U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	22-065/S-006
Drug Name:	Ixabepilone
Indication(s):	Labeling change reflecting pediatric studies
Applicant:	Bristol-Myers Squibb
Date(s):	Submission Date: January 18, 2011
	PDUFA Date: July 17, 2011
Review Priority:	Priority (pediatric)
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Qiang (Casey) Xu, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader
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Keywords:

Pediatric written request, recurrent solid tumor, sample size

Table of Contents

1. EXECUTIVE SUMMARY

The Pediatric Exclusivity Board convened on April 5, 2011 to discuss the fulfillment of the Pediatric Written Request (PWR) based on the results from Studies CTEP-5425 (Phase I) and ADVL0524 (Phase II). The Board members voted unanimously favoring granting the pediatric exclusivity.

Among 80 patients treated with ixabepilone combining the Phase I and Phase II studies, no objective response was observed. Studies CTEP-5425 and ADVL0524 consistently indicated that there was no clinical activity of ixabepilone in pediatric patients.

The Board members pointed out that these two studies achieved the primary goal, which was to estimate the efficacy of ixabepilone in pediatric patients. Due to a lack of clinical activity in this population, smaller number of patients who met the age criterion specified in PWR was justified from scientific and ethical perspectives.

The Board further recommended that (1) communications with regard to PWR should be enhanced between investigators and sponsors; (2) in future sponsors should be advised to submit written study amendments to explain study changes, e.g. the decrease in sample size in the case of ixabepilone; and (3) the template of PWR in oncology studies should avoid words with vague meaning, such as “approximately”, and any outstanding PWR with similar languages should be retrospectively clarified.

2. INTRODUCTION

2.1 Overview

Ixabepilone (IXEMPRA® 40 mg/m^2, administered as a single intravenous [IV] dose over 3 hours, every 3 weeks) was approved on Oct 16, 2007 by the FDA as a monotherapy for the treatment of metastatic or locally advanced breast cancer in subjects whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine. Ixabepilone was also approved as a combination therapy with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.

Ixabepilone, a semisynthetic analog of the natural product epothilone B, binds directly to β-tubulin subunits on microtubules, leading to suppression of microtubule dynamics; and thus blocks cells in the mitotic phase of the cell division cycle, leading to cell death.

Bristol-Myers Squibb (BMS) submitted this Supplemental New Drug Application (sNDA) to fulfill the Pediatric Written Request (PWR) of Jun 22, 2007, amended on Apr 22, 2008 and Oct 25, 2010 based on two National Cancer Institute (NCI) sponsored studies: CTEP-5425 and ADVL0524 as summarized in the table below.

Table 2.1.1: List of all studies included in analysis

Study	Phase and Design	Primary Objective	# of Subjects	Study Population
CTEP-5425	Phase 1 and Pharmacokinetic Study	Find MTD in pediatric patients	21 subjects across 5 dose levels	Pediatric patients with refractory solid tumors
ADVL0524	Phase 2	Determine response rate in each tumor stratum at the MTD in CTEP5425	59 treated patients combining 6 tumor strata	Pediatric patients with refractory solid tumors

2.2 Data Sources

Electronic submission including the study reports for the two pediatric clinical studies, CTEP5425 and ADVL0524, and datasets is located in

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3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There is no efficacy demonstrated in either study. The sponsor submitted only tabulations of two studies.

3.2 Evaluation of Efficacy

Neither CTEP5425 nor ADVL0524 demonstrated efficacy. As a result, the sponsor does not intend to pursue a pediatric indication in this sNDA.

3.2.1 Study CTEP5425

Study Design and Endpoints

This was a Phase 1, single-center, open-label, dose-escalation study of ixabepilone administered IV over 1 hour daily for 5 consecutive days, every 21 days in pediatric subjects with advanced, refractory solid tumors including brain tumors.

Hematologic Dose-Limiting Toxicity (DLT) was defined as 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 purposes of this trial, if a subject received a platelet transfusion for a platelet count that was < 20,000/μL but > 10,000/μL, this was 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.

