10 years must have a Lansky performance of ≥ 50.

7. HEMATOLOGIC FUNCTION: Patient's must have a platelet count ≥20,000/μL (may receive platelet transfusions) and Hemoglobin of ≥8.0 gm/dL (may receive RBC transfusions).

8. HEPATIC FUNCTION: Patients must have adequate liver function defined as bilirubin <1.5 x the upper limit of normal , SGPT (ALT) and SGOT (AST) < 2.5 x the upper limit of normal.

9. RENAL FUNCTION: Patients must have an age-adjusted normal serum creatinine (see Table 3) OR a creatinine clearance of ≥60 mL/min/1.73 m^2.

10. INFORMED CONSENT: All patients or their legal guardians (if the patients is <18 years old) must sign a document of informed consent (screening protocol) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardians must sign the protocol specific informed consent to document their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (other than the studies which were performed to determine patient eligibility).

11. DURABLE POWER OF ATTORNEY (DPA): Patients who are 18 years of age will be offered the opportunity to assign a DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

12. BIRTH CONTROL: Subjects of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while they are being treated on this study.

EXCLUSION CRITERIA FOR REFRACTORY SOLID TUMORS AND LEUKEMIAS

1. Clinically significant unrelated systemic illness, such as serious infections, hepatic, renal or other organ dysfunction, which in the judgment of the Principal or Associate Investigators of this protocol would compromise the patient's ability

to tolerate the investigational agent or are likely to interfere with the study procedures or results.

2. Pregnant or breast feeding females are excluded because BMS-247550 may be harmful to the developing fetus or nursing child.

3. Patients currently receiving other investigational agents.

4. CONCOMITANT MEDICATION RESTRICTIONS:

    - Patients may not be currently receiving strong inhibitors of CYP3A4, and may not have received these medications within 1 week of entry. These include:
        - Antibiotics: Clarithromycin, erythromycin, troleandomycin
        - Anti-HIV agents: delaviridine, nelfinavir, amprenavir, ritonavir, idinavir, saquinavir, lopinavir
        - Anti-fungals: itraconazole, ketoconazole, fluconazole (doses > 3mg/kg/day), voriconazole
        - Anti-depressants: nefaxodone, fluovoxamine
        - Calcium Channel Blockers: verapamil, diltiazem
        - Anti-emetics: Do not use aprepitant (Emend) as it is a CYP3A4 substrate, moderate inhibitor and inducer
        - Miscellaneous: amiodarone
        - In addition, grapefruit juice should be avoided as it inhibits CYP34A.
    - Patients must also avoid St. John's Wort, an inducer of CYP34A.
    - Patients may not be taking enzyme-inducing anticonvulsants, and may not have received these medications within 1 week of entry, as these patients may experience different drug disposition. These medications include:

        - Carbamazepine (Tegretol)
        - Felbamate(Felbtol)
        - Phenobarbital
        - Phenytoin (Dilantin)
        - Primidone (Mysoline)
        - Oxcarbazepine (Trileptal)

    - Patients with preexisting grade 2 or greater sensory neuropathy.
    - Patients with known severe prior hypersensitivity reaction to agents containing Cremophor EL.
    - For patients with solid tumors only: Patients with a history of bone marrow transplantation within the previous 6 months or extensive radiotherapy (craniospinal radiation, total body radiation, or radiation to more than half of the pelvis).

- For patients with leukemia only: Patients with active CNS leukemia (CNS3).

Treatment Compliance:

The NCI CCR will audit this trial via contract for compliance and safety. Independent monitors will visit participating sites and review case report forms and source documentation. Missing or spurious information and protocol deviations will be communicated in a report to the trial coordinating center. Protocol deviations, which may result in compromise to safely administer study drug, or to determine study endpoints will be included in the annual protocol review for the NCI IRB.

Study Treatments, Concomitant Medications, and Dose Modifications:

STUDY TREATMENTS

BMS-247550 will be administered on a days 1, 2, 3, 4, and 5 of each 21 day cycle as a one hour intravenous infusion. The infusion start time may be adjusted no more than 2 hours on subsequent treatment days from the start time on the previous day. Administration may be through either a peripheral IV site or a central venous access catheter.

CONCOMITANT MEDICATIONS

There is a potential for hypersensitivity reactions because of the presence of CremophorEL® in the formulation of BMS-247550. The suggested regimen for treatment of hypersensitivity reactions is as follows:

Primary prophylaxis (1 hour to 30 minutes prior to BMS-247550):

H1 blocker (diphenhydramine 1 mg/kg IV or PO, maximum single dose 50 mg).
H2 blocker (ranitidine 1 mg/kg IV, maximum single dose 50 mg IV **OR** 2 mg/kg PO, maximum single dose 150 mg PO **OR** another equivalent H2 blocker).

- Cancer chemotherapy, radiation therapy, immunotherapy, or investigational agents other than agents specified in this protocol cannot be administered to patients receiving BMS-247550. If these treatments are administered the patient will be removed from study.
- Patients with brain tumors may receive corticosteroids for the control of symptoms related to tumor-associated edema.
- Filgrastim (G-CSF) can be administered at 5 µg/kg/day subcutaneously only if neutropenia lasts for longer than 5 days or if the patient experiences clinical or culture confirmed septicemia associated with neutropenia.

- Erythropoietin may be administered at the discretion of the primary physician of the patient or an associate investigator of the protocol.
- The use of other growth factors as sargramostim (G-MCSF), and IL-11 is not allowed while on study.
- No other investigational agents may be used while enrolled on this trial.
- Patients may continue standard intrathecal prophylactic therapy.
- Allopurinol is recommended for any patient with an elevated white blood cell count (blast count ≥20,000/µl).

CONCOMITANT MEDICATION RESTRICTIONS:

Patients may not be currently receiving strong inhibitors of CYP3A4, and may not have received these medications within 1 week of entry. These include:

- Antibiotics: Clarithromycin, erythromycin, troleandomycin
- Anti-HIV agents: delaviridine, nelfinavir, amprenavir, ritonavir, idinavir, saquinavir, lopinavir
- Anti-fungals: itraconazole, ketoconazole, fluconazole (doses > 3mg/kg/day), voriconazole
- Anti-depressants: nefaxodone, fluovoxamine
- Calcium Channel Blockers: verapamil, diltiazem
- Anti-emetics: Do not use aprepitant (Emend) as it is a CYP3A4 substrate, moderate inhibitor and inducer
- Miscellaneous: amiodarone
- In addition, grapefruit juice should be avoided as it inhibits CYP34A.
- Patients must also avoid St. John's Wort, an inducer of CYP34A.
- Patients may not be taking enzyme-inducing anticonvulsants, and may not have received these medications within 1 week of entry, as these patients may experience different drug disposition. These medications include:

    - Carbamazepine (Tegretol)
    - Felbamate(Felbtol)
    - Phenobarbital
    - Phenytoin (Dilantin)
    - Primidone (Mysoline)
    - Oxcarbazepine (Trileptal)

DOSE REDUCTIONS

All dose modifications should be discussed first with the Principal Investigator or an associate investigator.

- Patients who have not experienced a DLT may be continued on therapy if, in the opinion of the investigator, they are deriving some benefit as evidenced by a

decrease in the size or stabilization of the tumor or a decrease in tumor-related symptoms such as pain; and the off-study criteria have not been fulfilled.

- Patients who experience a DLT from BMS-247550 on dose levels 1-4 should have a dose reduction of BMS-247550 to the next lower dose level (2 mg/m^2/dose -33% dose reduction- for patients treated at dose level 1) for their subsequent course of treatment, if in the judgment of the treating physician they have benefited from the prior dose of BMS-247550.
- Patients who experience DLT after a dose reduction can have a second dose reduction to the next lower dose level (1.4 mg/m2/dose -30% dose reduction- for patients treated at dose level 1), but if DLT occurs after the second dose reduction, the patient should be removed from the study.
- No dose re-escalation will be allowed after a dose reduction.
- For Leukemia patients who achieve a PR or CR (Section 5.2.5) after administration of BMS-247550, and peripheral counts do not recover (ANC >1000/µl, platelet >75,000/µl) by day 35 after start of administration of BMS-24570, a bone marrow examination will be performed to assess the disease status. If the bone marrow examination confirms disease progression, BMS-247550 treatment will be discontinued permanently. If the bone marrow continues to be consistent with partial or complete remission, the next cycle of BMS-247550 will be held, and these patients will be started on Filgrastim (granulocyte colony stimulating factor), administered subcutaneously (s.c.) at a daily dose of 5 µg/kg until the ANC has recovered to >1000/µl. Filgrastim will then be discontinued, and the following cycle of BMS-247550 will restart at a reduced dose (dose level below current dose). For patients who remain in CR, but develop repeated grade 4 neutropenia, further dose de-escalations may be performed after contacting the Principal Investigator of the protocol.
- Patients who present with grade 4 neutropenia (ANC <500/µl) and a bone marrow examination consistent with a complete response at the end of cycle evaluation will continue the rest period until counts recover to ANC >1000/µl. If peripheral counts do not recover by day 35 after start of administration of BMS-247550, these patients will be started on Filgrastim (granulocyte colony-stimulating factor), administered subcutaneously (s.c.) at a daily dose of 5 µg/kg until the ANC has recovered to >1000/µl. Filgrastim will then be discontinued, and these patients will restart BMS-247550 at a reduced dose (dose level below current dose).
- Patients who present with a non-diagnostic hypocellular bone marrow at the end of cycle bone marrow evaluation will continue the rest period, and another bone marrow aspiration will be performed within 7 to 14 days to assess the disease status prior to starting subsequent cycles of BMS-247550.

<u>Dose escalation:</u>

The starting dose of BMS-247550 is 3 mg/m^2/dose for 5 consecutive days (days 1-5) every 21 days, and the dose escalation scheme is described in Table 4. This study follows a 3x3 dose escalation design.

Table 4 Dose escalation schema for Study CTEP-5425

BMS-247550	
Dose Level	Dose mg /m^2/day
1	3
2	4.5
3	6
4	8

Should the fourth dose level (8 mg/m^2/day) be tolerated, subsequent dose levels will be at 30% increments (i.e., 10 mg/m^2/day, 13 mg/m^2/day, etc.). If dose level 1 exceeds the maximum tolerated dose (MTD), subsequent patients will be entered at a 2 mg/m^2/dose level, which is a 33% dose reduction from dose level 1.

Patients with leukemia will receive BMS-247550 at a dose of 8 mg/m^2/dose daily x 5 days every 21 days. If this dose is tolerated, there will be no further dose escalation. If ≥33% of patients experience a DLT, an additional 6 to 9 patients with refractory leukemia will be treated one dose level below at 6mg/m^2/dose daily x 5 days every 21 days.

Intrapatient dose escalations to the next highest dose level will be allowed in patients if the patient's worst BMS-related toxicity on the prior dose level was grade ≤1 non-hematologic toxicity, and grade ≤2 hematologic toxicity. Intrapatient dose escalations should not be performed if the patient is being treated at the MTD (i.e., the next higher dose level has been determined to be too toxic). Patients may only be escalated one dose level above the enrollment dose level.

Discontinuation/Withdrawal from Study

ADMINISTRATIVE

- Patient refusal of further treatments: Reasons must be noted on the patient's record.
- It is deemed in the best interest of the patient. In this instance the Principal Investigator should be notified and the reasons for withdrawal should be noted in the patient's record.
- Serious protocol violation as determined by the PI.

TOXICITY

- Any patient who develops significant irreversible (≥2 weeks duration) organ dysfunction (grade 4, hematologic or non-hematological toxicity – CTC v.2) considered primarily to be BMS-247550 toxicity will be removed from study. The Principal Investigator should be notified immediately in the event of severe or life-threatening toxicity.
- Patients who develop DLT attributable to BMS-247550 (Section 3.1.4) following 2 dose reductions will be removed from the study.

TUMOR PROGRESSION

- Any patient with clinical or radiographic evidence of progressive disease following any treatment cycle will be removed from study. If possible, tumor progression should be documented by the appropriate radiological study.
- For the expanded leukemia cohort, patients will be removed from the protocol in the absence of objective response or clinical improvement.

CONCURRENT SERIOUS MEDICAL CONDITION

- The development of a concurrent serious medical condition that might preclude or contraindicate the further administration of BMS-247550.

CRITERIA FOR OFF STUDY

- Thirty days after last dose of investigational agent.
- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission
- Entry onto another therapeutic study

Patient evaluations:

Ixabepilone (Ixempra) is approved for the following indications in adults:

- in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane
- as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine

However, there is no approved indication for the pediatric population.

