Pediatric
ONCOLOGY BRANCH

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CLINICAL TRIALS

Pediatric Oncology Branch
National Cancer Institute

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PHASE I TRIALS

06-C-0152 D:	A Phase I Trial Cediranib (AZD2171), an Orally Bioavailable Antiangiogenic Agent, in Children and Adolescents with Refractory or Recurrent Solid Tumors or Acute Myelogenous Leukemia
Background	• AZD2171 is a potent orally bioavailable inhibitor of VEGFR1, VEGFR2, VEGFR3 tyrosine kinase activity, but also inhibits c-kit and PDGFR-β *in vitro*. • Phase I trials of AZD2171 are ongoing in adults and the drug is well tolerated at doses up to 45 mg/d. The toxicity profile includes hypertension, hypoglycemia, elevated LFTs, fatigue, dysphonia, diarrhea, nausea and vomiting. • In this pediatric phase I dose-escalation trial, AZD2171 will be administered orally once daily for 28 days with no breaks between cycles.
Eligibility	**Inclusion Criteria** **Age:** >2 years and <19 years of age. **Diagnosis:** • Solid Tumors (dose escalation component of the trial): Histologically confirmed extracranial malignant 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, and germ cell tumors. • Leukemia (entered at the solid tumor MTD or recommended dose): Histologically confirmed acute myeloid leukemia with M3 bone marrow (>25% leukemic blasts), circulating peripheral blast count ≥ 1,000/μL (for pharmacodynamic studies), and no evidence of CNS leukemia (<5 nucleated cells/μL and negative CSF cytology performed within 2 weeks of study enrollment). **Measurable Disease:** • Patients with solid tumors must have measurable or evaluable disease. • Patients with AML must have >25% leukemic blasts in the BM and ≥1,000 leukemic blasts in the peripheral blood. • Patients must be able to swallow tablets intact. **Prior Therapy:** • The patient's cancer must have relapsed after or failed to respond to frontline standard therapy and no other standard curative treatment options are available. Standard therapy may include surgery, radiation therapy, chemotherapy, or any combination of these modalities. • Patients with solid tumors must have had their last fraction of radiation therapy at least 4 months prior to study entry for large ports (>50% pelvis, TBI, or craniospinal); for other radiation in solid tumor patients or for any type of radiation in leukemia patients, at least 4 weeks prior to study entry. • Patients with solid tumors must have had their last dose of cytotoxic chemotherapy at least 21 days prior to study entry. For patients with AML, the last dose of cytotoxic therapy must be at least 14 days prior to study entry. • Patients must have had their last dose of biological therapy that was administered for the treatment of cancer at least 7 days prior to study entry. • Patients must have had their last dose of immunotherapy (antibody) at least 30 days prior to study entry • Patients must have had their last dose of any investigational cancer therapy at least 30 days prior to study entry. • Patients who have received an allogeneic BM or SC transplant must be at least 3 months post-transplant; and patients who have received an autologous BM or SC transplant must be at least 2-months post-transplant. • Patients must have recovered from the acute toxic effects of prior therapy before entry onto this trial. • 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. Patients receiving PEG-filgrastim (Neulasta™) must be at least 7 days from the last dose.

Concomitant Medications:

- Patients requiring systemic full dose anticoagulation with systemic thrombolytics, heparin, coumadin, low molecular weight heparin, or other anticoagulants for therapy of active thrombosis within the prior 3 months are excluded.
- Patients receiving prophylactic anticoagulation for thrombosis are eligible if they meet criteria for adequate hemostatic function (PT and PTT ≤ 1.5 x ULN) and the thrombotic episode occurred > 3 months prior to enrollment. Use of anticoagulants or thrombolytics for care and maintenance of central venous catheters (e.g., intralumenal TPA) is acceptable.
- Patients on thyroid replacement (levothyroxine, synthroid™) must be on a stable dose for at least 1 month.
- Patients receiving a medication that has a known risk of QTc prolongation with in the last 2 weeks are excluded. Please contact us to review medications.

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.

Hematological Function:

- Patients with solid tumors must have adequate bone marrow function, defined as a peripheral absolute neutrophil count of ≥1,500/μL, and a platelet count ≥100,000/μL (transfusion independent).
- Patients with AML must have ≥1000/μL circulating blasts. There is no minimum required ANC or platelet count for patients with AML.

Coagulation: Patients must have adequate hemostatic function defined as PT and PTT ≤ 1.5 x ULN. It is recommended that PT and PTT be drawn by peripheral venipuncture rather than from an indwelling central venous catheter.

Cardiac : Patients must have

- QTc (Bazett's Correction) ≤ 480 msec on ECG.
- Normal Left Ventricular Diastolic Function: Echogardiogram with ejection fraction ≥55% or shortening fraction ≥ 27%.

Hepatic Function: Patients must have adequate liver function, defined as bilirubin ≤1.5 x ULN, SGPT (ALT) ≤ 2.5 x ULN.

Renal Function:

- Proteinuria ≤ 1 + on dipstick when urine specific gravity is ≤1.015 or 24 hr urine total protein ≤ 500 grams/24hr
- 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)	Serum Creatinine (mg/dl)	
	Male	**Female**
2 ≤ age < 6	0.8	0.8
6 ≤ age < 10	1.0	1.0
10 ≤ age < 13	1.2	1.2
13 ≤ age < 16	1.5	1.4
≥16	1.7	1.4

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 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:** Patients of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while they are receiving protocol therapy and for 2 weeks after the last dose of AZD2171. **Exclusion Criteria** • Patients with primary brain tumors, active CNS metastasis, or active spinal cord metastasis or compression. AML patients with CNS leukemia. • Patients with a history of congenitally prolonged QTc, or history of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia, uncontrolled atrial fibrillation, left bundle branch block) that is symptomatic or requires treatment (except for controlled atrial fibrillation) • Patients receiving medication for treatment of hypertension or patients with a diastolic blood pressure 5mmHg greater than the 95% for gender and age (Appendix 8) on 3 measurements using an appropriate size cuff are excluded. • Patients who have had major surgery within the past 3 months. Patients having minor surgery (e.g., central line placement) within the past 2 weeks. • Patients with history of arterial or venous thrombosis within the prior 3 months. • Patients requiring systemic full dose anticoagulation with systemic thrombolytics, heparin, coumadin, or low molecular weight heparin or other anticoagulants for therapy of active thrombosis within the prior 3 months. • Patients experiencing significant hemorrhage (hemoptysis, melena, or hematemesis) within the past 2 weeks. • Clinically significant unrelated systemic illness, such as serious infections, hepatic, renal, gastrointestinal 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 active GVHD are excluded. • Pregnant or breastfeeding females are excluded because AZD2171 may be harmful to the developing fetus or nursing child. • Patients currently receiving other investigational agents. • Patients previously known to be Hepatitis B, Hepatitis C, or HIV infected because of the unknown interaction of AZD2171 with antiviral therapy. • Patients or first degree relatives of persons that are involved in the planning and conduct of this trial are excluded. • Patients who have previously received AZD2171. • Patients who are allergic to AZD2171 or its excipients (mannitol, sodium starch glycollate and magnesium stearate)
DESIGN	• AZD2171 will be administered orally, once daily for 28 days. The dose will be omitted on day 2 of cycle 1 to permit full assessment of pharmacokinetics. There will be no breaks in treatment between each 28 day cycle. Treatment cycles can be repeated immediately upon completion of the previous 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 treatment have not been met. • Detailed pharmacokinetic and pharmacodynamic studies will be performed during the first 28 day treatment cycle. • The dose levels for patients with solid tumors are 8, 12, 17, 25, 35, and 50 mg/m^2/d in cohorts of 3 to 6 patients per dose level. • A separate cohort of 3 to 6 patients with AML will be enrolled at one dose level below the solid tumor MTD. If tolerated, an additional cohort of 3 to 6 patients with AML will be enrolled at the solid tumor MTD.
TRIAL STATUS	Open to accrual. Up to 40 patients will be entered on this trial.
REFERRAL	Contact Dr. Beth Fox (301-402-6641), Dr. Frank Balis (301-496-0085), or Dr. Brigitte Widemann (301-496-7387) for evaluation and treatment.

07-C-0040 A: A Phase I Trial of Monoclonal Antibody HGS-ETR2 (Lexatumumab) in Patients with Refractory Pediatric Solid Tumors

Background

- Pediatric solid tumors represent approximately one-fourth of cancer diagnoses in children. Despite intensive regimens, patients with metastatic or recurrent tumors have unsatisfactory survival rates. Therefore, new therapies are needed to improve outcomes.
- Members of the TNF ligand superfamily induce death in tumor cells through direct ligation of death receptors and apoptosis induction.
- TRAIL (TNF-related apoptosis inducing ligand) has specific anti-tumor activity against a wide range of tumor cells without inducing death in normal cells. TRAIL-induced apoptosis has been demonstrated in a wide variety of pediatric solid tumors, including Ewing's sarcoma, osteosarcoma, neuroblastoma, and rhabdomyosarcoma.
- HGS-ETR2 (Human Genome Sciences; human monoclonal antibody) is a fully human monoclonal antibody that agonistically binds TRAIL receptor 2 and, like TRAIL itself, induces apoptosis in a variety of malignant cell types with little effect on normal cells.

Eligibility

Inclusion Criteria

Age: Patients must be ≥ 1 year and ≤ 21 years of age.

Diagnosis: Patients must have had 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, Wilm's tumor, Hodgkin's or non-Hodgkin's lymphoma. Patients with primary or untreated metastatic CNS tumors or primary or metastatic hepatic tumors will not be treated on this study.

Measurable Disease: Patients must have measurable or evaluable tumors.

Prior Therapy:

- The patient's cancer must have relapsed following or failed to respond to standard therapy, and patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
- Patients must have completed their last dose of irradiation, chemotherapy, monoclonal antibody, or investigational therapy at least 4 weeks prior to enrollment or their last dose of nitrosurea (CCNU, BCNU) 6 weeks prior to enrollment. For patients who have undergone autologous stem cell transplantation, at least 3 months must have elapsed since transplant.
- Patients must have recovered from the toxic effects of all prior therapy prior to enrollment.
- Patients must have been off colony stimulating factors (e.g. G-CSF, GM-CSF, Epo) for at least 72 hours prior to enrollment.

Performance status: Patients > 10 years old must have a Karnofsky score of ≥ 50, and children ≤ 10 years old must have a Lansky score of > 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.