Non-hematologic DLT was defined as any Grade 3 or Grade 4 non-hematologic toxicity related to study drug or failure to recover to Grade ≤ 1 toxicity or to baseline toxicity, if greater than Grade 1 by Day 28 or the treatment cycle with the exception of: (1) Grade 3 nausea or vomiting during the first treatment cycle, which could be successfully treated with antiemetics. In subsequent treatment cycles antiemetics were administered prior to administration of study drug; (2) Grade 3 elevations in serum glutamic-pyruvic transaminase (SGPT) or serum glutamic-oxaloacetic transaminase (SGOT), which recovered to ≤ Grade 1 toxicity by day 28 of the treatment cycle.

The Maximum Tolerated Dose (MTD) was defined as the dose level immediately below the dose level at which ≥ 2 subjects in a cohort of 2 to 6 subjects experienced a DLT. A standard 3+3 design was used for dose escalations.

This study enrolled subjects (≥ 1 years and ≤ 18 years of age) with a histologically confirmed, measurable or evaluable solid tumor refractory to standard treatment. Subjects were enrolled onto sequential cohorts to 5 dose levels. The starting dose was 3 mg/m^2/day × 5 every 21 days, which represents 50% of the MTD determined in the adult Phase 1 trial using the same dose schedule. Planned sequential dose escalations of ixabepilone were: 3 mg/m^2/day; 4.5 mg/m^2/day; 6 mg/m^2/day; and 8 mg/m^2/day. If the 8 mg/m^2/day dose level was tolerated, subsequent dose levels were planned at 30% increments (i.e., 10 mg/m^2/day, 13 mg/m^2/day, etc.). If the 3 mg/m^2/day dose level exceeded the MTD, subsequent subjects were entered at a 2 mg/m^2/day dose level, a 33% dose reduction.

According to the study protocol and PWR, up to 12 subjects were to be enrolled at the MTD dose, including a minimum of 3 subjects who were < 12 years of age (at least 2 who are ≤ 5 years of age) and a minimum of 3 subjects who were ≥ 12 years of age, if possible.

Reviewer's Comment:

At the MTD, 3 patients were < 12; 5 were ≥ 12 years of age; and 2 were ≤ 5 years of age. The enrollment fulfill the requirement of age at baseline in the PWR.

Efficacy was not a primary endpoint of CTEP5425. Each subject's best overall tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]) was assessed by the investigator for all treated subjects according to Response Evaluation Criteria in Solid Tumors (RECIST).

Patient Disposition, Demographic and Baseline Characteristics

The study enrolled 21 subjects. All enrolled subjects were treated 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).

The most common reason for discontinuation of study drug was disease progression (19 subjects, 90.5%). Other reasons were completed treatment (1 subject, 4.8%) and other (1 subject, 4.8%; started radiation) (Table 3.2.1.1).

Table 3.2.1.1 Patient Disposition in CTEP5425

	Number of Subjects (%)					
	Ixabepilone					
Dose (mg/m^2/day)	3	4.5	6	8	10	Total
N	N = 3	N = 4	N = 3	N = 8	N = 3	N = 21
All enrolled	3 (100)	4 (100)	3 (100)	8 (100)	3(100)	21 (100)
Never treated	0	0	0	0	0	0
Treated	3 (100)	4 (100)	3 (100)	8 (100)	3 (100)	21(100)
Still on treatment	0	0	0	0	0	0
Off treatment[a]	3 (100)	4 (100)	3 (100)	8 (100)	3 (100)	21(100)
Reason off treatment[a]						
Completed treatment[b]	0	1 (25.0)	0	0	0	1 (4.8)
Disease progression	3 (100)	2 (50.0)	3 (100)	8 (100)	3 (100)	19 (90.5)
Other[c]	0	1 (25.0)	0	0	0	1 (4.8)
Subjects with eligibility deviations	0	0	0	1 (12.5)	0	1 (4.8)

[a] Percentages are based on the number of subjects who received treatment.

[b] For the 1 subject with a reason off treatment due to "completed treatment," the option on the Case Report Form was defined as "completed treatment period but refused the protocol-specified follow-up. Date off treatment and date off study must have been the same."

[c] The 1 subject reported as off-treatment due to "Other" had started radiation

Demographics and baseline disease characteristics are summarized in Tables 3.2.1.2 and 3.2.1.3.