Table 1 includes a brief regulatory history regarding the proposed pediatric development plan, Proposed Pediatric Study Request (PPSR), and the PWR (amended twice) issued for use of ixabepilone in children with cancer.

Table 1 lists the required observations for the solid tumor cohort while Table 6 lists the required observation for patients with leukemia.

Table 5 Schedule of required observations for solid tumor patients on CTEP-5425

OBSERVATION	Prior to Each Cycle	Weekly	Twice Weekly	Post Study
History & Physical examination + tumor measurements	X	X		X
Neurological exam (PEG board, WEST-hand esthesiometer test)	X			X
Performance status	X			X
Body Surface Area	X			
Urinalysis	X			X
Urine pregnancy test*	Cycles 1,4,7,10			
CBC, differential, platelets	X		X	X
PT, PTT	X			X
Electrolytes, BUN and creatinine	X	X		X
Ca^{+2}, Mg^{+2}, PO_4^-, uric acid	X	X		X
LDH, AST, ALT, bilirubin, Alk Phos, bilirubin (T + D)	X	X		X
Total protein, albumin, cholesterol, triglycerides	X			X
Tumor measurements (radiology)	Cycles 1,2,4,6,8			X
Pharmacokinetic Studies*	Days 1-7			
Pharmacodynamic Studies*	Day 1,			
Nerve Growth Factor	Cycles 1,2, 3**			X

*First cycle only

**And if development of neuropathy

Table 6 Schedule of required observations for leukemia patients on CTEP-5425

OBSERVATION	Prior to Each Cycle	Weekly	Twice Weekly	Post Study
History & Physical examination	X	X		X
Bone Marrow Aspirate[1]	X[2]			
CSF cytology[3]	Cycle 1			
Neurological exam	X			X
Performance status	X			X
Body Surface Area	X			
Urinalysis	X			X
Urine pregnancy test	Cycles 1,4,7,10			
CBC, differential, platelets	X		X	X
PT, PTT	X			X
Electrolytes, BUN and creatinine	X	X		X
Ca^{+2}, Mg^{+2}, PO_4^-, uric acid	X	X		X
LDH, AST, ALT, bilirubin, Alk Phos, bilirubin (T + D)	X	X		X
Total protein, albumin, cholesterol, triglycerides	X			X
Tumor measurements (radiology)[4]	X			X
Pharmacokinetic Studies[5]	Days 1-7			
Pharmacodynamic Studies[5]	X[6]			

[1] Bone Marrow Biopsy recommended if unable to obtain adequate aspirate
[2] Prior to cycle 2 and 3 and then subsequently every other cycle
[3] Subsequent cycles required only if clinically indicated
[4] To be done only if extramedullary disease is present
[5] Cycle 1 only
[6] For patients with circulating blasts: 5ml of peripheral blood to be collected at the time of marrow examination and also at day 1 post BMS infusion and day 5 pre and post BMS infusion (see Section 3.6.1).

Criteria for Efficacy Assessment:

RESPONSE CRITERIA FOR PATIENTS WITH SOLID TUMORS
The CTEP response criteria for solid tumors (RECIST) will be used to assess response in patients with solid tumors.

RESPONSE CRITERIA FOR PATIENTS WITH LEUKEMIA

- Complete Response (CR): M1 bone marrow (<5% blasts) with adequate bone marrow cellularity, no evidence of circulating blasts or extramedullary disease and normalization of peripheral blood counts (neutrophil count ≥1,500/µL and platelets ≥ 100,000/µL).

- Partial Response (PR): M2 bone marrow (≥5% but <25% blasts), with no evidence of circulating blasts or extramedullary disease and normalization of peripheral blood counts (neutrophil count ≥1,500/µL and platelets ≥ 100,000/µL).

- Progressive Disease (PD): An increase of at least 25% in the absolute number of circulating leukemic cells, development of extramedullary disease, or other laboratory or clinical evidence of PD.

All patients initially considered evaluable will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories:

1. complete response,
2. partial response,
3. stable disease,
4. progressive disease,
5. early death from malignant disease,
6. early death from toxicity,
7. early death because of other cause, or
8. unknown (not assessable, insufficient data).

All of the patients, who met the eligibility criteria and are evaluable, will be included in the main analysis of responses. Patients in response categories 4-8 will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of a response. All conclusions will be based on all eligible patients. Sub-analyses may be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.).
However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

Criteria for Safety Assessment:

This study will utilize the Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 for toxicity and Adverse Event reporting with the exception of grading motor or sensory neuropathy, which will be graded as outlined below.

DEFINITION OF DOSE-LIMITING TOXICITY (DLT) FOR PATIENTS WITH SOLID TUMORS

Toxicity will be graded according to the version 2.0 of the NCI Common Toxicity Criteria (CTC v 2.0) (http://ctep.info.nih.gov) with the exception of motor or sensory neuropathy. The criteria defined below, will be used to grade sensory and motor neuropathy:

Motor neuropathy:

Grade 1: Subjective weakness, but no deficits detected on neurological exam
Grade 2: Weakness that alters fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
Grade 3: Unable to perform fine motor tasks (buttoning shirt, writing or drawing, using eating utensils) or unable to ambulate without assistance
Grade 4: Paralysis

Sensory neuropathy:

Grade 1: Paresthesias, pain, numbness that do not require treatment or interfere with extremity function
Grade 2: Paresthesias, or pain, or numbness that are controlled by non-narcotic medications or alter fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
Grade 3: Paresthesias or pain that are controlled by narcotics or impair extremity function (gait, fine motor skills as outlined above) or quality of life (loss of sleep, ability to perform normal activities severely impaired).
Grade 4: Complete loss of sensation or pain that is not controlled by narcotics.

For the definition of the maximum tolerated dose (MTD), dose-limiting toxicity will be determined from observations during the first treatment cycle.

Hematologic (HDLT) and non-hematologic (NH-DLT) dose-limiting toxicity will be defined differently as follows:

H-DLT: Grade 4 neutropenia (<500/μL) of ≥5 days duration or grade 4 thrombocytopenia (<10,000/μL) occurring on ≥2 days of a treatment cycle (for the purpose of this trial, if a patient receives a platelet transfusion for a platelet count that is <20,000/μL but >10,000/μL, this will be scored as grade 4 thrombocytopenia), or failure to recover a neutrophil count to ≥1,500/μL or a platelet count of ≥75,000/μL by day 28 of the treatment cycle.

NH-DLT: Any grade 3 or 4 non-hematologic toxicity related to BMS-247550 or failure to recover to grade ≤1 toxicity or to baseline toxicity, if greater than grade 1 by day 28 of the treatment cycle with the exception of:

- Grade 3 nausea or vomiting during the first treatment cycle, which can be successfully treated with antiemetics. In subsequent treatment cycles antiemetics will then be administered prior to administration of BMS-247550.
- Grade 3 elevations in SGPT or SGOT, which recover to ≤ grade 1 toxicity by day 28 of the treatment cycle.

DEFINITION OF DOSE-LIMITING TOXICITY (DLT) FOR LEUKEMIA PATIENTS

Toxicity will be graded using the same criteria as in solid tumors. However, hematologic (H-DLT) and non-hematologic (NH-DLT) dose-limiting toxicity will be defined differently as follows:

H-DLT:
Patients with leukemia will not be evaluable for hematological toxicity (i.e. a drop in the blood counts will not be used to assess tolerability, because blood cell production is compromised by the underlying bone marrow infiltration by leukemia cells).

NH-DLT: Any grade 3 or 4 non-hematologic toxicity related to BMS-247550 or failure to recover to grade ≤1 toxicity or to baseline toxicity, if greater than grade 1 by day 28 of the treatment cycle with the exception of:

- Grade 3 nausea or vomiting during the first treatment cycle, which can be successfully treated with antiemetics. In subsequent treatment cycles antiemetics will then be administered prior to administration of BMS-247550.
- Grade 3 elevations in SGPT or SGOT, which recover to ≤ grade 1 toxicity by day 28 of the treatment cycle.
- Serious events that are judged to be disease-related including the following non-hematological toxicities will not be considered dose limiting:
  - Coagulation: Grade 3 or 4 DIC in patients with APL or AML
  - Metabolic/Laboratory: Grade 3 or 4 hypokalemia, hypomagnesaemia, hyponatremia, or hypophosphatemia that is related to administration of antifungal medications and is corrected with IV or oral supplementation.
  - Tumor lysis syndrome: Grade 3, present

5.3.2 Study ADVL0524

Study ADVL0524 was the study used to evaluate the efficacy of ixabepilone in the treatment of 6 cohorts of patients with pre-specified types of pediatric solid tumors. This study corresponds to study #2 on the pediatric written request.

Study Title

"Phase II trial of ixabepilone (BMS-247550), an Epothilone B Analog, in children and young adults with refractory solid tumors"

Study milestones and amendments

May 31, 2006: Study initiation

April 02, 2007: Amendment 1

1. Editorial/administrative changes
2. Age at diagnosis for Wilms tumor and Neuroblastoma clarified as "≤21 years"
3. Age at diagnosis for other study cohorts clarified as "≤35 years"
4. Use of steroids for pain or nausea allowed
5. Baseline Hgb requirement increased from ≥8 to ≥10 gm/dl
6. Baseline creatinine requirement increased from ≥60mL/min/1.73m^2 to ≥70mL/min/1.73m^2 gm/dl.
7. Definition of Liver function as defined by SGPT (ALT) levels revised to meet COG standards
8. Criteria for dose reduction clarified: patients needed to have at least stable disease to remain on study if dose reduced.
9. Radiation therapy removed from list of allowed agents on study
10. Clarified that hypersensitivity reactions are common with initial doses of ixabepilone, are not dose related and will not be considered dose-limiting.
11. Removed requirement for additional bone marrow studies except at study entry.
12. Safety profile information including risks for pregnancy updated.

October 22, 2007: Amendment 2

1. Editorial/administrative changes
2. Definition of DLT clarified: "doses which require reduction or treatment modification during subsequent treatment cycles, will be considered dose-limiting".
3. Updated CMC and administration guidelines updated.
4. Updated section on prevention and treatment of hypesensitivity reactions.
5. Instructions/warnings regarding co-administration with CYP3A4 inducers/inhibitors and anti-HIV agents added.
6. Safety information updated.
7. Changes to informed consent.

Reviewer's note: The amendments were all administrative/editorial in nature and did not affect the study design and outcome.

December 5, 2008: Study completion

Study Objectives:

- To determine the response rate to ixabepilone in various strata of recurrent solid malignant tumors of childhood and young adulthood. The target tumors are:

    1. Embryonal or alveolar rhabdomyosarcoma
    2. Osteosarcoma
    3. Ewing sarcoma/Peripheral neuroectodermal tumor (PNET)
    4. Synovial sarcoma or malignant peripheral nerve sheath tumor (MPNST)
    5. Wilms tumor
    6. Neuroblastoma

- To determine the time to progression for each tumor strata.

- To prospectively evaluate the feasibility and utility of automated volumetric tumor measurement in patients with measurable pulmonary metastases, and descriptively compare volumetric measurements to 1D (RECIST criteria) and 2D (WHO criteria) measurements.

- To further define and describe the toxicities of ixabepilone.

Study Design:

Study ADVL0524 was a multi-center, cooperative group study that was performed by the Children's Oncology Group (COG). This study was a single-arm, open-label, phase 2, study designed to assess the activity of ixabepilone in 6 strata of pediatric solid tumors. Within each category a two stage design was used such that if ≥1 out of the first 10 patients had an objective response (CR or PR), 10 additional patients were enrolled for a total of 20 patients. If ≥3 of the 20 enrollees had an objective response, the agent was considered active. Table 7 summarizes the design of this study.

Table 7 Design of ADVL0524

Stage	Total # of responders at the end of the stage	Decision
Stage 1: enter 10 patients	0	Terminate stratum. Agent ineffective.
	≥1	Proceed to stage 2
Stage 2: Enter 10 additional patients	≤2	Terminate stratum. Agent ineffective.
	≥3	Terminate stratum. Agent effective.

Eligibility Criteria

Inclusion criteria:

- Age
  - Patients must be ≥ 12 months old at trial entry.
  - Patients with neuroblastoma or Wilms tumor must have been ≤ 21 years of age when originally diagnosed with the malignancy to be treated on this protocol.
  - All other patients must have been ≤ 35 years of age when originally diagnosed with the malignancy to be treated on this protocol.

Reviewer's note: Inclusion of patient's older than 35 is a violation of the terms of the WR.