Hematological Function: Patients must have adequate bone marrow function, defined as a peripheral absolute granulocyte count of ≥ 1000/μL, hemoglobin ≥ 8 gm/dl, and a transfusion independent platelet count ≥ 75,000/μL.

Hepatic Function: Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5-fold the upper limit of normal. Direct bilirubin within normal limits.

Renal Function: Patients must have a creatinine clearance ≥ 60 ml/min/1.73 m^2 OR a normal age-adjusted serum creatinine as follows:

Age (Years)	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 patient is <18 years old) must sign a

	document of informed consent prior to participation. **Durable Power of Attorney:** 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. **Birth Control:** Patients of childbearing or child-fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study and for 60 days following the last dose. **Exclusion Criteria** • Patients with clinically significant unrelated systemic illness, such as serious infections or organ dysfunction, which in the judgment of the Principal or Associate Investigators would compromise the patient's ability to tolerate the agents or are likely to interfere with the study procedures or results. • Patients with history of allogeneic bone marrow transplantation. Patients who have received autologous stem cell transplantation are eligible > 3 months after completion of therapy if they meet other eligibility requirements. • Patients with hepatic tumors or metastases are excluded due to the potential for hepatotoxicity with agents that target the TRAIL-R pathway. Patients with primary CNS tumors will be excluded due to unknown penetration into the CNS. • Untreated CNS metastases will render the patient ineligible, however, patients with a previous history of CNS metastases are eligible if: – the metastases have been treated with surgery and/or radiotherapy and are clinically stable as evidenced by no requirements for corticosteroids – the patient has no evolving neurologic deficits and no change in residual brain abnormalities without specific therapy over 6 weeks • Pregnant or breastfeeding females are excluded because the risks of HGS-ETR2 to the developing fetus or nursing child are unknown. • Patients currently receiving other investigational agents. • History of any infection requiring hospitalization or parenteral antibiotics within 2 weeks of study entry. • Co-existing medical illness that would place the subject at undue risk. • On immunosuppressant therapy (with the exception of prednisone up to 10 mg/day, or dexamethasone up to 4 mg/day), or with known human immunodeficiency virus (HIV) infection or hepatitis B or C. Subjects with immune deficiency are excluded due to their increased risk of life threatening toxicity when treated with anticancer agents.
DESIGN	• Patients will receive HGS-ETR2 administered as a 60 minute IV infusion once every 14 days (two doses per single 28 day treatment cycle). • The starting dose will be 3 mg/kg, with inter-patient dose escalation up to 10 mg/kg until the MTD is reached. No intra-patient dose escalation will be permitted. • Once the MTD is reached, the MTD cohort will be expanded to include 12 patients (with at least 6 patients ≤ 12 years old) to obtain additional pharmacokinetic and tolerability data.
TRIAL STATUS	Open to accrual.
REFERRAL	For evaluation and treatment, contact Cyndi Donovan (301-402-8899), Dr. Crystal Mackall (301-402-5940), or the NCI Pediatric Oncology Patient Referral Line (1-877-624-4878).

07-C-0054 B:	A PHASE I TRIAL AND PHARMACOKINETIC STUDY OF TRABECTEDIN (YONDELIS™, ET-743) IN CHILDREN AND ADOLESCENTS WITH RELAPSED OR REFRACTORY SOLID TUMORS
BACKGROUND	• Trabectedin (ET-743) is a natural product derived from the marine tunicate *Ecteinascidia turbinata*. It binds to the minor groove of DNA and interacts with various transcription factors resulting in cell cycle arrest. In also inhibits transcription coupled nucleotide excision repair system inducing lethal DNA strand breaks. • In preclinical and clinical studies, trabectedin has been found to be active in many soft tissue sarcomas including leiomyosarcoma, synovial cell sarcoma, neuroblastoma, rhabdomyosarcoma, melanoma, breast, ovarian, non-small cell lung, renal and prostate carcinoma. • In adult phase I and phase II studies, trabectedin has been well-tolerated up to dose levels of 1.9 mg/m2/dose with the most common toxicities being fatigue, neutropenia, and reversible transaminase elevations. Objective responses were seen at doses equal to or greater than 1.5 mg/m2/dose. Trabectedin 1.5 mg/m2 administered as a 24-hour continuous intravenous infusion is the recommended dose and schedule in adults. • A pediatric phase I study of trabectedin administered as a 3-hour infusion has been completed in the Children's Oncology Group. The maximum tolerated dose was 1.1 mg/m2. Dose limiting toxicity was reversible elevation of hepatic transaminases.
ELIGIBILITY	**Inclusion Criteria** **Age:** Patients must be ≥ 4 years and < 17 years of age. **Diagnosis:** Patients must have had 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, Wilm's tumor, hepatic tumors, germ cell tumors, and brain tumors. **Measurable Disease:** Patients must have measurable or evaluable disease. **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. • Patients must have fully recovered to less than or equal to grade 1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. • *Myelosuppressive Chemotherapy*: The last dose of all myelosuppressive anticancer drugs must be at least 3 weeks prior to study entry. • *Growth Factors*: The last dose of growth factors such as filgrastim and epoetin must be at least one week prior to study entry, the last dose of long-acting colony stimulating factors, such as pegfilgrastim, must be 2 weeks prior to study entry. • *Investigational Anti-cancer Agents*: The last dose of all investigational agents must be at least 30 days prior to study entry. • *Biologic Anti-cancer Agents*: The last dose of non-myelosuppressive biologic agents for the treatment of the patient's cancer (example, retinoids) must be at least 7 days prior to study entry. • *Radiation Therapy*: The last dose of radiation to more than 25% of marrow containing bones (pelvis, spine, skull) must be at least 4 weeks prior to study entry, TBI and craniospinal radiation must be completed at least 4 months prior to study entry. The last dose of all other local palliative radiation must be at least 2 weeks prior to study entry. • *Stem Cell Transplantation.* Patients must be at least 2 months post-autologous transplant and recovered from treatment-related toxicities. Patients who have received an allogeneic transplant are excluded. **Concomitant Medications**: Patients with brain tumors must be on stable or tapering dose of corticosteroids for 7 days prior to the date of the baseline scan performed for the purpose of assessing response to therapy on this study.

Performance status: Patients > 10 years of age must have a Karnofsky performance level ≥ 60%, and children ≤ 10 years must have a Lansky performance level ≥ 60.

Hematological Function: Patients must have a peripheral absolute neutrophil count greater than or equal to 1,500/μL and a platelet count greater than or equal to 75,000/μL independent of transfusion, and a hemoglobin of greater than or equal to 8 gm/dl (transfusion permitted to achieve this level).

Hepatic Function:

- ALT (SGPT) and AST (SGOT) must be ≤ 2.5 x the upper limit of normal (ULN)
- Bilirubin must be ≤ ULN. If the patient has Gilbert's syndrome, normal bilirubin is not required but should be discussed with the PI or study chair.
- Alkaline phosphatase must be ≤ ULN for age and sex or if alkaline phosphatase greater than ULN then 5' nucleotidase must be ≤ ULN to be eligible.

Normal Values for Alkaline Phosphatase at the NIH Clinical Center (U/L)		
Age	Normal Value (U/L) in Males	Normal Value (U/L) in Females
4-6 yrs	93-309	96-297
7-9 yrs	86-315	69-325
10-12 yrs	42-362	51-332
13-15 yrs	74-390	50-162
16- 18 yrs	52-171	47-119

Other: Creatine kinase ≤ 2.5 x ULN.

Renal Function: Patients must have creatinine clearance ≥ 60 ml/min/1.73 m^2 OR a serum creatinine based on age as follows:

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

Exclusion Criteria

- Patients with severe uncontrolled infections or other unrelated systemic illnesses, which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate trabectedin or are likely to interfere with the study procedures or results.
- Patients with known history of xeroderma pigmentosum or other diseases with reduced DNA repair.
- Pregnant or breast-feeding females. Sexually active patients must be willing to use an effective form of birth control.
- Patients currently receiving other investigational agents.
- Patients who have received allogeneic stem cell transplants.
- Patients who have had prior therapy with trabectedin (ET-743, Yondelis).

DESIGN

- Trabectedin will be administered as a continuous 24-hour infusion on day 1 of every 21 day cycle. Patients will be pretreated with dexamethasone and filgrastim or peg-filgrastim will be administered 36 to 48 hours after the infusion. Cycles may be repeated indefinitely unless unacceptable toxicity or disease progression occurs.
- The starting dose of trabectedin will be 1.1 mg/m^2. The dose will be conservatively escalated to 1.5 mg/m^2 and then a maximum of 1.7 mg/m^2 in subsequent cohorts. Intrapatient dose escalation will be permitted for patients enrolled at dose level 1 (1.1 mg/m^2).
- Pharmacokinetics and pharmacodynamics will be performed during cycle 1. The maximum tolerated dose will also be determined based on toxicity occurring during cycle 1 only.

TRIAL STATUS

Open to accrual.

REFERRAL

Contact Dr. Beth Fox (301-402-6641), Dr. Meredith Chuk (301-594-6104), or Dr. Frank Balis (301-496-0085) for evaluation and treatment.