Table 3.2.1.2 Patient Demographic Characteristics at Baseline in CTEP5425

	Number of Subjects (%)					
	Ixabepilone					
Dose (mg/m^2/day)	3	4.5	6	8	10	Total
N	N = 3	N = 4	N = 3	N = 8	N = 3	N = 21
Age (years)						
Median	5.0	9.5	10.0	12.5	9.0	11.0
Min - Max	4 -17	4 -17	4 -15	2 -18	4 -17	2 -18
Gender						
Male	3 (100)	1 (25.0)	2 (66.7)	4 (50.0)	2 (66.7)	12 (57.1)
Female	0	3 (75.0)	1 (33.3)	4 (50.0)	1 (33.3)	9 (42.9)
Performance score (Lanksy or Karnofsky)						
100	1 (33.3)	1 (25.0)	1 (33.3)	0	1 (33.3)	4 (19.0)
90	2 (66.7)	2 (50.0)	0	4 (50.0)	0	8 (38.1)
80	0	0	1 (33.3)	3 (37.5)	2 (66.7)	6 (28.6)
70	0	0	1 (33.3)	1 (12.5)	0	2(9.5)
60	0	1 (25.0)	0	0	0	1 (4.8)
Tumor Type						
Embryonal rhabdomyosarcoma	0	0	0	1 (12.5)	0	1 (4.8)

*From Table 5.3.1 in the sponsor's CSR.

Table 3.2.1.2 Patient Demographic Characteristics at Baseline in CTEP5425 (Cont.)

	Number of Subjects (%)					
	Ixabepilone					
Dose (mg/m^2/day)	3	4.5	6	8	10	Total
N	N = 3	N = 4	N = 3	N = 8	N = 3	N = 21
Ewing's sarcoma	0	0	0	1 (12.5)	0	1 (4.8)
Extraskeletal Ewing's sarcoma	0	0	1 (33.3)	0	0	1 (4.8)
Hemangioendothelioma	0	1 (25.0)	0	0	0	1 (4.8)
Hepatoblastoma	0	0	0	1 (12.5)	1 (33.3)	2 (9.5)
Monophasic synovial sarcoma	0	0	0	1 (12.5)	0	1 (4.8)
Monophasic papillary Wilms tumor	0	0	0	0	1 (33.3)	1 (4.8)
MPNST	0	1 (25.0)	0	0	0	1 (4.8)
Neuroblastoma	1 (33.3)	0	0	0	0	1 (4.8)
Osteogenic sarcoma	0	0	0	0	1 (33.3)	1 (4.8)
Osteosarcoma	0	0	0	1 (12.5)	0	1 (4.8)
Osteosarcoma poorly differentiated	0	0	1 (33.3)	0	0	1 (4.8)
Pleuropulmonary blastoma	0	1 (25.0)	0	0	0	1 (4.8)
Pre-B ALL	0	0	0	1 (12.5)	0	1 (4.8)
Pre-B ALL CNS negative	0	0	0	1 (12.5)	0	1 (4.8)
Rhabdomyosarcoma	0	0	1 (33.3)	0	0	1 (4.8)
Rhabdomyosarcoma, embryonal	1 (33.3)	0	0	0	0	1 (4.8)
Undifferentiated sarcoma	0	1 (25.0)	0	0	0	1 (4.8)
Undifferentiated spindle sarcoma	0	0	0	1 (12.5)	0	1 (4.8)
Wilms Tumor	1 (33.3)	0	0	0	0	1 (4.8)

Abbreviations: ALL = acute lymphoblastic leukemia; CNS = central nervous system; MPNST = malignant peripheral nerve sheath tumor; Pre-B proliferation of the blasts

*From Table 5.3.1 in the sponsor's CSR.