- Histologic Diagnosis

  The target tumors are:

  - Embryonal or alveolar rhabdomyosarcoma
  - Osteosarcoma
  - Ewing sarcoma/Peripheral neuroectodermal tumor (PNET)
  - Synovial sarcoma or malignant peripheral nerve sheath tumor (MPNST)
  - Wilms tumor
  - Neuroblastoma

- Patients must have had histologic verification of the malignancy at original diagnosis or at recurrence.

- All patients must have had refractory or recurrent tumors with no known curative treatment options.

For patients with sarcoma and Wilms tumor: Patients must have measurable disease. Measurable disease is defined as lesions that can be measured in at least one dimension by medical imaging techniques (CT or MRI scan). Ascites, pleural effusions, bone marrow disease, and lesions detectable only by bone scan will not be considered measurable disease.

For patients with neuroblastoma: Patients with either clinically or radiographically measurable disease or evaluable disease by ^{123}I-MIBG or bone scan are eligible.

- For evaluable tumor, ^{123}I-MIBG or bone scan must be positive at a minimum of one site. If the lesion was previously radiated, a biopsy must be done at least 6 weeks after radiation is complete and demonstrate viable neuroblastoma.

- Performance Level

  Patients must have an ECOG performance status of 0, 1 or 2, or Karnofsky ≥ 50% (patients > 16 years of age) or Lansky ≥ 50% (patients ≤ 16 years).

- Life Expectancy

  Patients must have a life expectancy of ≥ 8 weeks.

- Prior Therapy

  Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy or radiotherapy prior to entering this study.

  - Myelosuppressive chemotherapy: Must not have received within 2 weeks of entry onto this study (4 weeks if prior nitrosourea).
  - Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent.
  - XRT: ≥ 2 wks for local palliative XRT (small port); ≥ 6 months must have elapsed if prior craniospinal XRT or if ≥ 50% radiation of pelvis; ≥ 6 wks must have elapsed if other substantial BM radiation.
  - Stem Cell Transplant (SCT): No evidence of active graft vs. host disease. For allogeneic SCT, ≥ 4 months must have elapsed; for autologous SCT ≥ 2 months must have elapsed.
  - Study specific limitations on prior therapy: Patients may not have received prior taxane (paclitaxel, docetaxel) therapy.

- Concomitant Medications Restrictions

No other cancer chemotherapy, radiation therapy or immunomodulating agents will be used. However, steroids may be used for the treatment and prevention of hypersensitivity reactions and as clinically indicated, for example, for the treatment of pain or chemotherapy associated nausea or vomiting, if necessary.

- Growth factor(s): Must not have received within 1 week of entry onto this study, with the exception of erythropoietin.
- Study Specific: Patients may not be currently receiving strong inhibitors of CYP3A4, and may not have received these medications within 1 week of entry. These include:

    - Antibiotics: clarithromycin, erythromycin, troleandomycin
    - Anti-HIV agents: delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir
    - Antifungals: itraconazole, ketoconazole, fluconazole (doses > 3 mg/kg/day), voriconazole
    - Antidepressants: nefazodone, fluovoxamine
    - Calcium channel blockers: verapamil, diltiazem
    - Antiemetics: Do not use aprepitant (Emend®) as it is CYP3A4 substrate, moderate inhibitor and inducer.
    - Miscellaneous: amiodarone
    - In addition, grapefruit juice should be avoided, as it inhibits CYP3A4.

- Patients must also avoid St. John's Wort, an inducer of CYP3A4.
- Patients may not be taking enzyme –inducing anticonvulsants, and may not have received these medications within 1 week of entry, as these patients may experience different drug disposition. These medications include:

    - Carbamazepine (Tegretol)
    - Felbamate (Felbtol)
    - Phenobarbital
    - Phenytoin (Dilantin)
    - Primidone (Mysoline)
    - Oxcarbazepine (Trileptal)

- Organ Function Requirements
  All patients must have:

    - Adequate Bone Marrow Function Defined As

        - Peripheral absolute neutrophil count (ANC) ≥ 1500/μL (off growth factors)

- Platelet count ≥ 75,000/μL (transfusion independent)
- Hemoglobin ≥ 8 gm/dL at study entry (may receive RBC transfusions)

- Adequate Renal Function Defined As
  Creatinine clearance or radioisotope GFR ≥ 70mL/min/1.73m^2 OR- A serum creatinine based on age/gender as follows:

Estimated Creatinine Clearance (in mL/min/1.73 m^2)** =

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC

- Adequate Liver Function Defined As

  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.

- Nervous System Function Defined As

  - Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled. Enzyme inducing anticonvulsant drugs are not allowed on this trial.
  - CNS toxicity ≤ Grade 2.
  - Existing sensory or motor neuropathy must be grade ≤1.

Exclusion Criteria

- Clinically significant unrelated systemic illness, such as serious infections, hepatic, renal or other organ dysfunction, which would, in the judgment of the treating physician, compromise the patient's ability to tolerate the investigational agent or is likely to interfere with the study procedures or results.

- Pregnant or breast-feeding females, because ixabepilone may be harmful to the developing fetus or nursing child. Patients of child-bearing potential must use appropriate birth control measures.

- Patients with known severe prior hypersensitivity reaction to agents containing Cremophor EL.

- Patients with active brain metastases.

- For patients with sarcoma and Wilms tumor: Ascites, pleural effusions, bone marrow disease, and lesions detectable only by bone scan will not be considered measurable disease. Patients who have disease in these locations without radiographically measurable (CT, MRI) disease are excluded.

- For patients with neuroblastoma: Patients with elevated urinary catecholamines and/or bone marrow evidence of tumor, without measurable or evaluable disease clinically or by imaging modalities (CT, MRI, MIBG, or Bone Scan) are excluded.

Regulatory

- All patients and/or their parents or legal guardians must sign a written informed consent.

- All institutional, FDA, and NCI requirements for human studies must be met.

Treatment Compliance

Site visits were conducted at approximately 4-6 month intervals for review of documents, CRFs, regulatory study binder and drug accountability. Monitor visits included assessment of protocol adherence and compliance to ICH and GCP guidelines.

Study Treatments, Concomitant Medications, and Dose Modifications

Study treatment:

Ixabepilone was administered IV daily as a 1-hour infusion for 5 consecutive days every 21 days. The dose selected for this trial was 8 mg/m^2/day (maximum 16 mg/day), the MTD in the pediatric phase I study.

Concomitant medications:

All patients received primary prophylaxis for hypersensitivity reactions:

Primary prophylaxis (1 hour to 30 minutes prior to Ixabepilone):
• H1 blocker (diphenhydramine 1 mg/kg IV or PO, maximum single dose 50 mg).
• H2 blocker (ranitidine 1 mg/kg IV, maximum single dose 50 mg IV, **or** 2 mg/kg PO, maximum single dose 150 mg PO, **or** another equivalent H2 blocker).

Dexamethasone 0.3 mg/kg, maximum single dose 20 mg orally or intravenously 12 hours and 6 hours prior to the administration of ixabepilon was permitted for management of hypersensitivity reactions and secondary prophylaxis.

Patients who experienced dose-limiting neutropenia during any cycle received a granulocyte colony stimulating factor, such as filgrastim, on subsequent cycles.

RESTRICTIONS

No other cancer chemotherapy, radiation therapy or immunomodulating agents were allowed. However, steroids may could be used for the treatment and prevention of hypersensitivity reactions and as clinically indicated, for example, for the treatment of pain or chemotherapy associated nausea or vomiting, if necessary.
Growth factor(s): Must not have been received within 1 week of entry onto this study, with the exception of erythropoietin.

Study Specific: Patients could not currently be receiving strong inhibitors of CYP3A4, and may not have received these medications within 1 week of entry. These include:

- Antibiotics: clarithromycin, erythromycin, troleandomycin
- Anti-HIV agents: delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir
- Antifungals: itraconazole, ketoconazole, fluconazole (doses > 3 mg/kg/day), voriconazole
- Antidepressants: nefazodone, fluovoxamine
- Calcium channel blockers: verapamil, diltiazem
- Antiemetics: Do not use aprepitant (Emend®) as it is CYP3A4 substrate, moderate inhibitor and inducer.
- Miscellaneous: amiodarone
- In addition, grapefruit juice should be avoided, as it inhibits CYP3A4.

Patients had to avoid St. John's Wort, an inducer of CYP3A4.

Patients could not be taking enzyme –inducing anticonvulsants, and may not have received these medications within 1 week of entry, as these patients may experience different drug disposition. These medications included:

- Carbamazepine (Tegretol)

- Felbamate (Felbtol)
- Phenobarbital
- Phenytoin (Dilantin)
- Primidone (Mysoline)
- Oxcarbazepine (Trileptal)

Dose Reductions

Patients who demonstrate at least stable disease in the face of dose limiting toxicity or who have treatment delays beyond Day 28 from their prior cycle of treatment will have their subsequent dose of the agent decreased.

The following ixabepilone-related toxicities will be considered Dose Limiting Toxicities (DLTs) and require dose reduction or treatment modifications on subsequent treatment cycles:

- Dose limiting toxicities ≥ Grade 3 non-hematologic toxicity with the exception of ≥ Grade 3 nausea and vomiting controlled with antiemetics and ≥ Grade 3 elevations in serum transaminases that return to baseline by Day 28 of the treatment cycle.
- In addition, hypersensitivity reactions, which typically occur after the initial doses of Ixabepilone, and are not dose related, will not be considered dose-limiting.
- Lymphopenia of any grade will not require treatment modifications.
- Grade 4 neutropenia (ANC <500/μL) on two consecutive measurements at least 3 days apart
- Grade 4 thrombocytopenia
- Treatment delay due to toxicity beyond Day 28 of the treatment cycle
- Patients experiencing Grade 4 neutropenia (ANC <500/μL) on two consecutive measurements at least 3 days apart, or treatment delay beyond Day 28 for neutropenia, should be treated on subsequent cycles at the same dose of ixabepilone with the addition of granulocyte colony stimulating factor, such as filgrastim. Patients who continue to experience neutropenia on subsequent cycles despite the addition of a granulocyte colony stimulating factor should have their Ixabepilone dose reduced as described below:

    - Patients experiencing DLTs other than neutropenia, or who experience Grade 4 neutropenia (ANC <500/μL) on two consecutive measurements at least 3 days apart at the 8 mg/m^2/dose x 5 days dose level (maximum daily dose of 16 mg) following addition of granulocyte colony stimulating factor should have their dose of ixabepilone reduced to 6 mg/m^2/dose x 5 days (maximum daily dose of 12 mg) for subsequent cycles.

- Patients experiencing any of these toxicities at the 6 mg/m^2/dose x 5 days dose level should have their dose reduced to 4.5 mg/m^2/dose x 5 days for subsequent cycles.

Patients who experience any of these toxicities after 2 dose reductions of ixabepilone should be removed from the trial.

Dose escalation

There will be no dose escalation on this trial.

Discontinuation/Withdrawal from Study

Criteria for Removal from Protocol Therapy

- Progressive disease. If possible, tumor progression should be documented by the appropriate radiological study.
- Significant irreversible (≥ 2 weeks duration) organ dysfunction (Grade 4 nonhematological toxicity – CTCAE v 3.0) considered to be primarily ixabepilone toxicity
- Refusal of further protocol therapy by patient/parent/guardian.
- Physician determination that it was in patient's best interest.
- Patients who experience DLT after 2 dose reductions
- Development of a second malignant neoplasm

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study. Follow-up data were required unless consent was withdrawn.

Off Study Criteria

- Death.
- Lost to follow-up.
- Entry into another COG therapeutic study.
- Withdrawal of consent for any further data submission.
- The fifth anniversary of the study closure to accrual

Patient Evaluations

Patient evaluations were performed based on the schedule in Table 8.

Table 8 Evaluation schedule for study ADVL0524

All entry/eligibility studies must be performed within 1 week prior to entry onto the trial (unless otherwise specified). Imaging studies are required within 2 weeks of study entry.

STUDIES TO BE OBTAINED	Prior to Each Cycle	Weekly	Mid-Cycle[a]	Post Study
History & Physical examination (Ht, Wt, BSA, BP[b], + palpable tumor measures)	X			X
Neurological exam	X			X
Performance Status	X			X
CBC, differential, platelets	X	X[c]		X
Urinalysis	X			X
Urine pregnancy test	Cycles 1,3,5,7,9			
Electrolytes including Ca++, PO_4, Mg++ and BUN, Creatinine	X		X	X
LDH, ALT, bilirubin (sum of conjugated + unconjugated), Alk Phos	X		X	X
PT, PTT, INR if on warfarin	X			X
Tumor Disease Evaluation (CT/ MRI of tumor)[d,e]	Cycles 1, 3, 5, 7, etc.			X

[a] between Day 7-14

[b] BLOOD PRESSURE: For the first cycle of Ixabepilone, blood pressure will be monitored with an automated sphygmomanometer prior to, and every 15 minutes during the 60-minute infusion and every 30 minutes for 1 hour after completion of the infusion. Thereafter, if abnormal, blood pressure will be monitored every 30 minutes until it returns to baseline.