07-C-0189 C:	PHASE I/II TRIAL OF VANDETANIB (ZD6474, ZACTIMA) IN CHILDREN AND ADOLESCENTS WITH HEREDITARY MEDULLARY THYROID CARCINOMA
BACKGROUND	• Hereditary medullary thyroid carcinoma (MTC), which is a rare calcitonin-producing tumor arising from the parafollicular C cells of the thyroid, is often a manifestation of multiple endocrine neoplasia (MEN) types 2A and 2B and can be detected in children as young as 5 years in MEN 2A and 1 year in those with MEN 2B. • MEN results from an activating mutation in the RET proto-oncogene resulting in a constitutively activated receptor tyrosine kinase (RTK). • Vandetanib is an orally bioavailable multi-RTK inhibitor that blocks the mutant RET gene product and has anti-tumor activity in adults with hereditary MTC.
ELIGIBILITY	**Inclusion Criteria** **Age:** Participants must be 5 to 18 years of age, inclusive. The first cohort of 3 to 6 participants enrolled on the trial will be at least 13 years of age. **Diagnosis:** Hereditary (MEN 2A or MEN 2B) medullary thyroid carcinoma (histologically confirmed) that is unresectable, recurrent, or metastatic. Participants must have previously had characteristic germline mutation in the RET proto-oncogene documented. Results of the germline mutation testing will be obtained from the referring institution. **Measurable Disease:** Participants must have measurable disease as defined in RECIST as the presence of at least one lesion that can be accurately measured in at least one dimension with longest diameter of at least 20 mm using conventional techniques or at least 10 mm with spiral CT scan. Superficial (easily palpable) lymph nodes will be considered measurable. **Administration:** Participants must be able to take one of the oral formulations of vandetanib. **Prior Therapy:** There are no standard chemotherapy regimens known to be effective for MTC. Therefore, previously untreated participants are eligible if their tumor(s) are not surgically resectable. • Participants must be at least 4 weeks from prior surgical procedures and surgical incisions must be healed. • Participants must have had their last fraction of external beam radiation therapy at least 4 weeks prior to enrollment. • Participants must have had their last dose of cytotoxic chemotherapy at least 28 days prior to enrollment, their last dose of biological therapy, such as biological response modifiers (e.g., cytokines), immunomodulatory agents, vaccines, differentiating agents, used to treat their cancer at least 7 days prior to enrollment, their last dose of a monoclonal antibody at least 30 days prior to enrollment, and their last dose of any investigational agent at least 30 days prior to enrollment. • Participants must have received their last dose of short acting colony stimulating factor, such as filgrastim or sargramostim at least 72 hours prior to enrollment and their last dose of long-acting colony stimulating factors, such as PEG-filgrastim at least 7 days prior to enrollment. • Participants must have recovered from the acute toxic effects of prior therapy to a grade 1 level prior to enrollment. **Performance Status:** Lansky (for participants 10 years of age or younger) or Karnofsky (for participants older than 10 years) performance score greater than 50. **Concomitant Medications:** Participants who have previously had a thyroidectomy should be on thyroid hormone replacement therapy. **Hematological Function:** The peripheral absolute neutrophil count must be at least 1,500/µL and the platelet count must be at least 100,000/ µL within 72 hours prior to enrollment. **Coagulation:** PT and PTT must not be more than 1.5 x ULN within 72 hours prior to enrollment. PT and PTT should be drawn by venipuncture, rather than from a central venous catheter when feasible. **Hepatic Function:** Bilirubin must not be more than 1.5 x ULN and the AST and ALT must not be

more than 2.5 x ULN within 72 hours prior to enrollment. AST and ALT may be up to 5 x ULN within 72 hours prior to enrollment in participants with hepatic metastases.

Renal Function: Participants must have an age-adjusted normal serum creatinine (see Table) or a creatinine clearance of at least 60 ml/min/1.73 m^2.

Age (Years)	Serum Creatinine (mg/dl)	
	Male	**Female**
5 ≤ age < 10	1.0	1.0
10 ≤ age < 13	1.2	1.2
13 ≤ age < 16	1.5	1.4
≥16	1.7	1.4

Birth Control/Pregnancy: Participants of child-bearing or child-fathering potential must be willing to use a medically effective form of birth control, which includes abstinence, while taking vandetanib and for 2 months after the last dose. Women of childbearing potential must have a negative pregnancy test.

Informed Consent: Participants who are 18 years of age or legal guardians of participants who are younger than 18 years must sign an informed consent for the POB Screening Protocol to determine eligibility for this trial. After confirmation of eligibility, participants or legal guardians must sign an informed consent document for this trial, indicating awareness of the investigational nature of the proposed treatment, risks and benefits of participation, and the alternatives to participation.

Inclusion Criteria for Optional Biopsy to Obtain Tumor for Research

- **Age:** Participants must be older than 12 years of age
- **Tumor Location:** Easily accessible tumor site that is:
  - Superficial
  - Extra-cavitary (i.e. not within the chest or abdominal cavity)
  - Sufficiently distant from vital structures to avoid direct damage from insertion of the biopsy needle
  - The biopsy must be taken from within a site that has NOT been previously radiated
- **Coagulation Studies:** Participant must have a platelet count > 100,000/mcL and a normal PT and PTT within 72 hours of each biopsy
- **Anesthesia:** Must be able to perform the biopsy under local anesthesia
- **Consent/Assent:** The parent/guardian must sign a separate biopsy consent and the participant must sign an assent describing the biopsy.

Exclusion Criteria

- Pregnant or breast-feeding females because the anti-angiogenic properties of vandetanib may be harmful to the developing fetus or nursing infant.
- Participants with pheochromocytoma as evidenced by elevated plasma free metanephrines.
- *Electrolytes*: Participants with a serum potassium less than 3.5 mmol/L or a serum calcium or magnesium below the lower limits of normal. Correction of these electrolyte abnormalities with supplements is allowed.
- *Cardiac*:
  - Participants with a history of arrythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia, uncontrolled atrial fibrillation, left bundle branch block) that is symptomatic or requires treatment (except for controlled atrial fibrillation)
  - Participants with a history of congenitally prolonged QTc, a first degree relative with unexplained sudden death under 40 years of age, or a measured QTc (Bazett's correction) longer than 480 msec on ECG. ECGs should be performed after correction of electrolyte abnormalities. Participants with a prolonged QTc should have a repeat ECG at least 24 hours after the first, and the mean of the 2QTcs should not exceed 480 msec.
  - Participants who experienced QTc prolongation with other medications requiring discontinuation of that medication.

	– Participants receiving a medication that has a known risk of QTc prolongation within 14 days (28 days for levomethadyl) of enrollment • *Hypertension*: Diastolic blood pressure above the 95% for age on at least 2 of 3 measurements with an appropriate-size cuff or patients who are currently taking anti-hypertensive therapy. • Other clinically severe or uncontrolled systemic illness that could compromise the participant's ability to tolerate vandetanib or could compromise study procedures or endpoints.
DESIGN	• Vandetanib will be administered as a once daily dose, continuously (1 cycle = 28 days) at a dose of 150 mg/m2/d. • To ensure the safety of the adult dose in children and adolescents, a limited intra-patient dose escalation will be performed in the initial cohort of patients, with older patients (13-18 yrs) being studied before younger patients (5-12 yrs). • Patients will be enrolled at a dose of 100 mg/m2/d (180 mg/d in adults) for two 28 day cycles and escalated to 150 mg/m2/d (270 mg/d in adults) on cycle 3, if dose-limiting toxicity was not observed at the lower dose. If the 150 mg/m2/d dose level is tolerable on cycles 3 and 4, all subsequent patients will be enrolled at this dose level. • Pharmacokinetics of vandetanib will be studied at steady state at the end of cycle 2 and trough levels will be obtained prior to the second dose on cycle 1, and on cycles 4 and 5. • Response of measurable tumors will be assessed by RECIST. Biomarker and clinical response will also be monitored. Twenty-one patients will be studied to determine if the response rate in children and adolescents with hereditary MTC is consistent with the 28% objective response rate in adults.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Frank Balis (301-496-0085), Dr. Beth Fox (301-402-6641), or Dr. Brigitte Widemann (301-496-7387) for evaluation and treatment.

08-C-0010 B:	MULTIPLE ASCENDING DOSE (MAD) PHASE I STUDY OF THE IGF-1R ANTAGONIST R1507 ADMINISTERED AS AN INTRAVENOUS INFUSION IN CHILDREN AND ADOLESCENTS WITH ADVANCED SOLID TUMORS
BACKGROUND	• The Insulin-like Growth Factor (IGF) pathway appears to play important roles in the development and progression of a variety of childhood sarcomas, Wilms tumor, neuroblastoma, and brain tumors. • R1507 is a fully human recombinant monoclonal antibody of IgG1 subclass that binds to the extracellular domain of IGF-1 Receptor (IGF-1R) with a high selectivity and inhibits receptor activation. • In adults, R1507 was well tolerated on a weekly and every three week administration schedule at doses ranging from 1 to 16 mg/kg/dose. Dose-limiting toxicity was not observed and an MTD was not defined. The recommended doses of 9 mg/kg/dose weekly and 16 mg/kg/dose q3 weeks were selected because they achieved trough concentrations that were active in preclinical models.
ELIGIBILITY CRITERIA	The study will enroll patients 2 to 17 years of age (inclusive), with recurrent or refractory malignant solid tumors that have no potentially curative treatment options available. Under no circumstances are patients who enroll in this study and who have completed treatment as specified permitted to be re-enrolled to this study. **Inclusion Criteria** **Age**: ≥2 to <18 years of age. **Diagnoses**: Histologically confirmed solid tumors, which may include but are not limited to rhabdomyosarcoma and other soft tissue sarcomas, Ewing 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 can be waived if a biopsy was not performed. **Tumor Status**: Measurable or evaluable tumors. Patients with neuroblastoma that is only detectable by MIBG are eligible and considered to have measurable disease using the Curie scale. Patients with neuroblastoma that is only detected by bone marrow aspirate/biopsy are eligible and considered to have evaluable disease. **Prior therapy**: The patient's cancer must have relapsed after or failed to respond to frontline curative therapy or 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 fully recovered to grade ≤1 from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. • *Myelosuppressive chemotherapy*: The last dose of all myelosuppressive anticancer drugs must be at least 3 weeks prior to study entry. • *Biologic (anti-cancer agent)*: The last dose of all biologic agents for the treatment of the patient's cancer (such as retinoids) must be at least 7 days prior to study entry. The last dose of other monoclonal antibodies must be at least 30 days prior to study entry. • *Investigational anti-cancer agent*: The last dose of all investigational agents must be at least 30 days prior to study entry. • *Radiation therapy*: The last dose of radiation (including therapeutic ^{131}I-MIBG) to more than 25% of marrow containing bones (pelvis, spine, skull) must be at least 4 weeks prior to study entry. The last dose of all other local palliative (limited port) radiation must be at least 2 weeks prior to study entry. • *Stem Cell Transplantation.* Patients must be at least 2 months post-autologous transplant and must have recovered from toxicities. Patients must be at least 6 months post-allogeneic transplant, must have recovered from toxicities, and must have no evidence of active graft-versus-host disease. Patients must also have been off of immunosuppressive treatment at least 30 days.

- *Number of prior treatment regimens*: No limitation on the number of prior chemotherapy regimens that the patient may have received prior to study entry.
- *Colony stimulating factors*: The last dose of colony stimulating factors, such as filgrastim, sargramostim, and epoetin, must be at least 48 hours prior to study entry, and the last dose of long-acting colony stimulating factors, such as pegfilgrastim, must be at least 10 days prior to study entry.