Table 3.2.1.3 Patient Disease Characteristics at Baseline in CTEP5425

	Number of Subjects (%) N=21
Subjects with at least one target lesion	13 (61.9)
Subjects with no target lesion	8 (38.1)
Site of target lesion (a)	
Abdomen	2 (9.5)
Bone	1 (4.8)
Chest	2 (9.5)
Leg	1 (4.8)
Liver	2 (9.5)
Lung	9 (42.9)
Lymph node(s) Inguinal	1 (4.8)
Ocular Orbits	1 (4.8)
Pleura	2 (9.5)

*From Table 5.3.2 in the sponsor's CSR

Results and Conclusions

No objective tumor responses (CR or PR) were observed in this study in the 21 subjects who were assessable for response. The best response was SD in 6 (28.6%) subjects, PD in 12 (57.1%) subjects, or unknown (subject's best response information was missing) in 3 (14.3%) subjects (Table 3.2.1.4).

The MTD of ixabepilone when administered intravenously daily for 5 days every 21 days in pediatric subjects with refractory solid tumors was established as 8 mg/m^2/day. The DLTs included neutropenia, febrile neutropenia, fatigue, neuropathy, myalgia, pharyngitis, decreased appetite, dehydration, nausea, and stomatitis (Table 3.2.1.5). Please refer to the clinical reviewer's report for the detailed safety evaluation.

Table 3.2.1.4 Best Overall Response in Treated Patients in CTEP5425

Number of Subjects (%)

	Ixa 3mg/m2/day (N=3)	Ixa 4.5mg/m2/day (N=4)	Ixa 6mg/m2/day (N=3)	Ixa 8mg/m2/day (N=8)	Ixa 10mg/m2/day (N=3)	Total (N=21)
Best Overall Response						
CR	0	0	0	0	0	0
PR	0	0	0	0	0	0
SD	1 (33.3)	1 (25.0)	1 (33.3)	3 (37.5)	0	6 (28.6)
PD	2 (66.7)	1 (25.0)	2 (66.7)	4 (50.0)	3 (100.0)	12 (57.1)
Unknown (a)	0	2 (50.0)	0	1 (12.5)	0	3 (14.3)

*From Table 7.1 in the sponsor's CSR

Table 3.2.1.5 Dose Limiting Toxicities by Doses in CTEP5425

Ixabepilone Dose Level (mg/m^2/day)	Number of Subjects with DLT / Total Treated at Dose Level N = 21	DLTs System Organ Class Grade: Preferred Term
3	0/3	---
4.5	0/4	---
6	0/3	---
8	1/8	Blood and lymphatic system disorders Grade 3: febrile neutropenia Nervous system disorders Grade 3: peripheral sensory neuropathy Musculoskeletal and connective tissue disorders Grade 3: myalgia Infections and infestations Grade 3: pharyngitis Metabolism and nutrition disorders Grade 3: decreased appetite Grade 3: dehydration GI disorders Grade 3: nausea Grade 3: stomatitis
10	2/3	Blood and lymphatic system disorders Grade 4: neutropenia General disorders and administrative site conditions Grade 3: fatigue

*From Table 3 in the sponsor's CSR

3.2.2 Study ADVL0524

Study Design and Endpoints

Study ADVL0524 was a Phase 2, open-label study of ixabepilone administered IV over 1 hour daily for 5 consecutive days, every 21 days in children and young adults with refractory solid tumors. The ixabepilone dose for this study was 8 mg/m^2/day (maximum 16 mg/day), the MTD in CTEP-5425.

This study enrolled subjects with a histologically confirmed malignancy at original diagnosis or recurrence. The target tumors were: (1) embryonal or alveolar rhabdomyosarcoma, (2) osteosarcoma, (3) Ewing sarcoma/PNET, (4) synovial sarcoma or MPNST, (5) Wilms tumor, or (6) neuroblastoma. According to the PWR, all subjects were required to be at least 1 year of age, and $\leq$ 21 years of age.

The study was primarily aimed to determine the objective response rate (CR+PR) per RECIST to ixabepilone in each stratum of solid malignant tumors, using a 2-stage design (Table 3.2.2.1) with a targeted response rate of 30%. Within each stratum, the following 2-stage design was employed:

Table 3.2.2.1 Study Design of ADVL0524

	Cumulative Number of Responses at the End of the Stage	Decision
Stage 1: Enter 10 subjects	0	Terminate the trial for this stratum because the agent is ineffective
	1 or more	Proceed to stage 2
Stage 2: Enter 10 additional subjects	2 or less	Terminate the trial for this stratum because the agent is ineffective
	3 or more	Terminate the trial for this stratum because the agent is effective

* From Table 3.1 in the sponsor's CSR

If the true response rate was 30%, then this design would provide a power of 95% in each stratum at a type I error of 0.07 under the null hypothesis that the response rate was only 5%.