- If systolic or diastolic blood pressure dropped >20 mm Hg during first cycle: above procedure should be repeated for subsequent cycles.
- If blood pressure was normal during first cycle, for subsequent cycles blood pressure should be monitored prior to infusion then every 30 minutes until 30 minutes after completion of the infusion.

[c] twice weekly if ANC< 500/μL or if platelets< 50,000/μL

[d] For patients with Neuroblastoma: Tumor disease evaluation includes: CT/ MRI of tumor, and bilateral bone marrow aspiration and biopsies within 2 weeks of study entry for all patients. For patients with neuroblastoma and negative bone marrow aspirates and biopsies at trial entry, bone marrow aspirates and biopsies will only have to be repeated if concerns about bone marrow involvement or about delayed bone marrow recovery develop during the study. Patients with MIBG-avid tumors should also have ^{123}I-MIBG. Patients with HVA/VMA producing tumors should also have urine for catecholamines. (See sections 11.3-11.5 for neuroblastoma patients)

[e] Tumors should be evaluated by both RECIST criteria (section 11.2) and WHO criteria (section 11.7). Patients with measurable disease on chest CT will also be evaluated by volumetric analysis. Please send all chest CTs of patients with measurable chest lesions to the DVL Image repository at CHLA (See section 7.2)

Criteria for Efficacy Assessment

Efficacy assessment in each disease cohort of study ADVL0524 was performed as outlined in Table 7.

The investigators considered ixabepilone not of sufficient interest for further evaluation in a disease category if the true response rate was 5%. If ixabepilone had a true response rate of 5%, the rule described above was to identify the agent of sufficient activity for further study with probability 0.07 (type I error). If ixabepilone had a true response rate of 30%, the rule described above was to identify the agent of sufficient activity for further study with probability 0.95 (power against the alternative hypothesis p

= 0.30). In addition to making the decision to accept or reject the drug, the final results were to be reported after all patients had been identified as having a CR, PR, or PD as their response according to protocol specified criteria.

Patients who were considered evaluable for response were to be included in an analysis of time to progression. Time to progression was to be estimated using the product-limit method of Kaplan and Meier. The probability of progression free survival at 6 months was also to be summarized. Response rates were to be calculated as the percent of patients whose best response is a CR or PR, and the fraction of responses obtained would have a 95% confidence interval, which takes into consideration the two-stage nature of the design.

Any patient who was enrolled and received at least one dose of Ixabepilone was considered evaluable for response provided:

1. the patient demonstrated progressive disease or death while on protocol therapy;
2. the patient was observed on protocol therapy for at least one cycle and the tumor was not removed surgically prior to the time complete response or partial response was confirmed; or
3. the patient demonstrated a complete or partial response as confirmed according to protocol criteria.

Patients who electively terminated therapy before receiving all 5 doses of ixabepilone during the first treatment cycle and did not expire within 28 days from start of treatment were replaced. Patients who demonstrate a complete or partial response confirmed by central review were to be considered to have experienced a response for the application of the rule given in Table 7. The evaluation period for determination of the best response was 6 treatment cycles. All other patients were considered non-responders. All patients considered to have a response (CR or PR according to RECIST or MIBG scan criteria) were to have imaging studies reviewed centrally at the COG. In addition, select patients considered to have stable disease were to have scans reviewed by COG radiologists for blinding purposes. Centers were notified by the COG about requests for scans of patients with stable disease. Preliminary assessment of activity using institutionally provided tumor measurements were collected quarterly. The central review by COG was provided as the final reviewed assessment of response when such became available.

For the primary study objective response was measured by the 1-D (RECIST) Response Evaluation Criteria in Solid Tumor from the NCI. In addition, as a secondary trial objective, 2-D (WHO) measurements were performed for each patient on each evaluation to allow for a comparison of RECIST and WHO criteria.
In addition for patients with Neuroblastoma and disease evaluable by ^{123}I-MIBG at baseline, standard COG criteria for assessing tumor burden using ^{123}I-MIBG were utilized.

Time to progression (TTP) was defined as the number of days from enrollment until:

1. disease progression;
2. death because of treatment complications;
3. resection of measurable tumor; or
4. last patient follow-up whichever was first.

Patients were considered to have experienced a progression event if (1) or (2) occured. Otherwise, the patient was considered censored for time to progression.

Reviewer's note: TTP was not calculated for any patients as none of the patients enrolled on study was considered a responder (CR or PR).

In addition to the above analysis, all chest CTs for patients with measurable disease on chest CT had to be forwarded by the treating institution to an Image Repository at Children's Hospital of LA via secure electronic transfer (phase I institutions only) or via CD or DVD format for volumetric analysis. These lesions were to be reviewed at the National Cancer Institute by a single reviewer for 1-D, 2-D and 3-D measurements.

Reviewer's note: This analysis was not performed as detailed in communications from the applicant. The WR was amended accordingly.

Criteria for safety Assessment

All adverse event data were to be reported using the NCI's Adverse Event Expedited Reporting System (AdEERS). NCI CTCAE v. 3.0 was used to grade the all adverse events. Toxicity information recorded was to include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Tables were to be constructed to summarize the observed incidence by severity and type of toxicity.

Reviewer's note: No laboratory data or vital signs were collected and/or reported after baseline unless reported as an AE.

6 Evaluation of the Applicant's Fulfillment of the Pediatric Written Request Requirements

Table 9 lists each item as requested in the PWR and this reviewer's conclusion as to whether it has been fulfilled or not. All discrepancies between the terms of the PWR and the performed studies are highlighted in Table 9 for quick reference. The primary discrepancy from the terms of the PWR was the enrollment of 7 patients ≥21 years old on study ADVL0524. These patients were distributed in 3 disease cohorts (rhabdomyosarcoma cohort, Ewing sarcoma/Primitive NeuroEctodermal Tumor cohort and the synovial sarcoma/malignant peripheral nerve sheet tumor cohort) out lined in the "Age group and population" section of table 9. Additionally, the total number of patients enrolled on the Ewing sarcoma/PNET cohort was 9 patients instead of 10 as specified in the WR.

Regardless of these discrepancies, study ADVL0524 clearly demonstrated that ixabepilone administered using the current dose and schedule was inactive in the pediatric solid tumors studied. In addition, the studied age groups correctly reflect the age groups in which these diseases are prevalent. Therefore, this deficiency does not change the overall conclusion that treatment with ixabepilone did not provide an overall benefit in the treatment of pediatric patients with the studied solid tumors.

This information contained in the revised ixabepiole (Ixempra®) labeling will be helpful to physicians and should be made available to the healthcare community.

This reviewer therefore concludes that the applicant has fairly fulfilled the requirements set forth in the PWR.

Table 9 The applicant's fulfillment of the Pediatric Written Request requirements

Written Request Items	Information Submitted
Types of studies requested: **Study 1** A phase 1, open-label, dose finding, safety and pharmacokinetic study of intravenous ixabepilone in pediatric patients with advanced, refractory solid tumors including brain tumors. **Study 2** A phase 2 single-arm, safety and efficacy study of ixabepilone (BMS-247550) in children and young adults with refractory solid tumors	**Types of studies performed:** **Study 1 (CTEP-5425)** Phase 1 trial and pharmacokinetic study of BMS-247550 (NSC 710428, ixabepilone), an epothilone B analog, in pediatric patients with refractory solid tumors and leukemias. **Study 2 (ADVL0524)** Phase II trial of ixabepilone (BMS-247550), an epothilone B analog, in children and young adults with refractory solid tumors.
Populations to be studied: **Study 1** Advanced, refractory, histologically confirmed solid tumors, which include but are not limited to [1] 1. Rhadomyoscarcoma and other soft tissue sarcomas, 2. Ewing's sarcoma family of tumors, 3. Osteosarcoma, 4. Neuroblastoma, 5. Wilms' tumor, 6. Hepatic tumors, 7. Germ cell tumors, 8. Primary brain tumors. In patients with brain stem or optic gliomas the requirement for histological confirmation may be waived. **Study 2** The target tumors are distributed into the following categories: 1. Embryonal or alveolar	**Indication(s) studied:** **Study 1 (CTEP-5425)** Ixabepilone was administered to patients with advanced, refractory, histologically confirmed solid tumors and/or advanced or refractory leukemia. 1. Rhadomyoscarcoma and other soft tissue sarcomas, (n=7) 2. Ewing's sarcoma family of tumors, (n=2) 3. Osteosarcoma (n=3) 4. Neuroblastoma (n=1) 5. Wilms' tumor (n=2) 6. Hepatic tumors (n=2) 7. Germ cell tumors (n=0) 8. Primary brain tumors (n=0) 9. Hemangioendothelioma (n=1) 10. Pleuropulmonary blastoma (n=1) 11. Acute lymphoblastic Leukemia (n=2) **Study 2 (ADVL0524)** Ixabepilone was administered to subjects with 1. Embryonal or alveolar rhabdomyosarcoma

[1] The highlighted areas represent areas of discrepancy between the written request and the performed studies.

<table>
<tr>
<td>rhabdomyosarcoma,
2. Osteosarcoma,
3. Ewing's sarcoma/peripheral neuroectodermal tumor (PNET),
4. Synovial sarcoma or malignant peripheral nerve sheath tumor (MPNST),
5. Wilms' tumor, and
6. Neuroblastoma.</td>
<td>(n=10)
2. Osteosarcoma (n=10)
3. Ewing's sarcoma/peripheral neuroectodermal tumor, (n=9)
4. Synovial sarcoma or malignant peripheral nerve sheath tumor, (n=10)

5. Wilms'tumor (n=10)
6. Neuroblastoma (n=10)</td>
</tr>
<tr>
<td>Age group in which studies will be performed:

Study 1
Patients of ≥ 1 year and ≤ 18 years of age

Study 2
Patients must be ≥ 1 year and ≤ 21 years of age at trial entry</td>
<td>Age group and population in which study was performed:

Study 1 (CTEP-5425)
The study enrolled and treated 21 patients aged 2 to 18 years of age, distributed among the following age groups:
• 2 - 12 years (N=12)
• 13 to 18 years of age (N=9)

Study 2 (ADVL0594)
The study enrolled 61 patients, 59 patients aged 3 to 36 years of age, distributed among the following age groups:
• 3 – 12 years (N=28)
• 13 to 21 years (N=24)
• 22 to 36 years (N=7)
All subjects were ≥ 3 years of age at study entry. Subjects with osteosarcoma, neuroblastoma or Wilms tumor were ≤ 21 years of age when originally diagnosed. All other subjects were ≤ 35 years of age when originally diagnosed.

A clinical reviewer's summary of enrolled patients with their age ranges is provided.
<table>
<tr><th rowspan="2">Category</th><th colspan="2"># of patients</th><th rowspan="2">Age Group Enrolled</th><th rowspan="2"># of Patients <21 Enrolled</th></tr>
<tr><th>Required (approx.)</th><th>Enrolled</th></tr>
<tr><td>Ewing's.</td><td>10</td><td>9</td><td>10-36</td><td>6</td></tr>
<tr><td>Rhabdo.</td><td>10</td><td>10</td><td>4-25</td><td>7</td></tr>
<tr><td>Osteosarcoma</td><td>10</td><td>10</td><td>8-20</td><td>10</td></tr>
</table>
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<tr><td></td><td>
<table>
<tr><td>Wilms Tumor</td><td>10</td><td>10</td><td>3-15</td><td>10</td></tr>
<tr><td>Neuroblatoma.</td><td>10</td><td>10</td><td>3-12</td><td>10</td></tr>
<tr><td>Syn/MPNST</td><td>10</td><td>10</td><td>7-24</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>Study endpoints:
(Revised 4/22/2008 and 10/25/2010)

Study:

1. Determine the MTD and DLT of BMS-247550 administered as a one hour infusion daily for 5 consecutive days every 21 days in children with cancer.

2. Define the toxicity spectrum of ixabepilone on the daily x 5 schedule every 21 days in children with cancer.
3. Determine the plasma pharmacokinetics of ixabepilone.