PERFORMANCE SCORE: 60-100 (Karnofsky scale, for patients ≥10 years of age) or 60-100 (Lansky scale, for children younger than 10 years of age) (Appendix 2)

Hematologic Function:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Patients with an ANC < 1.5 x 10^9/L or platelet count < 100 x 10^9/L due to bone marrow involvement by tumor or the effects of prior therapy are eligible only for the expanded cohort at the optimal dose/MTD, but will not be evaluable for hematological toxicity. These patients should have an ANC > 0.5 x 10^9/L and a platelet count > 50 x 10^9/L

Renal Function: Age-adjusted normal serum creatinine (see Table below) OR a creatinine clearance ≥60 mL/min/1.73 m^2 based on a 24 h urine collection.

Normal Serum Creatnine in Children

Age (Years)	**Maximum Serum Creatinine** (mg/dl)	
	Male	Female
2 to less than 6 years	0.8	0.8
6 to less than 10 years	1	1
10 to less than 13 years	1.2	1.2
13 years to less than 16 years	1.5	1.4
Greater than 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.

Hepatic Function:

- Serum total bilirubin ≤ 1.5 x ULN
- ALT/AST ≤ 2.5 x the ULN (≤ 5 x the ULN for patients with known hepatic metastases)

Cardiac Function: Left Ventricle Shortening fraction ≥28% (or equivalent left ventricular ejection fraction > 45%) by echocardiogram

Other:

Patients with CNS metastases are eligible for enrollment if they have received prior surgical resection of or radiotherapy to site(s) of CNS disease and have been off corticosteroids for at least 2 weeks. Neurological deficits in these patients must have been stable for at least 4 weeks.

- Patients must being willing to participate in the pharmacokinetic studies that are performed on cycle 1, because this represents the primary endpoint of the trial.
- Patients and their legal representatives must be able to read, understand and provide written informed consent to participate in the trial (see section 12.2 for patients incapable of providing consent)
- Females of childbearing potential as well as fertile males and their partners must agree to use an effective form of contraception during the study and for 120 days following the last dose of study medication (effective forms of contraception include abstinence, a contraceptive or a double barrier method)

	Exclusion Criteria • Active infection or fever ≥38.5^0 C within 3 days of the first scheduled day of dosing unless the fever is felt to be tumor-related • Treatment with pharmacologic doses of corticosteroids within the past 2 weeks; current or past use of anti-IGF-1R antibodies; current treatment with immunosuppressive agents • Known hypersensitivity to any of the components of R1507 or who have had prior hypersensitivity reactions to monoclonal antibodies (see section 6.3 for study drug formulation) • Patients who are receiving concurrent investigational therapy (agents that have no FDA approved indication) or who have received investigational therapy within a period of 30 days prior to the first scheduled day of dosing. Investigational therapy is defined as treatment for which there is currently no FDA approved indication. • Patients with diabetes mellitus defined as o Casual serum glucose concentration of ≥ 200 mg/dL o Fasting serum glucose of ≥ 125 mg/dL o Need for use of an oral hypoglycemic agent or insulin in order to keep the serum glucose below the above levels. • Severe uncontrolled systemic disease • Patients who are pregnant or breast feeding • Patients with reproductive potential not willing to use an effective method of contraception, which includes abstinence. • Any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results • Known HIV or Hepatitis B or C (active, previously treated or both)
DESIGN	• This is an open-label, multi-center, sequential groups, phase I dose-finding trial of R1507 administered i.v. weekly and q3 weeks. Up to 58 participants will be required to complete the trial. • In the absence of dose-limiting toxicity, this trial is designed to identify an optimal dose of R1507 defined as the dose that achieves a mean drug exposure ($AUC_{0\text{-}7d}$ on the weekly schedule and $AUC_{0\text{-}21d}$ on the q3 week schedule) that is equivalent to (at least 85% of) the exposure achieved in adults at the recommended phase II dose of 9 mg/kg/dose on the weekly dosing schedule and 16 mg/kg/dose on the q3 week schedule. • If DLT is observed in two or more patients at a dose level, an MTD will be defined, • The first two dose levels on the weekly schedule and the first dose level on the q3 week schedule are identical to the dose levels in adults. An additional dose level, if necessary, will be calculated to achieve the target AUC, assuming linear pharmacokinetics
TRIAL STATUS	Open to accrual
REFERRAL	Contact Dr. Frank Balis (301-496-0085) Dr. Elizabeth Fox (301-402-6641), or Dr. Brigitte Widemann (301-496-7387) 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 should be sent ahead of or with the patient. When available, tissue (previously obtained) will be requested for immunohistochemical of IGF pathway components staining at the NIH.

08-C-0007 B:	PHASE I STUDY OF IPILIMUMAB (ANTI-CTLA-4) IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH TREATMENT REFRACTORY CANCER
BACKGROUND	• Solid tumors represent approximately one fourth of cancer diagnoses in children. Despite intensive regimens, patients with metastatic or recurrent solid tumors have unsatisfactory survival rates. Therefore new therapies are needed to improve outcomes. • Accumulating preclinical and clinical evidence supports the use of biologic approaches to heighten antitumor immunity in order to improve the effectiveness of immune based therapy. Both directly activating immune based therapies such as cytokines and tumor vaccines as well as therapies which disrupt negative counterregulatory signals such as those mediated by CTLA-4:B7 may enhance existent antitumor immune responses. • Antibodies directed against CTLA-4 potently augment immune responses in animal models and anti-CTLA-4 antibodies have demonstrated antitumor effects in a variety of preclinical tumor models. • Phase I and phase II studies using ipilimumab have been performed in adults with a variety of tumor types. Clinical responses have been observed in renal cell carcinoma, melanoma, and prostate cancer. No trials have yet been performed to evaluate ipilimumab in children with malignancy.
ELIGIBILITY CRITERIA	**INCLUSION CRITERIA** **AGE:** Patients must be ≥ 3 years and ≤ 21 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, Wilm's tumor, Hodgkin's or non-Hodgkin's lymphoma. Patients with melanoma are eligible. Patients with a previous history of CNS metastases are eligible if the metastases have been treated with surgery and/or radiotherapy, are clinically stable as evidenced by no requirements for corticosteroids, the patient has no evolving neurologic deficits and no change in residual brain abnormalities without specific therapy over 6 weeks. **MEASURABLE/EVALUABLE DISEASE:** Patients must have measurable or evaluable tumors. **PRIOR THERAPY**: The patient's cancer must have relapsed following or failed to respond to standard therapy and/or the patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. Patients must have completed their last dose of irradiation, chemotherapy, monoclonal antibody, or investigational therapy at least 4 weeks prior to enrollment. For patients who have undergone autologous stem cell transplantation, at least 3 months must have elapsed since transplant. Patients must have recovered from the toxic effects (to a grade 1 or less) of all prior therapy prior to enrollment, with the exception of the following: o Hematological toxicity: recovery to levels required below o Low electrolyte levels (Such individuals should receive appropriate supplementation) o For patients on anticoagulant therapy or with pre-existing coagulation abnormalities, PT, PTT must return to baseline. o Liver function tests must resolve to values required below o Grade 3 hypoalbuminemia o Alopecia o Sterility **PERFORMANCE STATUS:** Patients > 10 years old must have a Karnofsky Score of ≥ 50 and children ≤ 10 years old must have a Lansky score of >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

HEMATOLOGIC FUNCTION: Patients must have adequate bone marrow function, defined as a peripheral absolute granulocyte count of ≥ 1000/μL, hemoglobin ≥ 8 gm/dl, and a transfusion independent platelet count ≥75,000/μL.

HEPATIC FUNCTION: Aspartate transaminase (AST) and alanine transaminase (ALT), ≤ 2.5-fold the upper limit of normal (ULN). Normal direct bilirubin.

RENAL FUNCTION: Patients must have normal age-adjusted serum creatinine (see table below) **OR** a creatinine clearance ≥ 70 mL/min/1.73 m^2.

MAXIMUM SERUM CREATININE LEVEL FOR AGE

Age (yrs.)	Max Serum Creatinine (mg/dL)
≤ 5	0.8
5 < age ≤ 10	1.0
10 < age ≤ 15	1.2
>15	1.5

INFECTIOUS DISEASE:

- Negative serologic testing for hepatitis A (anti-hepatitis A IgM), B (HBsAg) and C (anti-HCV) will be required to limit confounding variables in the assessment of the potential hepatic toxicity of ipilimumab. A positive hepatitis B titer does not exclude a patient if immunization has been performed and if there is no history of disease.
- Negative serologic testing for human immunodeficiency virus (HIV) will be required given the uncertain impact of ipilimumab administration on viral replication and the potential alterations in the immune responses among patients concurrently infected with HIV.

INFORMED CONSENT: All patients or their legal guardians (if the patient 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 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, the risks of this study and their willingness to receive the therapy and undergo the research studies involved including pharmacokinetic studies. The consent must be signed before any protocol related studies are performed (This does not include routine laboratory tests or imaging studies required to establish eligibility). When appropriate, pediatric patients will be included in all discussions in order to obtain verbal assent.

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.

BIRTH CONTROL: Patients 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 and for 60 days following the last dose. Females of childbearing potential must have a negative pregnancy test within 14 days prior to initiation of study therapy and prior to each additional dose of ipilimumab.

EXCLUSION CRITERIA

Primary brain tumors

Clinically significant unrelated systemic illness, such as serious infections or organ dysfunction, which in the judgment of the Principal or Associate Investigators would compromise the patient's ability to tolerate the agents in this trial or are likely to interfere with the study procedures or results. This includes but is not limited to:

Critically-ill or medically unstable patients

Patients with active infection or other significant systemic illness

	Patients with active diarrhea Patients requiring supplemental oxygen Patients with active eye inflammation, uveitis Presence of a symptomatic pleural effusion Patients with symptoms of congestive heart failure or uncontrolled cardiac rhythm disturbance History of malignant hyperthermia Concurrent or history of autoimmune disease excluding stable asthma Positive ANA (> 2) Positive direct Coombs testing or history of hemolytic anemia Patients with a history of ongoing or intermittent bowel obstruction Concurrent radiation Patients with a history of allogeneic bone marrow transplantation. Untreated CNS metastases will render the patient ineligible however patients with a previous history of CNS metastases are eligible if: the metastases have been treated with surgery and/or radiotherapy, are clinically stable as evidenced by no requirements for corticosteroids, the patient has no evolving neurologic deficits and no change in residual brain abnormalities without specific therapy over 6 weeks. Patients with a history of previous therapy with ipilimumab will be excluded from study participation. Treatment with any of the following immunomodulatory agents within 14 days prior to study entry: • G-CSF (filgastrim)/GM-CSF (sarmogastrim) • Systemic corticosteroid therapy • Erythropoeitin • Retinoic acid • Fenretinide • Interferons or interleukins • Cytokine-fusion proteins • Growth hormone • IVIG Pregnant or breastfeeding females are excluded because ipilimumab may be harmful to the developing fetus or nursing child. Concurrent administration of any other investigational agent.
DESIGN	• A Phase I dose finding study with 4 planned dose levels. • Three patients will be enrolled at each dose level with an expanded cohort of 12 at the highest dose studied to include 6 patients < 12 years.
TRIAL STATUS	Open to accrual
REFERRAL	For evaluation and treatment, contact Donna Bernstein (301-435-7804), Dr. Crystal Mackall (301-402-5940), or the NCI Pediatric Oncology Patient Referral Line (1-877-624-4878).