Patient Disposition, Demographic and Baseline Characteristics

A total of 61 subjects were enrolled at 34 centers in 3 countries (USA, Canada, and Australia). Safety and efficacy results are presented for the 59 (96.7%) subjects who were administered ixabepilone. Two subjects were never treated due to refusal of protocol therapy by patient/parent/guardian (1 subject), and major deviation from protocol therapy (1 subject). The most common reason for discontinuation of study drug was clinical or radiographic disease progression (51 subjects, 86.4%). Patient Disposition is presented in Table 3.2.2.2.

Table 3.2.2.2 Patient Disposition in ADVL0524

	Number of Subjects (%)
	Ixabepilone N = 61
All enrolled	61
Never treated[d]	2 (3.3)
Treated	59 (96.7)
Still on treatment	0
Off treatment[e]	59 (100)
Reason off treatment[b]	
Clinical or radiographic disease progression	51 (86.4)
Death	1 (1.7)
Grade 4 non-hematological toxicity for ≥ 2 weeks	1 (1.7)
Physician determined it was in the patient's best interest	4 (6.8)
Refusal of further protocol therapy by patient/parent/guardian	2 (3.4)

[a] Two (2) subjects were never treated due to refusal of protocol therapy by patient/parent/guardian (1 subject), and major deviation from protocol therapy (1 subject).

[c] Percentages were based on the number of subjects who received treatment.

*From Table 5.1 in the sponsor's CSR

Among the 59 treated subjects, the median age was 13 years (range: 3 - 36 years). Thirty-four (57.6%) subjects were male; 44 (74.6%) subjects were white; and 34 (57.6%) subjects had received prior radiation therapy. Prior to study therapy, 10 (16.9%) subjects each had a tumor type of neuroblastoma, osteosarcoma, synovial sarcoma or malignant peripheral nerve sheath tumor (MPNST), Wilms tumor, or alveolar or embryonal rhabdomyosarcoma; and 9 (15.3%) subjects had a tumor type of Ewing sarcoma or peripheral neuroectodermal tumor (PNET) (Table 3.2.2.3). Table 3.2.2.4 presents target lesions using RECIST in treated subjects.

Table 3.2.2.3 Patient Characteristics at Baseline in ADVL0524

	Number of Subjects (%)
	Ixabepilone N = 59
Age (years)	
Median	13
Min - Max	3 - 36
Gender	
Male	34 (57.6)
Female	25 (42.4)
Race	
White	44 (74.6)
Black	10 (16.9)
Asian Indian, Pakistani	1 (1.7)
Korean	1 (1.7)
Other Asian, including Asian NOS and Oriental NOS	1 (1.7)
Other	1 (1.7)
Unknown	1 (1.7)
Performance score (Lanksy or Karnofsky)	
100	20 (33.9)
90	10 (16.9)
80	3 (5.1)
70	5 (8.5)
60	6 (10.2)
50	1 (1.7)
Unknown	14 (23.7)
Tumor Type	
Alveolar or embryonal rhabdomyosarcoma	10 (16.9)
Ewing's sarcoma or PNET	9 (15.3)
Neuroblastoma	10 (16.9)
Osteosarcoma	10 (16.9)
Synovial sarcoma or MPNST	10 (16.9)
Wilms tumor	10 (16.9)
Number of subjects who received prior chemotherapy	59 (100)
Number of subjects who had prior radiation therapy	34 (57.6)

Abbreviations: MPNST = malignant peripheral nerve sheath tumor; PNET = peripheral neuroectodermal tumor

*From Table 5.3.1 in the sponsor's CSR

Reviewer's Comments:

The PWR required approximately 10 patients be enrolled in each tumor type with a maximum of 21 years of age. Three patients in the category of Ewing's sarcoma or PNET were greater than 21 years of age (23-36); 3 patients in alveolar or embryonal rhabdomyosarcoma were greater than 21 years of age (22-25); and 1 patient in the category of synovial sarcoma or MPNST was 24 years of age. All other patients met the criterion for age.