4. Measure responses to ixabepilone.
5. Measure the time to disease progression in patients with objective responses.
6. Compare the tolerance, toxicity profile, MTD, DLT, pharmacokinetics and pharmacodynamics of ixabepilone in children treated on this study and adults who were treated with the same schedule of treatment

Study 2
The primary endpoint is objective response rate (CR + PR) using RECIST criteria.
Secondary endpoint is the time to disease progression.</td><td>Clinical endpoints used:

Study 1 (CTEP-5425)
The primary endpoints presented include:
1. A determination of the MTD and DLTs of the epothilone B analog, ixabepilone, administered as a 1 hour infusion daily for 5 consecutive days (daily x 5) every 21 days in children with cancer.
2. Defined toxicity spectrum of ixabepilone on the daily x 5 schedule in children with cancer.

3. Pharmacokinetic parameters for 16 subjects (2 to 18 years of age) for whom assessments of ixabepilone plasma concentration were available. Summary statistics of parameters were presented by dose level for subjects of all ages combined and for the age groups of 2 to 12 years (N=9) and 13 to 18 years (N=7) for all dose levels combined.
4. Measurement of responses to ixabepilone
5. Measurement of the time to disease progression in patients with objective responses. (not done due to lack of responses)
6. A comparison of the tolerance, toxicity profile, MTD, DLT, pharmacokinetics and pharmacodynamics of ixabepilone in children treated on this study and adults who were treated with the same schedule of treatment.

Study 2 (ADVL0594)
The primary endpoint reported was the response rate to ixabepilone in various strata of recurrent solid malignant tumors of childhood and young adulthood. There were no objective responses reported.
The secondary endpoints reported were the time to progression for all treated subjects and to further define and describe the toxicities of ixabepilone.</td></tr>
<tr><td>Dosage form in written request:</td><td>Dosage form used:</td></tr>
</table>

Ixabepilone 15 mg, 20 mg, and 30 mg lyophile per single-use vial. The Vehicle for constitution is comprised of an ethanol plus polyoxyethylated castor oil (Cremaphor® EL) mixture (1:1 by volume). The diluent is Lactated Ringer's Injection (USP).	Ixabepilone for injection lypholized, white to off-white, whole or fragmented cake in a vial. Ixabepilone was provided to the NCI for distribution to CTEP in 15 and 20 mg vials. The vehicle was an ethanol plus polyoxyethylated caster oil, which was clear to slight hazy, colorless to pale in color solution.
Route of administration requested: Intravenous	**Route of administration used:** Intravenous
Regimen: **Study 1** Ixabepilone will be administered IV daily as a one-hour infusion for 5 consecutive days every 21 days. The starting dose for this trial will be 3 mg/m^2/dose, which represents 50% of the adult MTD. The same dose levels will be tested in children as were studies in the adult trial - 3, 6 and 8 mg/m^2/dose. In addition, a 4.5 mg/m^2/dose level will be added, as the 6 mg/m^2/dose was the MTD in adults treated on the same schedule. If the 8 mg/m^2/dose is tolerable, subsequent dose levels will be at 30% increments. **Study 2** Ixabepilone will be administered as a one-hour infusion on Days 1 to 5 every 21 days at the recommended phase 2 dose determined from study 1.	**Regimen:** **Study 1 (CTEP-5425)** Ixabepilone was administered as a 1-hour infusion on Days 1-5 on a 21 day cycle. The starting dose was 3 mg/m^2/day x 5 days every 21 days which represented 50% of the MTD determined in the adult Phase 1 trial using the same dose schedule. Dose levels included 3 mg/m^2, 4.5 mg/m^2, 6 mg/m^2, 8 mg/m^2 and 10 mg/m^2. **Study 2 (ADVL0594)** Ixabepilone was administered IV daily as a 1-hour infusion for 5 consecutive days every 21-days. The dose for this study was 8 mg/m^2/day, the MTD in the pediatric Phase 1 study
Drug specific safety concerns in written request: Neutropenia, peripheral neuropathy, hypersensitivity reactions, cardiovascular events.	**Drug specific safety concerns evaluated:** Evaluations prior to every cycle of ixabepilone included history and physical examinations, neurological exams, height, weight, BSA, hematologic/chemistry/urinalysis laboratory sampling, radiographic evaluations and pharmacokinetic studies.
Statistical information, including power of study and statistical assessments requested: **(Revised 04/22/2008)**	**Statistical information (statistical analyses of the data performed):**

Study 1 This trial uses a conventional dose-escalation design to establish the MTD of ixabepilone based on severity of toxicity. Four dose levels are planned. At least 3 patients will be treated at each dose level (cohort) and if a DLT is observed in 1 of 3 patients, the cohort will be expanded up to 6 patients. MTD is defined as the dose level immediately below the level at which ≥ 2 patients in a cohort of 2 to 6 patients experienced a DLT. Patient accrual will be expanded at the MTD to at least 6 and as many as 12 patients, including at least 2 who are ≤ 5 years of age. In the expanded cohort at the recommended dose, < 25% of patients (3/12) should have experienced a DLT attributable to ixabepilone.	**Study 1 (CTEP-5425)** This was a Phase-1, dose-escalation trial and the sample size could not be precisely determined, but depended on the observed toxicity. A 3+3 design was used where 3 subjects were treated at each dose level (cohort); if DLT was observed in 1 of 3 subjects the cohort was expanded to up to 6 subjects. The MTD was defined as the dose level immediately below the level at which ≥ 2 subjects in a cohort of 2 to 6 subjects experienced a DLT. The study enrolled and treated 21 subjects in 1 of 5 ixabepilone dose cohorts: 3 mg/m^2/day (3 subjects), 4.5 mg/m^2/day (4 subjects), 6 mg/m^2/day (3 subjects), 8 mg/m^2/day (8 subjects), and 10 mg/m^2/day (3 subjects). Demographics and baseline characteristics were summarized for all treated subjects. Summaries of AEs and laboratory test were presented by worst CTC grade for all treated subjects. Adverse events and laboratory tests were graded according to the NCI CTCAE Version 2. Adverse events were summarized by system organ class and preferred term according to MedDRA Version 12.1. Best response on-treatment was summarized for all treated subjects. Summaries of AEs and laboratory tests were presented by worst CTC grade for all treated subjects. Individual listings and tabulations of summary statistics were provided for all derived PK parameters. Geometric means and coefficients of variation (%CV) were reported for Cmax and AUC (INF); means and standard deviations (SD) were reported for all other parameters.
Study 2 Evaluation of activity will be carried out by a standard procedure as follows. Within each category (stratum) of tumors, approximately 10 patients will be entered. If there are no patients with responses, the trial for this stratum will be terminated because the agent	**Study 2 (ADVL0594)** A two-stage design was considered for this study with 10 subjects per tumor type (stratum) in the first stage. If no responses were observed that cohort was terminated. If at least one response was observed, another 10 subjects were to be enrolled in the second stage. If 3 or more responses were

is ineffective. If ≥ 1 patient responds in a stratum, 10 additional patients will be entered. If there are ≤ 2 responses, the trial will be terminated for this stratum because the agent is inactive. If there are ≥ 3 patients with responses, the trial will be terminated for this stratum because the agent is active. The responses will be categorized by type (CR, PR or PD) according to protocol specified criteria. Response rate and time to progression will be described. Toxicity information recorded will include the type, severity, time of onset, time of resolution and the probable association with the study regimen.	observed at the end of second stage, that tumor stratum would be considered for further evaluation. If the true response rate was 30%, then there would be 95% chance of observing 3 or more responses. If the true response rate was only 5%, then there would be 7% chance of observing this. A maximum number of 120 subjects were anticipated. However, a total of 61 subjects were enrolled of which 59 were treated in six different tumor types: 1. Embryonal or alveolar rhabdomyosarcoma (n=10) 2. Osteosarcoma (n=10) 3. Ewing's sarcoma/peripheral neuroectodermal tumor, (n=9) 4. Synovial sarcoma or malignant peripheral nerve sheath tumor, (n=10) 5. Wilms' tumor (n=10) 6. Neuroblastoma (n=10) Demographics and baseline characteristics, including age, race, sex, and performance status and tumor type at baseline were summarized for all treated subjects. Prior therapy was presented in a subject listing. Median number of ixabepilone courses on treatment was presented. Subjects with dose reductions were presented in a dosing listing. Summaries of AEs and laboratory test were presented by worse CTC grade for all treated subjects. Adverse events and laboratory tests were graded according to the NCI CTCAE Version 2. Adverse events were summarized by system organ class and preferred terms according to MedDRA Version 12.1 Best response on-treatment was summarized for all treated subjects. Median PFS along with 95% confidence intervals (CIs) were estimated using the Kaplan-Meier (KM) product-limit method. Summaries of AEs and laboratory tests were presented by worst CTC grade for all treated subjects.
Labeling that may result from the studies based on written request: Appropriate sections of the label may be changed to incorporate the findings of the studies.	**Labeling that may result from the studies:** The effectiveness of IXEMPRA in pediatric patients has not been established. IXEMPRA was evaluated in one Phase 1 and one Phase 2 trial. The pediatric

	(b) (4)
Format of reports to be submitted: Full study reports and data sets not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the	**Format of reports submitted:** Full clinical study reports including analysis, assessment, and interpretation of the data were submitted. The reports included information on the representation of patients of ethnic and racial minorities.

following designations should be used: Hispanic/Latino or Not Hispanic/Latino.	
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before December 28, 2012.	**Timeframe for submitting reports of the studies:** Reports were submitted by January 18, 2011.

Reviewer's note:
1. In the section "Types of studies" study 1 differs from the WR as attempts were made to add a leukemia cohort to this study.
2. In the section "Indication(s) studied" the study ADVL0524 only recruited 9 of the 10 patients with Ewing Sarcoma/PNET that were requested in the WR.
3. Two inconsistencies were noted in section "Age group and population in which study was performed". Study CTEP-5425 did not enroll any patients <2 years in age (the leukemia cohort was open to patients ≥1 year in age). Additionally, study ADVL0524 enrolled 7 patients >21 years in age.
4. In section "Clinical endpoints used", TTP could not be calculated for any patients as there were no patients with objective responses on this study.
5. One inconsistency was identified in the section "Labeling that may result from the studies". Only 19 patients with solid tumors were treated on CTEP-5425. This section was corrected prior to inclusion in Table 9.

7 Review of Efficacy

Efficacy Summary

Data from 2 studies, CTEP-5425 and ADVL0524 were submitted as part of this NDA. A total of 78 patients with refractory solid tumors were treated in these two studies and were evaluable for efficacy. None of the patients enrolled in these two studies experienced an objective response (CR or PR). Based on this data there is no evidence of activity for ixabepilone in pediatric solid tumors. Only two patients with refractory acute leukemias were recruited to study CTEP-5425. Neither patient was evaluable for response to therapy. The investigators were unable to recruit any additional patients to the leukemia cohort of CTEP-5425 despite a concerted effort documented by the investigators.

7.1 Indication

The applicant is not seeking a pediatric indication for ixabepilone.

7.1.1 Methods

CTEP-5425

Supportive data was provided from CTEP-5425 which was a phase 1, single-center, open-label, dose escalation (3 + 3 design) study performed at the Pediatric Oncology Branch of the National Cancer Institute. This study was initiated on November 7, 2001 and ended on December 4, 2007.

Protocol Deviations
One patient (#20) was not on a stable or tapering dose of steroids prior to study enrollment as pre-specified in the eligibility criteria. This patient was treated on the 8 mg/m^2/day cohort.

ADVL0524

The primary efficacy analysis was based on study ADVL0524. This study was sponsored by the Cancer Therapeutics Evaluation Program (CTEP) of the National Cancer Institute (NCI) under IND 58,546 and conducted by the Children's Oncology Group (COG). This study was a COG-wide phase 2 study that enrolled patients in 34 centers in 3 countries (Australia, Canada and USA). This study was initiated on May 31, 2006 and completed on December 5, 2008.

Protocol Deviations

Two subjects had protocol deviations reported on this study. Subject #750424 had to receive local radiation therapy for spinal cord compression while subject # 760227 presented to clinic prior to starting therapy with fever and was not able to start therapy. No other deviations were reported on this study.

7.1.2 Demographics

CTEP-5425

The median age for the patients enrolled on CTEP-5425 was 11 years (range: 2 - 18 years). Twelve (57%) patients were male and 9 (43%) female. Seventeen (81%) patients were white, 3 (14%) Black/African-American and 1 (5%) Asian. The most common tumor types were rhabdomyosarcoma in 3 (14%) patients, osteosarcoma in 3 (14%) patients and Ewing Sarcoma and hepatoblastoma in 2 (10%) patients each.