PHASE I LEUKEMIA TRIALS

02-C-0031 F:	PHASE I TRIAL AND PHARMACOKINETIC STUDY OF BMS-247550 (IXABEPILONE), AN EPOTHILONE B ANALOG, IN PEDIATRIC PATIENTS WITH REFRACTORY SOLID TUMORS AND LEUKEMIAS
BACKGROUND	• BMS-247550 (ixabepilone) 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. • In phase I trials for adults with solid tumors objective responses were observed in patients refractory to taxanes. The mechanism of action, expanded range of activity and potency in preclinical studies, and preliminary results from early clinical trials make BMS-247550 a potentially important new agent for timely evaluation in the pediatric population.
ELIGIBILITY	**Inclusion Criteria** *Inclusion Criteria for Solid Tumor Patients****: This Cohort is Closed to Accrual*** **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)	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.

Inclusion Criteria for Expanded Cohort of Leukemia Patients: ***Leukemia Cohort Open to Accrual***

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

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

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.

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.

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 monocolonal 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 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.

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

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).

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 of ≥60 mL/min/1.73 m^2.

Age (Years)	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 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 for Refractory Solid Tumors and Leukemias

- 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.
- 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.
- 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).

DESIGN

- 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 trial follows a standard phase I design with 3 to 6 patients per dose level and standard definitions of MTD and DLT. At the solid tumor MTD, a total of 6 additional patients with relapsed or refractory leukemia will be evaluated. • Detailed pharmacokinetic and pharmacodynamic studies will be performed during the first treatment cycle.
TRIAL STATUS	Open to accrual to the leukemia cohort ONLY. 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.
REFERRAL	Contact Dr. Brigitte Widemann (301-496-7387), Dr. AeRang Kim (301-451-7025), or Dr. Elizabeth Fox (301-402-6641) for evaluation and treatment.

08-C-0123 A	PHASE I MULTI-CENTER, DOSE ESCALATION STUDY OF CAT-8015 IN PEDIATRIC CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH REFRACTORY CD22+ ACUTE LYMPHOBLASTIC LEUKEMIA (pALL) OR NON-HODGKIN'S LYMPHOMA (NHL)
BACKGROUND	• This is a phase I trial of the recombinant immunotoxin CAT-8015 (HA22) in pediatric patients with refractory and relapsed CD22-positive lymphoid malignancies (ALL, NHL). • Evidence for clinical activity and acceptable toxicity profile was demonstrated in a phase I trial of a related agent, CAT-3888 (BL22). CAT-8015 is an affinity-matured version of CAT-3888 and differs from CAT-3888 by a change in three contiguous amino acids in the heavy chain fragment.
ELIGIBILITY CRITERIA	**Inclusion criteria** **Age** ≥ 6 months and < 25 years **Histologically confirmed diagnosis** of acute lymphoblastic leukemia (ALL) or non-Hodgkin's lymphoma (NHL) including lymphoblastic lymphoma, Burkitt's lymphoma, and large cell lymphoma **Measurable or evaluable disease** **Evidence of CD22 positive malignancy** by one of the following criteria: • ≥ 30% of malignant cells from a disease site CD22+ by FACS analysis or **≥ 15 % of malignant cells from a disease site CD22+ by immunohistochemistry** **Stage of disease**: • Patients must have relapsed or refractory disease and have received at least one standard chemotherapy and one salvage regimen. • In the view of the PI and the primary oncologist, there must be no available alternative curative therapies and patients must either be ineligible for a hematopoietic stem cell transplant (BMT), have refused BMT, or have disease activity that prohibits the time required to identify a suitable stem cell donor. • Relapse after prior autologous or allogeneic BMT is allowed. In the event of relapse after prior allogeneic BMT, the patient must be at least day +100 post-transplant and have no evidence of ongoing active graft-vs-host disease. • Recovered from the acute toxic effects of all prior therapy before entry. **Performance status:** • Patients ≥ 12 years of age: ECOG score of 0, 1, 2, or 3 • Patients < 12 years of age: Lansky scale ≥ 40% • Patients who are unable to walk because of paralysis, but who are up in a wheel chair will be considered ambulatory for the purpose of calculating the performance score. **Informed consent** For patients <18 years old their legal guardian must give informed consent. Pediatric patients will be included in age appropriate discussion and verbal assent will be obtained for those ≥ 7 years of age. Female and male patients with childbearing potential and their sexual partners must agree to use an approved method of contraception during the study **Exclusion criteria** **Isolated testicular or CNS ALL** **Hepatic function:** Inadequate liver function defined as total bilirubin > 2.0mg/dl OR transaminases > 5x the upper limit of normal (ALT and AST) based on age- and laboratory- specific normal ranges **Renal function:** Greater than age-adjusted normal serum creatinine (see Table below) AND a creatinine clearance <60 mL/min/1.73 m^2.

Age (Years)	Maximum Serum Creatinine (mg/dl)
≤ 5	0.8

	10 < age ≤ 15 | 1.2 > 15 | 1.5 **Hematologic function:** For non-leukemic patients only, the ANC <1000/cmm, or platelet count <50,000/cmm, if these cytopenias are not judged by the investigator to be due to underlying disease (i.e. potentially reversible with anti-neoplastic therapy). A patient will not be excluded because of pancytopenia if it is due to disease based on the results of bone marrow studies **Central Nervous System (CNS) involvement by tumor (*Note: History of CNS involvement is NOT an exclusion criterion)*** CNS leukemia or lymphoma as manifested by any of the following: • CSF WBC >5/µl and confirmation of CSF blasts • Cranial neuropathies deemed secondary to underlying malignancy • Radiologically detected CNS lymphoma **Pregnant or breast-feeding females** **Prior treatment with CAT-3888 (BL22)** **Recent prior therapy:** • Systemic chemotherapy ≤2 weeks (6 weeks for nitrosoureas) and radiation therapy at ≤ 3 weeks prior to starting study drug. **Exceptions:** • There is no time restriction in regard to prior intrathecal chemotherapy provided there is complete recovery from any acute toxic effects of such • Patients receiving corticosteroids and/or hydroxyurea are allowed provided there has been no increase in dose for at least 2 weeks prior to starting study drug • For radiation therapy: the volume of bone marrow treated is less than 10% and also the patient has measurable disease outside the radiation port • Other investigational agents < 30 days prior to entry • Monoclonal antibody therapy (e.g., rituximab) < 1 month • Any history of pseudomonas-exotoxin (PE) immunotoxin administration **HIV positive serology** (due to increased risk of severe infection and unknown interaction of CAT-8015 with antiretroviral drugs) **Active hepatitis B or C infection** as defined by seropositive for hepatitis B (HbSAg) or hepatitis C and elevated liver transaminases **Uncontrolled, symptomatic, intercurrent illness** including but not limited to: congestive heart failure, unstable angina pectoris, cardiac arrhythmia, psychiatric illness, or social situations that would limit compliance with study requirements. **Second malignancy** other than non-basal cell carcinoma of the skin or *in situ* carcinoma of the cervix, unless the tumor was treated with curative intent at least two years previously and patient is in remission.
DESIGN	• This is a phase 1 multi-center trial of intravenous CAT-8015 (HA22) administered every other day for 6 doses. Cycles may be repeated every 21 days. • Cohorts of 3 to 6 patients will be accrued at each dose level starting at 5 µg/kg days every other day for 6 doses.
TRIAL STATUS	Open to accrual
REFERRAL	For evaluation and treatment contact Kelly Richards (krichards@mail.nih.gov), or call 301-496-4256.

PHASE II TRIALS

02-C-0193 I: A Phase II Study of Pegylated Interferon Alfa-2b (PEG-Intron™) in Children with Diffuse Pontine Glioma

Background

- Interferon-alpha is a cytokine that has been studied in patients with gliomas and has demonstrated some activity in prior clinical trials. Recent in vitro data suggest that the most significant inhibition of tumor growth, tumor vascularization, and maximal inhibition of angiogenesis-regulating genes may be demonstrated when there is continuous low-dose exposure to interferon-alpha.
- PEG-Intron™is a covalent conjugate of recombinant interferon alfa-2b with monomethoxy-polyethylene glycol (PEG). Pegylation increases the biologic half-life of the compound, enabling it to be administered once weekly, and also reduces the peaks and troughs in blood levels.
- In this study, we plan to administer pegylated interferon alfa-2b (PEG-Intron™) subcutaneously once a week to pediatric patients with diffuse pontine gliomas who have completed radiation therapy. The endpoint of the trial will be 2-year survival compared to historical controls.

Eligibility

Inclusion Criteria

Age: ≤21 years of age.

Diagnosis: Histologic confirmation is not required for this study. Patients must have a diffuse pontine glioma as diagnosed by MRI, with the epicenter presumed to be in the pons, and the T-2 weighted sequence must reveal a diffuse signal abnormality involving at least 50% of the pons.

Prior Therapy: The patient must have received adequate radiation therapy. Radiation must be completed between 2-10 weeks prior to the start of treatment with Peg-Intron™.

Performance status: Patients should have an ECOG performance score of 0, 1, 2 or 3 (see below). Patients who are wheelchair bound because of paralysis should be considered "ambulatory" for the purpose of calculating the performance score.

Score	Clinical Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden

Hematological Function: Patients must have an absolute granulocyte count >1,000/mm^3, a hemoglobin > 8.0 gm/dl, and a platelet count >100,000/mm^3 at study entry. Packed red blood cell and platelet transfusions are allowed to meet these criteria.