Table 3.2.2.4 Patient Target Lesions at Baseline in ADVL0524

	Number of Subjects (%) N=59
Subjects with at least one target lesion	59 (100.0)
Site of target lesion (a)	
Abdomen, NOS	6 (10.2)
Anterior mediastinum	1 (1.7)
Breast, NOS	1 (1.7)
Connective, subcutaneous and other soft tissues of abdomen	2 (3.4)
Connective, subcutaneous and other soft tissues of head, face, and neck (excludes connective tissue of orbit C69.6 and nasal cartilage C30.0)	2 (3.4)
Connective, subcutaneous and other soft tissues of lower limb and hip	2 (3.4)
Connective, subcutaneous and other soft tissues of pelvis	4 (6.8)
Connective, subcutaneous and other soft tissues of thorax (excludes thymus C37.9, heart and mediastinum C38._)	1 (1.7)
Connective, subcutaneous and other soft tissues of trunk, NOS	1 (1.7)
Head, face or neck, NOS	1 (1.7)
Intrathoracic lymph nodes	1 (1.7)
Jejunum	1 (1.7)
KIDNEY	1 (1.7)
LIVER AND INTRAHEPATIC BILE DUCTS	1 (1.7)
Liver	5 (8.5)
Long bones of lower limb and associated joints	2 (3.4)
Lower lobe, lung	20 (33.9)
Lung, NOS	10 (16.9)
Lymph nodes of inguinal region or leg	1 (1.7)
Mediastinum, NOS	5 (8.5)
Middle ear	1 (1.7)
Middle lobe, lung	5 (8.5)
Overlapping lesion of heart, mediastinum, and pleura	1 (1.7)
Overlapping lesion of retroperitoneum and peritoneum	1 (1.7)
Parietal lobe	1 (1.7)
Pelvic bones, sacrum, coccyx and associated joints	3 (5.1)
Pelvis, NOS	2 (3.4)
Peritoneum, NOS	1 (1.7)
Renal pelvis	1 (1.7)
Retroperitoneum	2 (3.4)
Rib, sternum, clavicle and associated joints	2 (3.4)
Short bones of lower limb and associated joints	1 (1.7)
horax, NOS	2 (3.4)
Upper lobe, lung	11 (18.6)
Upper respiratory tract, NOS	1 (1.7)
Vertebral column (excludes sacrum and coccyx C41.4)	1 (1.7)

(a) Subjects can have more than one target lesion.

*From Table 5.3.2 in the sponsor's CSR

Results and Conclusions

No objective tumor responses (CR or PR) were reported in this study. The best response was SD in 14 (23.7%) subjects, or unknown in 3 (5.1%) subjects (Table 3.2.2.5). For subjects with "unknown" tumor response, the subject's best tumor response on-study was missing.

