

02-C-0141 A Phase I Trial and Pharmacokinetic Study of ABT-751, an Orally Bioavailable Tubulin Binding Agent, on a 7-Day and 21-Day Dosing Schedule in Pediatric Patients with Refractory Solid Tumors

ABT-751 is a novel, orally-bioavailable sulfonamide antimitotic agent that binds to the colchicine binding site on β -tubulin and inhibits polymerization of microtubules. ABT-751 demonstrated a broad spectrum of activity in a panel of 30 tumor cell lines *in vitro* and in xenograft models of human tumors *in vivo* including those that are paclitaxel, vincristine, and doxorubicin-resistant due to the multidrug-resistant (MDR) phenotype (P-gp overexpression). ABT-751 was most active in a preclinical murine sarcoma model. In a phase I study of oral ABT-751 in adults with solid tumors on a daily x 5 days q 21 days schedule the maximum allowable dose (MAD) was 240 mg/m²/dose. The unique mechanism of action (colchicine β -tubulin binding site) for an antimitotic agent, broad spectrum of activity in preclinical studies, and oral bioavailability make ABT-751 a potentially important new agent for evaluation in the pediatric population. A pediatric phase I trial of ABT-751 will be performed to determine the, toxicity profile, dose-limiting toxicities, maximum tolerated dose (MTD) on a 7-day and 21-day dosing schedule, pharmacokinetics, and pharmacodynamics.

ELIGIBILITY CRITERIA:

Age: Patients must be ≤ 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 if a biopsy has not been performed.

Disease Status: Patients must have measurable or evaluable tumors. In patients with neuroblastoma measurable or evaluable tumors is not required because of the demonstration of clinical benefit in previously treated patients with neuroblastoma on this trial.

Prior Therapy:

- The patient's cancer must have relapsed after or failed to respond to frontline standard therapy and there must not be other standard treatment options available. Standard 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 30 days prior to study entry (42 days 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 old must have a Karnofsky performance level > 50 , and children ≤ 10 years old must have a Lansky performance level > 50 (See Appendix 1B).

Hematological Function: Patients must have adequate bone marrow function, defined as a peripheral absolute neutrophil count of $\geq 1,500/\mu\text{L}$, and a platelet count $\geq 100,000/\mu\text{L}$.

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 m².

Age (Years)	Maximum Serum Creatinine (mg/dl)
≤ 5	0.8
$5 < \text{age} \leq 10$	1.0
$10 < \text{age} \leq 15$	1.2
> 15	1.5

Cardiac Function: A normal left ventricular ejection fraction measured by Echocardiogram.

Informed Consent: All patients or their legal guardians (if the patients is <18 years old) must sign a document of informed consent (Pediatric Oncology Branch, NCI screening protocol for NIH patients) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardians must voluntarily sign the IRB approved 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 investigator, protocol chairperson or associate investigator would compromise the patient's ability to tolerate the investigational agent or are likely to interfere with the study procedures or endpoints.
- Patients with a history of bone marrow transplantation or extensive radiotherapy (craniospinal radiation, total body radiation, or radiation to more than half of the pelvis) within the previous 4 months.
- Pregnant or breast feeding females are excluded because ABT-751 may be harmful to the developing fetus or nursing child.
- Patients currently receiving other investigational agents.
- Patients with preexisting grade 2 or greater sensory or motor neuropathy.
- Patients with CNS tumor who have motor or sensory deficits that would obscure the assessment of sensory neuropathy.
- Patients with allergy to sulfa containing medications.
- Patients previously known to be HIV infected because of the potential suppression of the immune system by ABT-751.
- Inability to swallow intact capsules.

PRETREATMENT EVALUATION:

- History and physical, documentation of measurable disease, and signs and symptoms, height, weight and BSA.

- Neurological assessment and the Purdue Pegboard test, and WEST-Hand esthesiometry.
- Laboratory tests to access blood counts, organ function and metabolic status within 72 hours prior to enrollment
- Evaluation of measurable or evaluable disease sites or known prior disease sites (in patients without measurable or evaluable disease) by appropriate radiological evaluation must be performed within the 2 weeks prior to the start of therapy. Dynamic contrast-enhanced MRI of representative soft tissue tumor mass prior to the initiation of therapy with ABT-751 therapy on treatment cycle 1 in selected patients with soft tissue masses greater than 3 cm in diameter. This study will assess the effect of ABT-751 on tumor vascularity and tumor blood flow.
- EKG and echocardiogram

GENERAL TREATMENT PLAN:

Two dosing schedules will be studied and entry will be alternated between schedules. Patients will either receive ABT-751 (21 day treatment cycle) or orally (PO) on a once daily x 21 consecutive days (day 1-21), every 28 days. Treatment cycles can be repeated immediately upon completion of the previous 21 or 28 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 (7-day schedule) or 42 (21-day schedule) days to allow patients to recover from toxicity.

PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES:

Blood for pharmacokinetic studies of ABT-751 will be drawn according to the following schedule: 1) Relative to the day 1 oral dose: before the first oral dose, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, and 10 to 12 h following the first oral dose. 2) In addition, samples should be drawn on days 2, 5, and 7 prior to the oral administration of the daily dose of ABT-751.

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.