ADVL0524

The median age for patients enrolled on this study was 13.0 years (range: 3-36 years). Slightly more than half the patients were male with 75% being Caucasian. This is summarized in Table 10.

Reviewer's note: Seven patients enrolled on ADVL0524 were older than 21 years of age. These patients primarily had diagnoses that are most commonly seen in the adolescent/young adult (AYA) patient population. These patients are described in Table 11.The enrollment of patients in this age group represents a deviation from the pediatric written request which stated that enrollment on ADVL0524 should be limited to patients ≤ 21 years of age.

Table 10 Demographics of patients enrolled on ADVL0524

	# of patients (%) (n=59)
Age (years)	
Median	13.0
Range	3-36
Race	
White	44 (74.6)
Black	10 (16.9)
Asian Indian, Pakistani	1 (1.7)
Other Asian, including Asian NOS and Oriental NOS	1 (1.7)
Korean	1 (1.7)
Other	1 (1.7)
Unknown	1 (1.7)
Gender	
Male	34 (57.6)
Female	25 (42.4)
Tumor Type	
Alveolar or Embryonal Rhabdomyosarcoma	10 (16.9)
Ewing Sarcoma or Peripheral PNET	9 (15.3)
Neuroblastoma	10 (16.9)
Osteosarcoma	10 (16.9)
Synovial Sarcoma/Malignant Peripheral Nerve Sheet Tumor	10 (16.9)
Wilm's Tumor	10 (16.9)

Table 11 Patients older than 21 years of age enrolled on ADVL0524

Diagnosis	Age	Gender	Race
Alveolar or Embryonal Rhabdomyosarcoma	25	Male	White
Alveolar or Embryonal Rhabdomyosarcoma	22	Male	White
Alveolar or Embryonal Rhabdomyosarcoma	22	Male	White
Synovial Sarcoma or Malignant Peripheral Nerve Sheath Tumor	24	Male	White
Ewing Sarcoma or Peripheral PNET	26	Female	White
Ewing Sarcoma or Peripheral PNET	23	Male	White
Ewing Sarcoma or Peripheral PNET	36	Female	Korean

7.1.3 Subject Disposition

CTEP-5425

The "Enrolled Patient" population for study CTEP-5425 consisted of a total of 21 patients who signed the informed consent form and had a patient identification (PID) number (n=21). All of these patients were part of the "Treated subjects" population as they received at least 1 dose of ixabepilone and plasma samples from 16 subjects were available for PK analysis "Pharmacokinetic dataset". Three patients were entered in the 3 mg/m^2/day, four in the 4.5 mg/m^2/day cohort, three in the 6 mg/m^2/day, eight in the 8 mg/m^2/day cohort, and three in the 10 mg/m^2/day cohort.

All patients had received previous chemotherapy and 13 (62%) had received previous radiation therapy. The most common reason for discontinuation of study drug was disease progression in 19 patients (90%). Other reasons were "completed treatment" in 1 (5%) patient (#4) and "other: started radiation" in 1 (5%) patient (#5).

Reviewer's note: In the publication based on the results of this study, the investigators referred to 19 enrolled subjects, with 18 assessable for toxicity. The investigators assessed all patients who received all 5 daily doses of ixabepilone and completed the Cycle 1 evaluation period, and also any patient who received any number of doses but developed DLT during Cycle 1 for the primary endpoint (MTD and toxicity). Two subjects (02_C_0031-1-15 and 02_C_0031-1-20) at the 8 mg/m^2/day dose level were not included in their toxicity assessment. In addition, 1 subject (02_C_0031-1-5) at the 4.5 mg/m^2/day dose level was removed from study and was not considered evaluable for toxicity.

ADVL0524

Sixty-four patients were enrolled on study. Two patients were ineligible as they did not meet organ function enrollment criteria and 1 additional patient had signed an expired informed consent form, leaving 61 patients eligible for therapy. In addition, 2 of the eligible patients did not receive therapy: 1 patient (#760227) presented to clinic with fever and was unable to receive any subsequent therapy while a second patient/patient family (#738530) refused further treatment. Fifty-nine patients received at least one dose of therapy and were evaluable for safety and efficacy.

Reviewer's note: Enrolled patients were defined as patients who consented to treatment and received a study number while treated patients were defined as patients who received at least one dose of study drug.

All treated patients (59, 100%) had previously received multi-agent chemotherapy. Thirty four patients (58%) had received previous radiation therapy and 25 (42%) had previous surgery. Seven (12%) patients had undergone previous bone marrow transplantation.

All patients treated on ADVL0524 are now off study. Most common reason for patient discontinuation of therapy was progressive disease (51 patients, 86%). Table 12 summarizes reasons for discontinuation of therapy in the remaining 8 (14%) patients.

Table 12 Patients who discontinued therapy on ADVL0524 for reasons other than disease progression

Patient #	Reason for discontinuation	Diagnosis
734297	Physician determines it is in the patient's best interest	Wilms Tumor
735057	Physician determines it is in the patient's best interest	Alveolar or Embryonal Rhabdomyosarcoma
746384	Refusal of further protocol therapy by patient/parent/guardian	Neuroblastoma
763554	Death	Ewing Sarcoma or Peripheral PNET
763796	Physician determines it is in the patient's best interest	Ewing Sarcoma or Peripheral PNET
765009	Grade 4 non-hematological toxicity for ≥ 2 weeks	Synovial Sarcoma or Malignant Peripheral Nerve Sheath Tumor
765010	Physician determines it is in the patient's best interest	Osteosarcoma
81169	Refusal of further protocol therapy by patient/parent/guardian	Synovial Sarcoma or Malignant Peripheral Nerve Sheath Tumor

Reviewer's note: CRFs were only provided for patients #763554 and #765009. The reason for study withdrawal for both patients was confirmed. The cause of death for patient #763554 was unknown to the investigators. Potential causes of death included progressive disease, intra-cranial hemorrhage (coumadin reaction), pulmonary embolism and infection.

7.1.4 Analysis of Primary Endpoint(s)

CTEP-5425

The maximum tolerated dose (MTD) of ixabepilone in pediatric patients with cancer was defined as 8 mg/m2/day administered as a one hour infusion daily for five consecutive days (daily x 5), every 21 days. The toxicity spectrum in pediatric patients was found to be similar to the toxicity spectrum in adults. This will be discussed in section 8 Review of Safety. The pharmacokinetics of ixabepilone in children and

adolescents showed a clearance higher than adults, but the faster elimination did not appear to fully account for the 33% higher tolerable dose than in adults.

The following 3 primary endpoints were not analyzed. The reason for each is provided by the sponsor.

1. Evaluating the pharmacodynamic (PD) of ixabepilone
   Not performed as no reliable assay is available to measure PD in peripheral blood mononuclear cells.

2. Measuring Nerve Growth Factor (NGF)
   Not performed as the minimal neurotoxicity was observed in the pediatric patients treated on this study.

3. Expanded leukemia cohort objectives
   Not performed as the two patients enrolled in leukemia cohort were not evaluable and the investigators were unable to recruit any additional patients to this cohort.

ADVL0524

The primary endpoint in this study was to assess the activity of ixabepilone in patients with six categories of pediatric solid tumors by measuring objective tumor response rate to therapy. Response to therapy in all treated patients was assessed using Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 as all patients (59, 100%) had at least one target lesion measured by CT or MRI at baseline. All responses were assessed by local investigators/radiology. No patients on this study experienced a best overall response of partial response (PR) or complete response (CR). Fourteen (24%) patients were reported as having best overall response of stable disease and 42 (71%) had progressive disease. Best response in 3 (5.1%) patients remained unknown as it was not reported (Table 13). These 3 patients were removed from study early before radiographic documentation of progression.

Table 13 Patients with unknown best overall response

Patient #	Diagnosis	Total cycles of therapy	Off Study Reason
763554	Ewing Sarcoma or Peripheral PNET	2	Death
765010	Osteosarcoma	1	Physician determines it is in the patient's best interest
765574	Wilms Tumor	1	Clinical or radiographic disease progression

A 2-stage design was used in this study as described in Table 7. Ten patients were treated within each tumor cohort except for the Ewing sarcoma/peripheral PNET cohort

that included 9 patients (Table 10). No additional patients were treated in each category as no patients experienced an objective tumor response in the first stage of this study.

Reviewer's note:
1) RECIST is a standard and validated methodology for assessing objective tumor response to therapy in solid tumors.
2) Only 9 patients were enrolled and treated in the first stage of the Ewing sarcoma/peripheral PNET category. This represents a protocol deviation. Regardless of this violation, this study may still fulfill the WR which stated that "approximately 10" patients should be treated in the first stage of this study.

7.1.5 Analysis of Secondary Endpoints(s)

CTEP-5425

No objective tumor responses (CR or PR) were noted in any of the 21 patients enrolled on study CTEP-5425. Six (29%) patients had a best response of stable disease (SD), 12 (57%) had progressive disease (PD) and 3 (14%) had a response listed as unknown. Patients with best response of stable disease are summarized in Table 14.

Table 14 Patients with best response of "stable disease" on CTEP-5425

Patient #	Dose cohort	Best response	Courses administered	Diagnosis
17	8 mg/m^2/day	SD	2	Embryonal Rhabdomyosarcoma
8	6 mg/m^2/day	SD	2	Rhabdomyosarcoma
13	8 mg/m^2/day	SD	3	Undifferentiated Spindle Sarcoma
3	3 mg/m^2/day	SD	5	Neuroblastoma
18	8 mg/m^2/day	SD	7	Ewings Sarcoma
4	4.5 mg/m^2/day	SD	13	Malignant Peripheral Nerve Sheet Tumor

The starting dose of CTEP-5425 was at 3 mg/m^2/day which is at 50% of the adult MTD of 6 mg/m^2/day. Neutropenia was the primary DLT in adults at 8 mg/m^2/day and was also the DLT in this pediatric study at the dose of 10 mg/m^2/day. Pediatric patients therefore tolerated a 33% higher dose than their adult counterparts. The pharmacokinetics of ixabepilone were studied in a similar manner to the adult study at the National Institute of Health. The pharmacokinetic parameters were found to be similar in adults and children but there seemed to be more variability in pediatric population based on investigator assessment and the mean clearance of ixabepilone in children was 18% higher than in adults.

Reviewer's note: A comparison of the results of CTEP-5425 to the adult phase 1 study which was performed at the NIH was performed by the investigators and published. This publication was provided by the sponsor: "Phase I Trial and Pharmacokinetic Study of Ixabepilone Administered Daily for 5 Days in Children and Adolescents With Refractory Solid Tumors", Journal of clinical Oncology, Number 4, February 1, 2009.

ADVL0524

The secondary efficacy endpoints in this study included evaluation of time to progression. Time to progression was defined as time from start of treatment to the earlier of disease progression or death. The sponsor states that since this definition was synonymous with progression free survival (PFS) they will use that term in their assessments. Due to the small sample size within individual tumor stratum, PFS was analyzed pooled across all strata. The median progression free survival (PFS) was 1.2 months (95% confidence interval [CI]: 0.8 - 1.3). The six-month PFS rate, as estimated from the Kaplan-Meier plot, was 3.53% (95% CI: 0.66 10.79).

An additional secondary endpoint was to evaluate the feasibility and utility of automated volumetric tumor measurement in patients with measurable pulmonary metastases, and descriptively compare volumetric measurements to 1D (RECIST criteria) and 2D (WHO criteria) measurements. This analysis, however, was not performed since prospective volumetric measurements of lung lesions using the method described was not feasible for many subjects. The selected method required segmentation of both lungs, and the presence of certain findings in the specified subset of subjects did not allow for a separation of metastatic disease from non-malignant lesions. In addition, most subjects had progressive disease at the time of the first disease evaluation, limiting the potential utility of this method. Therefore, this objective could not be completed.

Reviewer's note: The WR was amended to reflect the inability of the investigators to perform the volumetric analysis. This issue was documented in a letter to the company from PI, Brigitta Widemann, on March 21, 2010.

7.1.6 Other Endpoints

ADVL0524 and CTEP-5425

There were no additional efficacy end points.

7.1.7 Subpopulations

CTEP-5425

This phase 1 study was performed in patients with solid tumors as described in section 7.1.2 Demographics. There were no objective tumor responses reported in any of the patients.

ADVL0524

This study included 6 subpopulations as described in Table 10. No objective tumor responses were documented in any of these 6 subpopulations.

7.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

7.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable.

8 Review of Safety

Safety Summary

The analysis of safety of ixabepilone in pediatric patients was performed by reviewing data from patients treated on ADVL0524 (n=59) and CTEP-5425 (n=21). A total of 80 patients from these studies were assessed for treatment exposure, adverse events (AEs), clinical laboratory abnormalities and deaths. Adverse events were analyzed by age, gender, and race when possible.