Table 3.2.2.5 Best Overall Response in Treated Patients

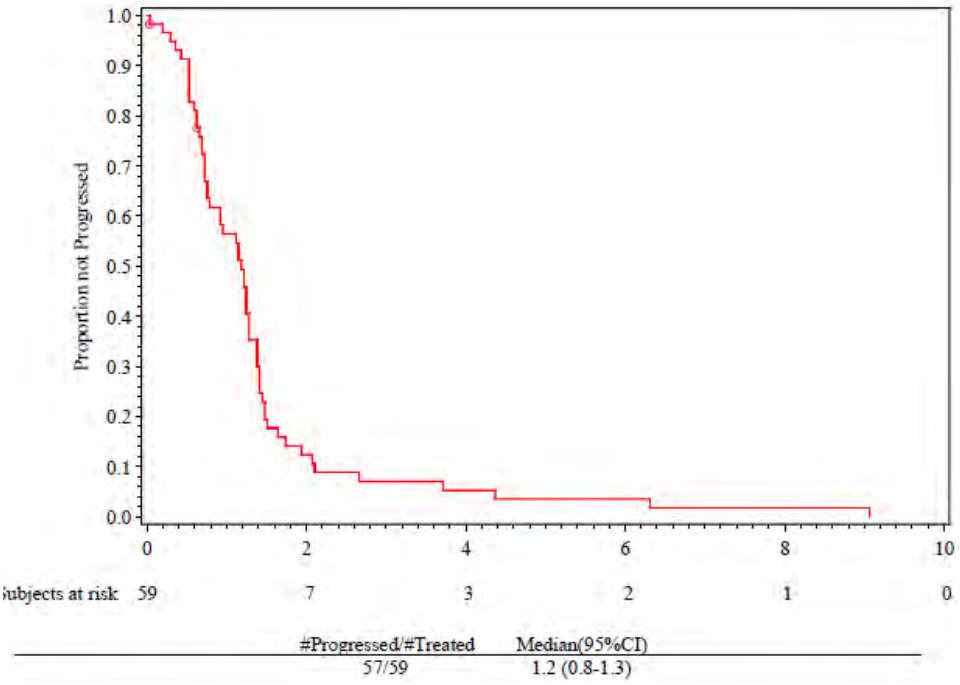
	Number of Subjects (%) (N = 59)
Best Overall Response	
Complete Response	0
Partial Response	0
Stable Disease	14 (23.7)
Progressive Disease	42 (71.2)
Unknown[a]	3 (5.1)

[a] Subject's best tumor response on-study was missing.

*From Table 7.1 in the sponsor's CSR

Among treated subjects, the median progression free survival (PFS) was 1.2 months (95% 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).

Figure 3.2.2.1: Kaplan-Meier Estimates for PFS in Treated Patients in ADVL0524



Reviewer's Comments: Since this is a single-arm study, the analysis of PFS is considered as exploratory.

A lack of objective tumor responses and short median progression free survival indicate a lack of meaningful clinical activity for ixabepilone in the treatment of recurrent solid malignant tumors in pediatric patients.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

No objective responses were observed in either study. Therefore, efficacy analyses by gender, race, and age specific subgroups are omitted.

4.2 Other Special/Subgroup Populations

No other special populations have been identified.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

A total of 21 patients were treated with ixabepilone in Study CTEP-5425 with 8 patients treated at MTD (8 mg/m^2/day). Out of these 8 patients, only 1 patient (12.5%) demonstrated DLT.

A total of 59 patients were treated at the MTD (8 mg/m^2/day) in Study ADVL0524. Among them, 10 patients each had a baseline tumor type of neuroblastoma, osteosarcoma, synovial sarcoma or malignant peripheral nerve sheath tumor (MPNST), Wilms tumor, or alveolar or embryonal rhabdomyosarcoma; and 9 subjects had a tumor type of Ewing sarcoma or peripheral neuroectodermal tumor (PNET). Three patients each with Ewing's sarcoma or PNET and alveolar or embryonal rhabdomyosarcoma and 1 patient with synovial sarcoma or MPNST were greater than 21 years of age, a maximum age required in PWR.

There was no objective tumor response (CR or PR) observed in either study. In addition, Study ADVL0524 demonstrated rapid disease progression with the median PFS of 1.2 months (95% CI: 0.8 - 1.3).

In summary, results from the Phase I and Phase II studies indicated that there was no clinical activity of ixabepilone in pediatric patients.

5.2 Conclusions and Recommendations

The Pediatric Exclusivity Board convened on April 5, 2011 to discuss the fulfillment of PWR based on the Phase I and Phase II studies, and voted unanimously favoring granting the pediatric exclusivity.

The Board members pointed out that these two studies achieved the primary goal, which was to estimate the efficacy of ixabepilone in pediatric patients. Due to a lack of clinical activity in this population, smaller number of patients who met the age criterion specified in PWR was justified from scientific and ethical perspectives.

The Board further recommended that (1) communications with regard to PWR should be enhanced between investigators and sponsors; (2) in future sponsors should be advised to submit written study amendments to explain study changes, e.g. the decrease in sample size in the case of ixabepilone; and (3) the template of PWR in oncology studies should avoid words with vague meaning, such as “approximately”, and any outstanding PWR with similar languages should be retrospectively clarified.

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/s/

QIANG XU
05/20/2011

SHENGHUI TANG
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