02-C-0031: Phase I Trial and Pharmacokinetic Study of BMS-247550 (NSC 710428), an Epothilone B Analog, in Pediatric Patients with Refractory Solid Tumors

BMS-247550 is a semi-synthetic analog of the natural product epothilone B. The epothilones are a novel class of microtubule-stabilizing agents obtained from the fermentation of the cellulose degrading myxobacteria, *Sorangium cellulosum*. Nanomolar concentrations of BMS-247550 are cytotoxic against a broad range of tumors in *in vitro* and *in vivo* preclinical models, and BMS-247550 has demonstrated activity in tumor cell lines that are naturally insensitive to or have developed resistance to paclitaxel. A pediatric phase I trial of BMS-247550 will be performed in children with refractory solid tumors to define the MTD, toxicity profile, dose-limiting toxicities, pharmacokinetics and pharmacodynamics. Results of this pediatric phase I trial will be compared to those of an ongoing Medicine Branch, NCI, phase I trial with BMS-247550 for adult patients with solid tumors, which uses the same dosing schedule and study endpoints.

ELIGIBILITY CRITERIA:

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

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.

Measurable/Evaluable Disease: Patients must have measurable or evaluable tumors.

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.

Performance status: Patients > 10 years must have a Karnofsky performance level ≥ 50, and children ≤ 10 years must have a Lansky performance level ≥ 50. (See Appendix 1A). 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.

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.

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.

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

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

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).

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.

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:

- 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.
- 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).
- Pregnant or breast feeding females are excluded because BMS-247550 may be harmful to the developing fetus or nursing child.
- Patients currently receiving other investigational agents.
- Patients currently receiving St. John Wort. The intake of other agents inducing CYP3A4 is not prohibited
- Patients receiving known inhibitors of CYP3A4 including grapefruit juice within 1 week prior to and following the administration of BMS-247550.
- Patients with preexisting grade 2 or greater sensory neuropathy.
- Patients with known severe prior hypersensitivity reaction to agents containing Cremophor EL

PRETREATMENT EVALUATION:

- History and physical, documentation of signs and symptoms and measurable disease, height, weight, BSA
- Neurologic assessment and the Purdue Pegboard test
- Laboratory work to assess blood counts, organ function and metabolic status within 72 hours prior to enrollment
- Radiographic evaluation within 2 weeks prior to the start of therapy

GENERAL TREATMENT PLAN:

BMS-247550 will be given intravenously over 1 hour daily for 5 consecutive days 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. Treatment cycles can be extended to 28 days to allow for patients to recover from toxicity. The starting dose of BMS-247550 is 3 mg/m^2 ,

escalations to 4.5. 6.0 and 8.0 mg/m^2. Intrapatient dose escalations will occur provided the BMS-247550 is tolerated on the prior cycle.

PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES:
Blood samples will be drawn after the first dose (cycle 1) out to 72 hours. Blood samples will also be obtained to measure nerve growth factor prior to treatment cycle 1, 2 and 3, and in any patient who develops peripheral neuropathy

HOSPITALIZATION: Not anticipated

ACCRUAL: Open to accrual. Patients meeting eligibility criteria can be referred to the Pediatric Oncology Branch, NCI, for evaluation and treatment. Patients should bring to NIH a summary of previous treatment, most recent laboratory work, copies of most recent radiologic studies including 2 scans that document disease progression from last treatment, and original pathology slides and report.