8.1 Methods

8.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from 80 patients enrolled on ADVL0524 (n=59) and CTEP-5425 (n=21) were reviewed.

8.1.2 Categorization of Adverse Events

CTEP-5425

Toxicity in this study was graded according to version 2.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All AEs including peripheral sensory and motor neuropathy were subsequently coded using MedDRA version 12.1.

ADVL0524

Toxicity in this study was graded according to version 3.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE). All AEs were subsequently were coded using MedDRA version 12.1.

8.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Data was not pooled across ADVL0524 and CTEP-5425. Each study was evaluated individually and data compared.

8.2 Adequacy of Safety Assessments

8.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

CTEP-5425

CTEP-5425 was a phase 1, dose escalation study with patients receiving therapy at 5 different dose levels. Table 15 summarizes each patient's dose cohort and the number of cycles of therapy that patient received.

Two patients (and # 18) had a dose reduction on this study from 8 to 6 mg/m^2/day. Reason for dose reduction in one patient (#13) was grade 3 diarrhea and a combination of Grade 3 febrile neutropenia, peripheral sensory neuropathy, myalgia, pharyngitis, decreased appetite, dehydration, nausea, and stomatitis in the other patient (#18).

Three subjects experienced DLTs: 2 patients at 10 mg/m^2/day (Grade 4 neutropenia; Grade 3 fatigue) and 1 patients at 8 mg/m^2/day (Grade 3 febrile neutropenia, peripheral sensory neuropathy, myalgia, pharyngitis, decreased appetite, dehydration, nausea, and stomatitis). The MTD was established as 8 mg/m^2/day and this dose level was expanded to a total of 8 patients.

ADVL0524

Patients received ixabepilone at 8 mg/m^2/day x 5 consecutive days every 3 weeks. The median number of cycles received by patients on ADVL0524 was 2 cycles (range: 1-38). Fifty-two (88%) patients only received ≤ 2 cycles of therapy. Six (10%) patients had to have at least 1 dose reduction with 2 (3%) of these patients receiving more than one dose reductions. Median total cumulative dose was 74 mg (range: 23 to 908.3).

Table 15 Dose exposure of patients on CTEP-5425

Patient #	Dose cohort	Maximum # of courses received	Cumulative dose received
1	3 mg/m^2/day	1	12 mg
2	3 mg/m^2/day	1	11.5 mg
3	3 mg/m^2/day	5	229 mg
4	4.5 mg/m^2/day	13	297 mg
5	4.5 mg/m^2/day	1	35.5 mg
6	4.5 mg/m^2/day	12	563 mg
7	4.5 mg/m^2/day	1	16 mg
8	6 mg/m^2/day	2	63 mg
9	6 mg/m^2/day	1	21 mg
10	6 mg/m^2/day	1	50 mg
11	8 mg/m^2/day	1	20 mg
12	8 mg/m^2/day	1	70 mg
13	8 mg/m^2/day	3	195 mg
14	10 mg/m^2/day	1	90 mg
15	10 mg/m^2/day	1	50.4 mg
16	10 mg/m^2/day	1	30 mg
17	8 mg/m^2/day	2	93 mg
18	8 mg/m^2/day	7	281.5 mg
19	8 mg/m^2/day	1	59.5 mg
20	8 mg/m^2/day	1	35 mg
21	8 mg/m^2/day	1	59.8 mg

8.2.2 Explorations for Dose Response

ADVL0524 and CTEP-5425

Explorations for Dose response were not possible as none of the patients treated with ixabepilone experienced an objective tumor response.

8.2.3 Special Animal and/or In Vitro Testing

Not applicable.

8.2.4 Routine Clinical Testing

CTEP-5425

Table 5 and Table 6 outline the clinical testing schedule for study CTEP-5425. This testing schedule was adequate for this phase 1 study.

ADVL0524

Table 8 above outlines the type and frequency of clinical testing in ADVL0524. This testing schedule, including laboratory testing and imaging, is adequate to ensure safe implementation of the study protocol.

Reviewer's note: For study ADVL0524 only baseline laboratory data was collected as part of this study. Any laboratory abnormalities during the study could only be reported as an AE. Additionally, actual tumor measurements were only reported at baseline. The only follow-up data available is based on local investigators and documents tumor response without specifying actual size.

8.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

8.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable.

8.3 Major Safety Results

8.3.1 Deaths

CTEP-5425

No deaths were reported on this study.

ADVL0524

Deaths were reported in 42 of the 59 (71%) patients treated on this study. Forty (68%) of these patients died due to disease progression. The cause of death for two patients was unknown. Six (10%) patients died within 30 days of the last dose of ixabepilone; the cause of death in 5 of these patients was due to underlying disease. The cause of death in one patient, # 763554, was unknown although progressive disease remained as one of the potential etiologies.

Reviewer's note: In ADVL0524 none of the patients who died within 30 days of the last dose of ixabepilone received more than one cycle of study therapy. This seems to suggest a pattern suggestive of the advanced disease nature of these patients.

8.3.2 Nonfatal Serious Adverse Events

CTEP-0524

Seven (33%) patients on CTEP-5425 were reported to have an SAE. Three of these patients were in the 8 mg/m^2/day cohort, 1 in the 6 mg/m^2/day cohort and 3 in the 4.5 mg/m^2/day cohort. In 3 (14%) patients (#11, 13 and 18) the SAE was considered related to the study drug. All reported ixabepilone-related SAEs occurred at the 8 mg/m^2/day dose level. SAEs occurring in more than one patient included febrile neutropenia, vomiting, pyrexia and dehydration, all occurring in 2 (10%) patients each. One patient was reported to have an SAE peripheral sensory neuropathy and 1 with peripheral motor neuropathy.

ADVL0524

Nineteen (32%) patients on study ADVL0524 reported at least one SAE. Nine subjects experienced an SAE considered by investigators as related to ixabepilone therapy. Three (5%) patients each experienced an episode of abdominal pain, hemoglobin decreased, neutrophil count decreased, decreased appetite or myalgia with 2 (3%) patients each experiencing death, disease progression, fatigue, constipation, nausea, peripheral sensory neuropathy, and lymphopenia.

Reviewer's note: The adverse event data sets submitted do not contain the necessary information that allows verification of data presented in the CSR for ADVL0524.

8.3.3 Dropouts and/or Discontinuations

CTEP-5425

Nineteen (90%) patients treated on CTEP-5425 discontinued study drug due to disease progression. Other reasons were discontinuation included "completed treatment" in 1 (5%) patient (#4) and "started radiation" in 1 (5%) patient (#5).

Reviewer's note: In study CTEP-5425 one patient (#15) in the 10 mg/m^2/day cohort, was reported to have been discontinued from therapy. In this patient therapy was interrupted after day 1 of cycle 1 due to a grade 2 hypersensitivity reaction. After this event resolved, therapy was resumed on day 2 after dexamethasone premedication. Patient was subsequently able to tolerate the remainder of the cycle but was discontinued on day 29 of cycle 1 due to progression of disease.

ADVL0524

One (2%) patient, #765009, was discontinued from study due to grade 4 non-hematological toxicity (hemorrhage intracranial) that lasted for ≥ 2 weeks after 1 course

of therapy.
This patient had been receiving treatment with low molecular weight heparin at time of first intracranial hemorrhage but then experienced worsening of this event 2 weeks later despite discontinuation of anticoagulation. He was subsequently discontinued from study.

8.3.4 Significant Adverse Events

Peripheral Neuropathy

CTEP-5425

Seven (33%) patients were reported to have peripheral neuropathy on study CTEP-5425. All of these patients had peripheral sensory neuropathy with one patient (#5) also having peripheral motor neuropathy. All cases of sensory neuropathy were attributed to the therapy while the motor neuropathy was not attributed to the therapy. Only one patient had an episode of grade 3 peripheral neuropathy with the remainder of events graded as grade 1 or 2.

ADVL 0524

Seven (12%) patients enrolled on ADVL0524 experienced an episode of peripheral neuropathy. Peripheral neuropathy in 5 (8%) of these patients was attributed to ixabepilone. All episodes were ≤ grade 3 in severity.

Reviewers note: Five (24%) patients on CTEP-5425 had an episode of constipation with episodes in 2 (10%) of them being attributed to study therapy. On ADVL0524 an additional 10 (17%) patients had an episode of constipation with 7 (12%) of these patients having an episode attributed to ixabepilone. All of these episodes were also ≤ grade 3 in severity. There were no reports of ileus. These may be secondary to the ixabepilone associated peripheral neuropathy.

8.3.5 Submission Specific Primary Safety Concerns

None.

8.4 Supportive Safety Results

8.4.1 Common Adverse Events

CTEP-5425

All patients on study CTEP-5425 experienced at least 1 adverse event. The adverse events seen in ≥ 15% of the patients treated on CTEP-5425 are summarized in Table 16.

ADVL0524

Fifty-four (92%) of the patients enrolled on ADVL0524 experienced at least 1 adverse event (AE). The adverse events seen in ≥ 15% of the patients treated on ADVL0524 are summarized in Table 17.

Table 16 Most common (≥15%) AEs on CTEP-5425

Adverse Events	Grades 1-4		Grades 3-4	
	N=21	%	N=21	%
White blood cell count decreased	18	86	15	71
Haemoglobin decreased	16	76	7	33
Decreased appetite	13	62	2	10
Vomiting	11	52	2	10
Fatigue	11	52	1	5
Hyponatraemia	11	52	0	0
Abdominal pain	10	48	0	0
Nausea	10	48	3	14
Aspartate aminotransferase increased	10	48	1	5
Platelet count decreased	10	48	4	19
Pyrexia	8	38	2	10
Hypoalbuminaemia	8	38	0	0
Diarrhoea	7	33	1	5
Hypophosphataemia	7	33	3	14
Peripheral sensory neuropathy	7	33	1	5
Lymphopenia	6	29	5	24
Alanine aminotransferase increased	6	29	0	0
Hypokalaemia	6	29	4	19
Alopecia	6	29	0	0
Constipation	5	24	0	0
Hypocalcaemia	5	24	0	0
Hypomagnesaemia	5	24	1	5
Headache	5	24	0	0
Cough	5	24	1	5
Febrile neutropenia	4	19	4	19
Sinus tachycardia	4	19	0	0
Hypersensitivity	4	19	0	0
Infection	4	19	2	10
Blood alkaline phosphatase increased	4	19	1	5
Blood bilirubin increased	4	19	0	0
Arthralgia	4	19	1	5
Bone pain	4	19	1	5
Myalgia	4	19	1	5
Pain in extremity	4	19	0	0
Agitation	4	19	0	0

Adverse Events	Grades 1-4		Grades 3-4	
	N=21	%	N=21	%
Anxiety	4	19	0	0
Rhinitis allergic	4	19	0	0
Pallor	4	19	0	0

Table 17 Most common (>15%) adverse events on ADVL0524

Adverse event	All grades		Grades 3 and 4	
	N=59	%	N=59	%
Haemoglobin decreased	30	51	12	20
White blood cell count decreased	28	47	16	27
Platelet count decreased	27	46	9	15
Neutrophil count decreased	22	37	16	27
Aspartate aminotransferase increased	20	34	2	3
Pyrexia	16	27	3	5
Alanine aminotransferase increased	16	27	1	2
Nausea	15	25	3	5
Hyponatraemia	15	25	2	3
Lymphopenia	13	22	10	17
Vomiting	13	22	1	2
Pain in extremity	13	22	3	5
Abdominal pain	12	20	5	8
Fatigue	12	20	2	3
Constipation	10	17	1	2
Diarrhoea	10	17	3	5
Hypoalbuminaemia	10	17	2	3
Headache	10	17	0	0
Decreased appetite	9	15	5	8
Hyperglycaemia	9	15	1	2
Cough	9	15	0	0

Forty-four (75%) of the patients treated on this study had an AE attributed to therapy by the investigators.

8.4.2 Laboratory Findings

CTEP-5425

Hematologic labs

The primary hematologic toxicity on this study was neutropenia. Grade 3/4 neutropenia was reported in 14 (67%) patients: 2 patients at 4.5 mg/m^2/day, 2 patients at 6 mg/m^2/day, 7 patients at 8 mg/m^2/day, and 3 patients at 10 mg/m^2/day. At the MTD (8 mg/m^2/day, N=8), Grade 3 neutropenia was reported in 4 patients and Grade 4 neutropenia was reported in 3 patients.
Grade 3 anemia was reported for 7 (33%) of patients: 1 patient at 3 mg/m^2/day, 4 patients at 8 mg/m^2/day, and 2 patients at 10 mg/m^2/day. Anemia was reported as Grade 1 for 8 (38%) patients, Grade 2 in 6 (29%) patients.
Thrombocytopenia was reported as Grade 4 for 1 (5%) patient (8 mg/m^2/day dose level), and as Grade 3 for 3 (14%) patients (1 patient at 6 mg/m^2/day, and 2 patients at 8 mg/m^2/day). Grade 1 thrombocytopenia was reported for 8 (38%) patients. No patients had Grade 2 thrombocytopenia.