Hepatic Function: Patients must have adequate liver function, defined as total bilirubin ≤2.0x the upper limit of normal, direct bilirubin within normal limits, and SGPT ≤ 2.5 x the upper limit of normal. Patients with Gilbert syndrome are excluded from the requirement of a normal bilirubin but they must have an indirect bilirubin of ≤6mg/dl, and a direct bilirubin of ≤.5 in order to be eligible. (Gilbert syndrome is found in 3-10% of the general population and is characterized by mild, chronic hyperbilirubinemia in the absence of liver disease or overt hemolysis).

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

	Steroids: Patients on steroids must be on a stable or decreasing dose of steroids for ≥1 week prior to study entry. **Informed Consent**: All patients or their legal guardians (if the patient is <18 years of age) must sign an IRB-approved informed consent indicating their awareness of the investigational nature and the risks of this study. When appropriate, minor patients will be included in all discussions in order to obtain verbal assent. **Durable Power of Attorney (DPA):** All patients ≥18 years of age will be offered the opportunity to assign DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired. **Exclusion Criteria** • Patients with known or suspected neurofibromatosis-1 • Patients who have received prior chemotherapy,including radiosensitizers, or who are currently receiving other investigational chemotherapeutic agents • Patients with a known hypersensitivity to interferon-alpha. • Pregnant or breast-feeding females • Patients with clinically significant unrelated systemic illness
DESIGN	• Treatment with pegylated interferon alfa-2b (PEG-Intron™) must begin within 72 hours of patient registration. Patients will be premedicated with acetaminophen 10-15 mg/kg (maximum 650 mg per dose) or ibuprofen 10 mg/kg within 1 hour of receiving PEG-Intron. The patients will continue on either acetaminophen or ibuprofen for up to 48 hours after PEG-Intron injection. • Each cycle of therapy will consist of pegylated interferon alfa-2b (PEG-Intron™) administered subcutaneously once weekly for 4 weeks. Each dose should be administered on the same day each week. • There will be no breaks between cycles. Each dose is 0.3 μg/kg subcutaneously. Nursing staff will instruct the patients or their caregivers regarding sites of injection and injection technique.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Kathy Warren (301-435-4683) or Robyn Bent (301-496-8009) for evaluation and treatment.

04-C-0001 F:	PHASE II STUDY OF SEQUENTIAL GEMCITABINE FOLLOWED BY DOCETAXEL FOR RECURRENT EWING'S SARCOMA, OSTEOSARCOMA, OR UNRESECTABLE OR LOCALLY RECURRENT CHONDROSARCOMA
BACKGROUND	• Gemcitabine and docetaxel are active antineoplastic agents with a broad spectrum of clinical activity. • The primary objective of this study is to determine the objective response rate of sequential gemcitabine-docetaxel in patients with recurrent Ewing's sarcoma, recurrent osteosarcoma, and unresectable or locally recurrent chondrosarcomas. Additionally, the pharmacokinetics of gemcitabine and docetaxel will be studied in this patient population and when available, tumor samples for cDNA microarray analysis of gene expression and development of cell lines and xenotransplantation models will be obtained. • The study will be conducted with the Sarcoma Alliance for Research through Collaboration (SARC).
ELIGIBILITY	**Inclusion Criteria** **Age:** ≥ 4 years. **Diagnosis:** Recurrent high grade osteosarcoma, Ewing's sarcoma, unresectable or locally recurrent unresectable chondrosarcoma. • Histological diagnosis from initial diagnosis is acceptable for local recurrences, however, biopsy confirmation is strongly recommended. • For isolated pulmonary recurrences, biopsy is required. **Measurable Disease**: defined as lesions that can be measured in at least one dimension by medical imaging techniques. Ascites, pleural effusions, and bone marrow disease will not be considered measurable disease. **Osteosarcoma and Ewing's sarcoma**: Must have progressed after standard therapy, and may have received no more than 2 additional salvage regimens. **Chondrosarcoma**: must be unresectable or locally recurrent and unable to be completely resected. **Prior Therapy:** • Patients must have recovered (defined as toxicity < grade 2) from toxic effects of all prior therapy before entering onto study. • A treatment free interval of at least 2 weeks since the last dose of myelosuppressive therapy is required. • At least 6 month interval since last dose of myeloablative therapy or total body irradiation is required. • A minimum of 6 weeks since local radiation and 4 months from extensive radiation (greater than 50% of pelvis or cranial spinal radiation) is required. • Patients who received filgrastim on a previous cycle of chemotherapy must be off filgrastim for at least 72 hours prior to entry onto study. **Performance status:** Patients ≥ 18 years must have an ECOG performance status of ≤ 2. Patients <18 years and >10 years must have a Karnofsky Score ≥ 50%. Patients ≤ 10 years must have Lansky score ≥ 50. **Hematological Function:** Must have adequate bone marrow function with an ANC ≥ 1500/mm^3, platelet count ≥ 100,000 mm^3 (transfusion independent) and hemoglobin > 8.0 g/dl (transfusions permitted). **Hepatic Function**: Must have adequate liver function, defined as bilirubin within normal limits, SGPT (ALT) ≤ 2.5 x the upper limit of normal. For patients with documented Gilbert syndrome, total bilirubin >ULN may be acceptable if the Principal Investigator in consultation with Medical Affairs approves a special exemption for treatment on this protocol. **Renal Function**: Must have adequate renal function with serum normal age adjusted

	serum creatinine (see table below) or creatinine clearance or radioisotope GFR>70 ml/min/1.73 m^2. For patients over 18 years of age, creatinine must be ≤ upper limit of normal range. **Age (Years)** / **Serum Creatinine (mg/dl)** < 5 — 0.8 5 ≤ age ≤10 — 1.0 10 < age ≤ 15 — 1.2 15 < age ≤ 18 — 1.5 **Neuropathy:** Sensory or Motor neuropathy due to prior chemotherapy, if present, must be ≤ grade 1. Neuropathy (Sensory or Motor) due to prior surgery or tumor involvement must be ≤ grade 2 and stable or improving. **Childbearing or child-fathering potential:** must be willing to use a medically acceptable form of birth control, which may include abstinence, while being treated on this study and for 3 months afterwards. **Informed Consent**: All patients or their legal guardians (if the patient is less than 18 years of age) must sign a document of informed consent indicating their awareness of the investigational nature and the risks of the study. When appropriate the patient will be included in all discussions in order to obtain assent. **Exclusion Criteria** • Pregnant or breast feeding females • Prior treatment with gemcitabine or taxanes • Active or uncontrolled infection • History of known hypersensitivity reaction to docetaxel or other agents formulated in polysorbate 80. • Recipient of prior allogeneic transplants.
DESIGN	• Chemotherapy will include: On day 1 of each cycle, gemcitabine (675 mg/m^2) will be administered intravenously (IV) over 90 minutes. On day 8, gemcitabine (675 mg/m^2) will be administered IV over 90 minutes followed by docetaxel (75 mg/m^2) IV over 60 minutes. • Filgrastim (5 mcg/kg) will be administered subcutaneously daily beginning 24 hours after administration of docetaxel and will continue until post nadir ANC ≥1200/mcL or pegfilgrastim (Neulasta™) can be administered subcutaneously as a single dose (6mg) per cycle to patients weighing ≥ 45 kg (99 lbs). • Cycles will be repeated every 21 days unless the patient experiences unacceptable toxicity or progressive disease. • Pharmacokinetic evaluation of gemcitabine and docetaxel will be performed during cycle 1 only • Patients will be enrolled in 3 cohorts based on diagnosis (recurrent osteosarcoma, recurrent Ewing's sarcoma, or unresectable or locally recurrent chondrosarcoma) and study will be conducted using baysean formulation for each cohort. • Correlative studies: tumor tissue will be processed for development of cell lines and murine xenotransplant models.
TRIAL STATUS	Open to accrual for the Ewing's sarcoma and chondrosarcoma cohorts at the POB and participating SARC institutions.
REFERRAL	Contact Donna Bernstein (301-435-7804) or Dr. Beth Fox (301-402-6641) for evaluation and treatment.

04-C-0173 G: Phase II Study Of UCN-01 In Relapsed Or Refractory Systemic Anaplastic Large Cell And Mature T-Cell Lymphomas

Background

- UCN-01, a non-specific protein kinase C (PKC) inhibitor, appears to have several mechanisms of action including PKC isoenzyme inhibition and cyclin dependent kinase activation and inhibition.
- We have demonstrated that cell lines derived from T-cell lymphomas, including those with the t (2; 5) translocation, are very sensitive to UCN-01. The t (2; 5) translocation, associated with three quarters of cases of anaplastic large cell lymphomas (ALCL), is an oncogenic fusion protein – nucleophosmin-anaplastic lymphoma kinase (NPM-ALK).
- ALK is one potential target for UCN-01 action, and ALCL derived SUDHL-1 cells containing the NPM-ALK protein have been shown to be very sensitive to UCN-01.

Eligibility

Inclusion Criteria

Age: 7 years or older

Diagnosis:

- Relapsed or refractory systemic Anaplastic Large Cell Lymphoma (ALCL)
- Relapsed or refractory mature T-cell lymphoma to include peripheral T-cell lymphoma unspecified and the following "specified" mature T-cell lymphomas: Adult T-cell lymphoma; Extranodal NK/T-cell lymphoma, nasal type; Enteropathy-type T-cell lymphoma; Hepatosplenic T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Angioimmunoblastic T-cell lymphoma. Histology confirmed by Laboratory of Pathology, NCI.

Disease status:

- Requires systemic therapy
- Not a candidate for potentially curative (i.e. transplant) treatment at the time of study entry or the patient has a window of opportunity to receive UCN-01 before a transplant. Patients are required to have considered a transplant. If, having done this, they refuse it or decide against it, they would be eligible for this study.

Measurable Disease: All patients must have measurable or evaluable disease on entry.

Prior Therapy:

- Patients should not have received systemic cytotoxic chemotherapy within 3 weeks of study entry.
- Have recovered from the toxic effects of prior therapy to a grade ≤ 1.
- Patients should not have received nitrosureas or mitomycin C in the 6 weeks prior to commencing UCN-01

Performance status: Patients must have ECOG ≤ 2.

Hematological Function: Patients must have an ANC > 500/mm^3 and platelet $\geq$ 50,000/mm^3; unless hematological impairment due to organ involvement by lymphoma.