Liver Function Tests

All AST, ALT and bilirubin abnormalities reported on CTEP-5425 were grade 1 or grade 2. Grade 1 AST values were reported for 14 (67%) patients, and Grade 2 AST for 1 (5%) patient. Grade 1 ALT values were reported for 3 (14%) patients, and Grade 2 ALT values were reported for 2 (10%) patients. Grade 1 bilirubin abnormalities were reported for 3 (14%) patients, Grade 2 bilirubin was reported for 1 (5%) patient.

Renal Function Tests

Overall there was only 1 (5%) patient who had a Grade 1 elevated serum creatinine reported. No other creatinine abnormalities were reported on this study.

ADVL0524

Hematologic labs

Thirty-nine (66%) patients treated on ADVL0524 had an abnormal hematological laboratory value reported. Twenty-seven patients (46%) had a grade 3 or 4 hematologic laboratory abnormality. Thirty (51%) patients were reported as having a low hemoglobin, 28 (47%) with thrombocytopenia and 22 (37%) with neutropenia.

Liver function tests

Twenty-four (41%) patients had an abnormal transaminase level reported on this study. Only 2 (3%) of these patients had a CTCAE grade 3 or 4 transaminase abnormality. Four (7%) patients had an elevated bilirubin and 2 (3%) patients had an abnormal GGT level reported. Only 1 one patient had a grade 3 GGT elevation with the rest of the GGT and bilirubin abnormalities graded as grade 1 or 2.

Renal function tests

Two (3%) patients had an increase in their serum creatinine reported and 1 (2%) patient was reported to have a decrease in his creatinine clearance. All three adverse events were ≤ grade 2 in severity.

Electrolyte abnormalities

Twenty-six patients had an abnormal electrolyte level reported. Only 3 of these patients had a grade 3 abnormality. The most common electrolyte abnormality reported was hyponatremia in 15 (25%) patients followed by hypocalcemia in 8 (14%) and hypomagnesemia in 5 (8%).

8.4.3 Vital Signs

No vital sign data was provided as part of this application.

8.4.4 Electrocardiograms (ECGs)

No EKG data was provided as part of this application.

8.4.5 Special Safety Studies/Clinical Trials

Not applicable.

8.4.6 Immunogenicity

Not applicable.

8.5 Other Safety Explorations

8.5.1 Dose Dependency for Adverse Events

CTEP-5425

The MTD of ixabepilone when administered intravenously daily for 5 days every 21 days in pediatric patients with refractory solid tumors was established as 8 mg/m^2/day. The DLTs reported included neutropenia, febrile neutropenia, fatigue, neuropathy, myalgia, pharyngitis, decreased appetite, dehydration, nausea, and stomatitis. Table 18 provides a summary of all reported hematologic adverse events on CTEP-5425 by dose cohort. Table 19 provides a summary of all deaths, SAEs, AEs leading to dose discontinuation and most common non-hematologic AEs on CTEP-5425.

Table 18 Hematologic AEs on CTEP-5425 (by dose cohort)

	Number of Subjects N = 21																				Number of Subjects (%) N = 21
	3 mg/m^2/day N = 3				4.5 mg/m^2/day N = 4				6 mg/m^2/day N = 3				8 mg/m^2/day N = 8				10 mg/m^2/day N = 3				
	Worst CTC Grade				Worst CTC Grade				Worst CTC Grade				Worst CTC Grade				Worst CTC Grade				
Laboratory Parameter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	Total
WBC	0	1	0	0	0	0	1	0	0	2	0	1	1	1	4	1	0	1	1	1	15 (71.4)
ANC	1	0	0	0	0	1	1	1	1	0	1	1	0	0	4	3	0	0	0	3	17 (81.0)
PLT	0	0	0	0	1	0	0	0	1	0	1	0	3	0	2	1	3	0	0	0	12 (57.1)
HGB	1	1	1	0	2	2	0	0	1	2	0	0	3	1	4	0	1	0	2	0	21 (100)

Abbreviations: ANC = absolute neutrophil count; HGB = hemoglobin; PLT = platelets; WBC = white blood cells
(Excerpted from Table 5, page 8 of CTEP-5425 CSR)

Table 19 Summary of AEs on CTEP-5425

	Number of Subjects N = 21																				Number of Subjects (%) N = 21
	3 mg/m^2/day N = 3				4.5 mg/m^2/day N = 4				6 mg/m^2/day N = 3				8 mg/m^2/day N = 8				10 mg/m^2/day N = 3				
	Worst CTC Grade				Worst CTC Grade				Worst CTC Grade				Worst CTC Grade				Worst CTC Grade				
Safety Parameter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	Total
Deaths	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0
Any SAE	0	0	0	0	0	0	2	1	0	0	1	0	0	0	2	1	0	0	0	0	7 (33.3)[a]
Any AE leading to discontinuation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1 (4.8)[b]
Any drug-related AE	0	1	2	0	0	0	3	1	0	1	1	1	0	0	4	4	0	0	0	3	21 (100)
Most common (≥25%) treatment-related non--hematologic AE																					
Vomiting	0	0	0	0	1	1	0	0	0	0	1	0	4	0	1	0	2	0	0	0	10 (47.6)
Fatigue	0	2	0	0	1	0	0	0	0	0	0	0	4	1	0	0	0	1	1	0	10 (47.6)
Decreased appetite	1	0	0	0	0	0	0	0	1	0	0	0	4	0	1	0	2	0	0	0	9 (42.9)
Nausea	0	0	0	0	0	1	1	0	0	0	1	0	2	1	1	0	2	0	0	0	9 (42.9)
Peripheral sensory neuropathy[c]	0	0	0	0	2	0	0	0	1	0	0	0	1	1	1	0	1	0	0	0	7 (33.3)
Alopecia	0	0	0	0	0	1	0	0	0	0	0	0	3	1	0	0	1	0	0	0	6 (28.6)

(excerpted from Table 4, page 7 of CTEP-5425 CSR)

ADVL0524

Dose dependency of AEs can not be ascertained as a single dose of ixabepilone was used on this study.

8.5.2 Time Dependency for Adverse Events

CTEP-5425

No conclusions can be reached regarding time dependency of AEs on this dose-escalation study as patients received 5 different doses of ixabepilone. Additionally only 7 patients received more than one course of therapy with ixabepilone of CTEP-5425.

ADVL0524

Time dependency of AEs can not be ascertained in this study as 52 (88%) patients on ADVL0524 received 2 or less courses of therapy with only 3 (<1%) of patients receiving more than 4 courses.

8.5.3 Drug-Demographic Interactions

CTEP-5425

Pk data was collected on 16 patients on CTEP-5425. Median age of these patients was 12 years (range: 2 to 18). Eight were less than 12 years old. Thirteen of these patients were white, 2 Black/African-American and 1 Asian. Seven of these patients were female and nine male. The pharmacokinetics of ixabepilone in children and adolescents showed a clearance higher than adults, but the more rapid elimination did not appear to fully account for the higher MTD (8mg/m^2/day) than in adults. No further conclusions however were possible due to the small size of the study, the variability of doses administered and the cumulative drug exposure of each patient.

ADVL0524

Forty-four (75%) patients were Caucasian and 10 (17%) Black. In addition 34 (58%) were male and 25 (42%) female. No significant variations were noted in rates of grade 1-4, grade 3-4 or grade 5 toxicities between the different demographic subgroups of patients treated on this study. This assessment however is limited by the lack of pk data, the small size of the study and the variability of the cumulative drug exposure of each patient.

8.5.4 Drug-Disease Interactions

Not applicable.

8.5.5 Drug-Drug Interactions

CTEP-5425

Patients were not allowed to receive St. John's Wort, an inducer of CYP3A4, or known inhibitors of CYP3A4 including grapefruit juice within 1 week of the administration of ixabepilone. Patients were also not allowed to be taking enzyme-inducing anticonvulsants, and were not allowed to be taking these medications within 1 week of entry.

ADVL0524

Patients on ADVL0524 were prohibited from receiving any strong inhibitors of CYP3A4 in addition to grape fruit during the study.

8.6 Additional Safety Evaluations

8.6.1 Human Carcinogenicity

Not applicable.

8.6.2 Human Reproduction and Pregnancy Data

Not applicable.

8.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric assessment of effects on growth was not performed.

8.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

8.7 Additional Submissions / Safety Issues

There was no 120-day safety update for this supplement as all safety follow-up had been finalized by the time of the initial submission of this supplement.

9 Postmarket Experience

Not applicable. Ixabepilone has not been marketed for any pediatric indication.

10 Appendices

10.1 Literature Review/References

1. Widemann BC, Goodspeed W, Goodwin A, Fojo T, Balis FM, Fox E. Phase I trial and pharmacokinetic study of ixabepilone administered daily for 5 days in children and adolescents with refractory solid tumors. Journal of Clinical Oncology. 2009 Feb 1;27(4):550-6. Epub 2008 Dec 15.

2. Jacobs S, Fox E, Krailo M, Hartley G, Navid F, Wexler L, Blaney SM, Goodwin A, Goodspeed W, Balis FM, Adamson PC, Widemann BC. Phase II trial of ixabepilone administered daily for five days in children and young adults with refractory solid tumors: a report from the children's oncology group. Clinical Cancer Research. 2010 Jan 15;16(2):750-4. Epub 2010 Jan 12.

10.2 Labeling Recommendations

Section 8.4 of the labeling was updated based on results of this study as outlined below:

"8.4 Pediatric Use

The effectiveness of IXEMPRA in pediatric patients has not been established. IXEMPRA was evaluated in one Phase 1 and one Phase 2 trial. The pediatric patients had a safety profile consistent with that seen in adults, and no new safety signals were identified.

In the Phase 1 open-label, dose-finding trial, the safety of IXEMPRA was evaluated in 19 pediatric patients with advanced or refractory solid tumors and 2 with acute leukemias. IXEMPRA was administered as a one-hour IV infusion daily for the first five days of a 21-day cycle at one of 5 dose levels, ranging from 3 to 10 mg/m^2. Among the 21 patients, 12 ranged in age from 2 to 12 years and 9 ranged from 13 to 18 years. The maximum tolerated dose was 8 mg/m^2 IV daily for 5 days every 21 days. No significant anti-tumor activity was observed. The pharmacokinetics of ixabepilone were characterized by population pharmacokinetic analysis of data for 16 patients from this trial who were aged 2 to 18 years (median 12 years). The pharmacokinetic parameters of ixabepilone in these pediatric patients were compared to the corresponding parameters of 130 adult patients enrolled in clinical trials with the same dosing schedule. The median BSA normalized clearance of ixabepilone in pediatric patients (17 L/h/m^2) was similar to that in adult patients (20 L/h/m^2).

In the Phase 2 trial of 59 patients with advanced or refractory solid tumors, 28 ranged in age from 3 to 12 years and 19 ranged in age from 13 to 18 years. Twelve additional

patients over the age of 18 were treated in this trial. IXEMPRA was administered at a dose of 8 mg/m^2 IV daily for 5 days every 21 days. This trial was terminated early due to lack of efficacy."

10.3 Advisory Committee Meeting

None.

10.4 Pediatric Exclusivity Board Meetings

This reviewer presented the review findings for pediatric exclusivity determination to the Pediatric Exclusivity Board (PEB) on April 5, 2011. Although the applicant did not completely meet the age requirements for patient enrollment set forth in the PWR, the overall conclusion that treatment with ixabepilone did not benefit pediatric patients with relapsed and refractory solid tumors was not affected. The Applicant fairly responded to the PWR by performing studies CTEP-5425 and ADVL0524. Thus, important information regarding the use of ixebepilone in the pediatric population has been obtained from these study results. Further, discussions at the PEB meeting indicated that including data generated from these studies in the labeling would be beneficial to physicians that participate in the care of pediatric oncology patients. The Pediatric Exclusivity Board granted pediatric exclusivity for ixabepilone (Ixempra®), effective April 5, 2011.

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/s/

AMIR SHAHLAEE
09/26/2011

KE LIU
09/27/2011