Hepatic Function: Patients must have a total bilirubin < 1.5 x ULN (patients with elevation of total bilirubin consistent with Gilbert's disease are eligible providing they have a normal direct bilirubin); AST ≤ 2.5 x ULN

Renal Function: Creatinine $\leq$ 1.5 mg/dl or creatinine clearance > 50 ml/min for patients at least 18 years. Pediatric patients should have a maximum serum creatinine by age as follows:

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

Alternatively, pediatric patients should have a creatinine clearance of greater than 50 ml/min/1.73m^2.

Informed Consent: All patients or their legal guardians must provide signed informed consent.

	Birth Control: Patients must be willing to use contraception and to continue for at least 8 weeks following the last treatment. **Exclusion Criteria** • Pregnant or nursing females are excluded, because the effects of the drug on the fetus and infant are unknown. • No active CNS lymphoma. • No history of diabetes mellitus requiring insulin treatment. • No symptomatic pulmonary disease. • No evidence of symptomatic cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, exertional angina pectoris, cardiac arrhythmia). • No HIV infection. • Patients may not be concurrently receiving any other investigational agents
DESIGN	• Patients will receive UCN-01 at a dose of 45 mg/m²/day over 72 hours on days 1-3 for cycle 1. For cycle 2 onwards the dosing will be 45 mg/m²/day over 36 hours. Cycles will be repeated every 28 days for cohort 1, and every 21 days for cohort 2. • Patients with stable or responding disease may receive UCN-01 for one year beyond achieving maximum response or stable disease, and restaging will be done every 2 cycles for the first 6 cycles and every 4 cycles thereafter. • Two sequential biopsies will be performed to investigate cDNA expression by microarray. Soluble Tac (CD25) will be serially followed in patients. • For each of the two histologies, this study will be conducted using a Simon two-stage optimal design.
TRIAL STATUS	Open to accrual. Up to 37 patients will be treated on this study.
REFERRAL	For evaluation and treatment, contact Cindy Love (lovec@mail.nih.gov), or call 301-496-4256.

06-C-0043 D: Phase II Trial of Chemotherapy in Sporadic and Neurofibromatosis Type 1 Associated High Grade Unresectable Malignant Peripheral Nerve Sheath Tumors

Background

- Malignant peripheral nerve sheath tumors (MPNSTs) account for 10% of all soft tissue sarcomas, and half of these malignancies arise in patients with neurofibromatosis type 1 (NF1). Surgery is the only curative treatment option. The prognosis of incompletely resected or metastatic MPNSTs is poor, and may be worse for patients with NF1 associated compared to sporadic MPNSTs.
- The administration of dose-intensive neoadjuvant chemotherapy has become standard therapy for children and adolescents with Ewing's sarcoma family tumors and other sarcomas and has resulted in increased long-term survival rates exceeding 50%. The role of chemotherapy for adult soft tissue sarcomas is less well defined, has been confined mainly to the adjuvant setting, and doxorubicin and ifosfamide are considered the most active agents.
- The response rate of MPNSTs to standard chemotherapy agents used to treat pediatric and adult sarcomas is unknown. However, responses of MPNSTs to doxorubicin containing regimens, and to ifosfamide/etoposide, have been reported, suggesting that MPNSTs may be responsive to standard sarcoma chemotherapy agents, and that patients with MPNSTs may benefit from a similar approach to that used to treat pediatric sarcomas.
- The purpose of this study is to determine the clinical response rate of high grade, unresectable, or metastatic sporadic or NF1 associated MPNSTs, not previously treated with chemotherapy or radiation therapy, after neoadjuvant chemotherapy with 2 cycles of ifosfamide + doxorubicin ('IA') followed by 2 cycles of chemotherapy with ifosfamide+etoposide ('IE'). As the outcome for NF1 associated MPNSTs may be worse compared to sporadic tumors, patients will be stratified for the presence of a sporadic or NF1 associated MPNST.

Eligibility

Inclusion Criteria

Age: Children and adults will be eligible with no upper or lower age limit.

Diagnosis:

- Unresectable sporadic or NF1 associated high-grade malignant peripheral nerve sheath tumors not previously treated with chemotherapy or radiation therapy
- Patients must have either a stage III (AJCC TNM staging system) or stage IV (metastatic) tumor.

Measurable Disease: Patients must have measurable disease, defined as at least one tumor that is measurable in two dimensions on CT or MRI scan.

Prior Therapy:

- Patients must not have received prior chemotherapy or radiation therapy for MPNST. Patients who have previously undergone surgical resection are eligible if they have residual or recurrent measurable disease.
- Patients with NF1 may have undergone treatment of a plexiform neurofibroma, optical pathway tumor, or other NF1 associated tumor in the past with biologic agents or chemotherapy excluding ifosfamide, doxorubicin, and etoposide. Patients must have recovered from the toxic effects of all prior therapy before entering this study. Recovery is defined as a toxicity < grade 2 (CTCAE-version 3), unless otherwise specified in the inclusion and exclusion criteria. These patients must have had the last dose of chemotherapy, or a biologic agent, 3 weeks prior to trial entry, and the last dose of radiation therapy at least six weeks prior to trial entry.

Performance status: Patients must have an ECOG performance status of 0, 1, or 2.

Score	Clinical Status
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden

	4 | Bedridden **Cardiac Function:** Patients must have normal cardiac function (ejection fraction by MUGA or ECHO that is within the institutional normal range). **Hematological Function:** Patients must have normal unsupported hematologic function (absolute neutrophil count ≥1500/μL, hemoglobin ≥ 9.0 g/dl and platelet count ≥ 100,000/μL). **Hepatic Function:** Patients must have adequate liver function (SGPT <5 x the upper limit of normal and bilirubin <2.5 x the upper limit of normal). **Renal Function:** Patients must have normal serum creatinine for age (see Table below) or creatinine clearance >60 ml/min/1.73 m^2. **Age (Years)** | **Serum Creatinine (mg/dl)** ≤5 | 0.8 5< age ≤10 | 1.0 10< age ≤15 | 1.2 >15 | within institutional normal limits **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 being treated on this study. **Informed Consent:** Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent from all patients or their legal guardians (if the patient is <18 years old). This can be accomplished through an IRB-approved institutional screening protocol or the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. An age appropriate assent form for children from 13 through 17 years was developed, and a one page information sheet for children from 7 through 12 years. **Durable Power of Attorney (DPA):** For cognitively or physically impaired patients, a durable power of attorney (DPA) will be obtained. **Exclusion Criteria** • Pregnant or breast feeding females because the chemotherapy administered on this trial could have a detrimental effect on the developing fetus or newborn. • Previous chemotherapy with doxorubicin, ifosfamide or etoposide. • Previous radiotherapy to the area involved by the MPNST.
DESIGN	• Patients will receive 2 cycles of ifosfamide with doxorubicin (IA) followed by 2 cycles of ifosfamide with etoposide (IE) administered at 21 days intervals. • In addition to uroprotection with mesna, patients will receive filgrastim or pegfilgrastim starting 24-36 hours after completion of chemotherapy. The use of dexrazoxane to protect from doxorubicin cardiotoxicity will be optional per institution. • Local control with surgery and/or radiation will commence after recovery from toxicities of cycle 4 of chemotherapy. Patients, who undergo surgery only, will receive 2 more cycles of 'IA' followed by 2 cycles of 'IE' beginning after recovery from surgery. Patients, who receive radiation therapy in addition to surgery, will receive 2 cycles of 'IE' during radiation treatment, as doxorubicin cannot be concurrently administered with radiation therapy, and 2 cycles of 'IA' after completion of radiation treatment. • The cumulative doxorubicin, ifosfamide, and etoposide dose will be 300 mg/m^2, 72,000 mg/m^2, and 2000 mg/m^2, respectively.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Brigitte Widemann (301-496-7387), Dr. Frank Balis (301-496-0085), or Dr. Beth Fox (301-402-6641) for evaluation and treatment.

07-C-0074 B	A PHASE II STUDY OF ABT-751, AN ORALLY BIOAVAILABLE TUBULIN BINDING AGENT, IN CHILDREN WITH RELAPSED OR REFRACTORY NEUROBLASTOMA (ANBL0621)
BACKGROUND	• 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. • In animal models, ABT-751 appears to have vascular targeting effects similar to other colchicine site binding agents such as combretastatin. • A Phase I study of ABT-751 in pediatric patients with refractory solid tumors has been completed. Two schedules were studied - daily x 7 days (d) every 21 d and daily x 21 d every 28 d. The maximum tolerated dose (MTD) of ABT-751 administered daily x 7 d every 21 d is 200 mg/m^2/d. Dose limiting toxicities (DLTs) included fatigue, sensory neuropathy, and hypertension. On the daily x 21 d every 28 d schedule, the MTD was 100 mg/m^2/d. DLTs were neuropathy, constipation, vomiting, dehydration, fatigue, pain, neutropenia, thrombocytopenia and elevated hepatic transaminases.
ELIGIBILITY CRITERIA	**Inclusion Criteria** **Age**: Patients must be less than 22 years of age at the time of enrollment. **Histologic Diagnosis**: Patients must have refractory (non-responsive) or relapsed neuroblastoma and have received all known curative treatment options and for which no additional therapy proven to prolong survival with an acceptable quality of life is available. **Patients must have either** • histologic verification of neuroblastoma at initial diagnosis or relapse or • demonstration of tumor cells in the bone marrow with increased urinary catecholamines at the time of initial diagnosis. **Patients must have either** • evidence of disease progression (enlargement of existing measurable tumors or the appearance of new tumors) on the prior treatment regimen or • if stable but non-responsive to the prior regimen, biopsy proven viable neuroblastoma at the time of enrollment. **If a soft tissue or boney lesion was previously irradiated**, either • biopsy must be done at least 6 weeks after radiation and demonstrate viable neuroblastoma, or • growth in the lesion must be demonstrated by CT or MRI scans. **Patients must have disease per one of the following two strata criteria**: • Measurable Disease: Patients with radiographically measurable disease (by CT or MRI scan). Measurable tumor on MRI or CT or X-ray is defined as a minimum 20 mm in at least one dimension; for spiral CT, measurable disease is defined as minimum of 10 mm in at least one dimension, patients in this stratum may have additional disease evaluable by ^{123}I-MIGB scintigraphy, or • Evaluable disease by ^{123}I-MIBG scintigraphy: For evaluable tumor, ^{123}I-MIBG 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. Patients enrolled on this stratum must not have measurable disease by CT/MRI scan. **Performance Level:** Patients must have a performance status of 50% (Appendix 1). Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. **Life Expectancy**: Patients must have a life expectancy of ≥ 8 weeks. **Prior Therapy** • Patients must have fully recovered to Grade ≤ 1 (exceptions described below) from the acute toxic effects (based on CTCAE v3) of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study. • Myelosuppressive chemotherapy: Patients must not have received within 2 weeks of entry onto this study. • Biologic (anti-cancer agent, example retinoids): At least 7 days since the completion of therapy with a biologic agent. • Radiation (XRT): ≥ 4 wks since last local palliative XRT (small port) or therapeutic radiolabeled ^{131}MIBG; ≥ 6 wks must have elapsed if other substantial radiation (> 50% pelvis, craniospinal, total body radiation) was administered.

- Stem Cell Transplant (SCT): No evidence of active graft vs. host disease. For allogeneic SCT, ≥ 4 months must have elapsed, and for autologous SCT ≥ 2 months must have elapsed since transplant. (Infusion of autologous peripheral blood mononuclear cells without high dose chemotherapy or preparative regimen is not considered a stem cell transplant).

Study specific limitations on prior therapy:

- There is no limitation on the number of prior chemotherapy regimens the patient could have received.
- ≥ 30 days have elapsed since last dose of investigational drug therapy.
- ≥ 30 days since immunotherapy (monoclonal antibody or vaccine) was administered.

Concomitant Medications Restrictions

- Growth factor(s): Must not have been received within 1 week prior to entry onto this study.
- Patients must not receive other anti-cancer agents (investigational or approved) while on study. This includes cytotoxic agents or biological agents (retinoids),
- Palliative radiation is not permitted during enrollment on this study,
- Patients must not be receiving medication for the treatment of graft versus host disease (GVHD).

Organ Function Requirements

- Adequate bone marrow function defined as: Hemoglobin ≥ 7.5 mg/dL (transfusions permitted), ANC >250/μL, platelet count >25,000/μL (without platelet transfusion support for greater than or equal to 7 days).
- Adequate renal function defined as: Normal Serum Creatinine for Age or Creatinine clearance or radioisotope GFR ≥ 60 ml/min/1.73m^2

Age (Years)	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 years 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

- Adequate liver function defined as: Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age and SGPT (ALT) < 5 x upper limit of normal (ULN) for age.
- Adequate cardiac function defined as: Shortening fraction of ≥ 27% by echocardiogram
- Adequate neurologic function defined as:
  - Patients with seizure disorder may be enrolled if receiving anticonvulsants and are well controlled.
  - Neurologic toxicity from prior therapy (surgery, chemotherapy, or radiation) or tumor involvement must be Grade ≤ 2.

Exclusion Criteria

- Patients who are pregnant or breastfeeding are excluded because of potential adverse effects of ABT-751 on fetus and nursing infant.
- Patients with documented allergy to sulfa containing medications are excluded.
- Patients who have previously received ABT-751 are excluded.
- Patients previously known to be HIV infected because of the potential suppression of the immune system by ABT-751 or drug interactions are excluded.
- Patients with clinically significant unrelated systemic illness, such as serious infections, which, in the judgment of the study chair or other study committee member, would compromise the patient's ability to tolerate the investigational agent or are likely to interfere with the study procedures or endpoints, are excluded.
- Patients with elevated urinary catecholamines and/or bone marrow evidence of tumor, without measurable or evaluable disease by imaging modalities (CT, MRI, MIBG) are excluded.

DESIGN	•A single stage, 2 strata, Phase II trial of ABT-751 limited institution study will be performed. •ABT-751 200 mg/m^2 will be administered by mouth daily for 7 days every 21 days. ABT-751 is available as 25 mg and 100 mg capsules and as a 25 mg/mL suspension. •Disease evaluation will be performed after cycles 2, 4, 6, 8, 10 then after every 4th cycle. RECIST for measurable disease and the Curie semiquantitative scale for MIBG scinitgraphy will be centrally reviewed by the COG and used to define disease progression. Progression Free Survival in patients enrolled on this study will be compared to an historical control population. •Quality of Life Testing (PedsQL™ v4.0) and measures of clinical benefit (performance status, hospitalizations, transfusions, episodes of fever and neutropenia) will be collected for each cycle.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Elizabeth Fox (301-402-6641)

08-C-0080 C:	PHASE II TRIAL OF R1507, A RECOMBINANT HUMAN MONOCLONAL ANTIBODY TO THE INSULIN-LIKE GROWTH FACTOR-1 RECEPTOR FOR THE TREATMENT OF PATIENTS WITH RECURRENT OR REFRACTORY EWING'S SARCOMA, SYNOVIAL SARCOMA, RHABDOMYOSARCOMA AND OTHER SARCOMAS: A SARC GLOBAL COLLABORATION
BACKGROUND	• Patients with recurrent sarcomas often fare poorly despite initially promising responses to local and systemic therapies. • There remains a need for new, effective, and safe treatments, particularly for those patients who are at high risk with recurrent or refractory disease. • R1507 is a human monoclonal (HuMab) anti-IGF-1R antibody of the IgG1 subclass. R1507 has shown anti-tumor effects and inhibition of tumor growth in preliminary laboratory and clinical studies in adult patients with Ewing's sarcoma. • This protocol will assess the response of pediatric solid tumors to R1507.

ELIGIBILITY	**Inclusion Criteria**
	Diagnosis: Patients must have histologically or cytologically confirmed
	• Ewing's sarcoma (Ewing's family of tumors, ESFT)
	  • Ewing's sarcoma primary cohort (defined as those patients who have relapsed ≤ 24 months from diagnosis, and received at least 2 prior chemotherapy programs (one initial and a second for 1st relapse) and are unresectable)
	  • Ewing's sarcoma non-primary cohort (defined as those patients who have relapsed ≥ 24 months from diagnosis or have only received only 1 prior chemotherapy program)
	• Osteosarcoma
	• Synovial sarcoma
	• Rhabdomyosarcoma
	• Other sarcomas of the following subtypes:
	  • Alveolar soft part sarcoma
	  • Desmoplastic small round cell tumors
	  • Extraskeletal myxoid chondrosarcoma
	  • Clear cell sarcoma
	  • Myxoid Liposarcoma
	• Patients must have had histological verification of malignancy by central pathology review (to be completed within 6 weeks of study entry).
	• All patients must have recurrent or refractory tumors with no known curative treatment options according to the judgment of the investigator and must have documented progressive disease by WHO criteria
	Age ≥2 years.
	Performance Status: Life expectancy of at least 6 weeks; Karnofsky performance status ≥ 70%
	Disease Status:
	• Patients must have measurable disease defined as lesions that can be measured in 2 dimensions by medical imaging techniques such as CT or MRI. Ascites, pleural fluid, bone marrow disease and lesions seen on PET scan only are not considered measurable.
	• Patients with central nervous system (CNS) disease are eligible for enrollment if they have received prior radiotherapy or surgery to sites of CNS metastatic disease, have been off glucocorticoids for at least 4 weeks, have no overt evidence of neurological deficit and are ≥ 6 weeks from completion of brain irradiation.
	• The ESFT population for whom the time from diagnosis to first relapse is ≤24 months, patients must have received at least two distinct chemotherapy programs (one for initial systemic therapy and a second for first relapse) and be surgically unresectable
	Organ function requirements defined as:
	• Bone marrow (in the absence of bone marrow involvement by neoplasia)
	  o Absolute neutrophil count ≥ 1.5 x 10^9/L (being ≥ 2 weeks off growth factors

- Platelet count ≥ 75,000/mL
- In patients with documented (confirmed by bone marrow biopsy) bone marrow involvement by neoplasia, no minimum ANC or platelet count is necessary at the discretion of the investigator

- Hepatic
  - Total bilirubin ≤ 1.5 times the upper limit of normal for age
  - ALT /AST (SGPT/SGOT) ≤ 3x the ULN for the reference lab (≤ 5 x the ULN for the reference lab in the presence of known hepatic metastasis, adjusted for age)
- Renal
  - Creatinine clearance ≥ 70 ml/min/1.73m^2 or
  - Serum creatinine < 1.5 x ULN per age.

Prior Therapy

- Time elapsed from previous therapy must be ≥ 3 weeks.
- Patients must be recovered (toxicities < grade 1 except for alopecia) from the effects of any prior surgery, radiotherapy or systemic therapy, including any investigational therapy.
- Patients who have undergone autologous hematopoietic stem cell transplantation (HSCT) will be eligible once they have recovered from all toxicities from therapy (≤ grade 1 except for alopecia).
- Patients who have received allogeneic HSCT will be eligible 6 months after the procedure provided there is no evidence of active graft-versus-host disease and immunosuppressive treatment has been discontinued for at least 30 days.

Consent: Patients or their legal representative must be able to read, understand and provide written informed consent to participate in the trial. Patients younger than 18 years of age should provide assent to participate in the trial.

Conception/Pregnancy/Breastfeeding: Females of childbearing potential as well as fertile males and their partners must agree to use an effective form of contraception during the study and for 120 days following the last dose of study medication. An effective form of contraception is use of an oral contraceptive, a double barrier method, or commitment to sexual abstinence.

Diabetic patients must have well controlled disease. Controlled disease is considered if there has been no change in medications (oral or insulin) greater than 10% for the past 30 days.

Exclusion Criteria

- Clinically significant unrelated systemic illness (such as serious infections requiring active systemic therapy; cardiovascular disease [congestive heart failure, recent myocardial infarction, unstable angina, inadequately controlled hypertension], poorly controlled diabetes; 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 be likely to interfere with the study procedures or results.
- Known hypersensitivity to any of the components of R1507 or prior hypersensitivity reactions to monoclonal antibodies (refer to section 8.3 for study drug formulation).
- Concomitant use of any other investigational agent(s). An investigational therapy is defined as treatment for which there is currently no approved indication from regulatory authorities. Prior use of investigational agent(s) is acceptable if at least 3 weeks have elapsed since last dose and no future doses are planned.
- Treatment within the past 2 weeks with pharmacologic doses of corticosteroids [equivalent to = 20 mg prednisone daily (or = 0.5 mg/kg in patients <10 years old)] or other immunosuppressive agents.
- Current or prior therapy with IGF inhibitor (monoclonal or specific kinase inhibitor).
- Pregnant patients or patients who are breast feeding. Subjects capable of pregnancy (post menarche and not post-menopausal, defined as over 12 months since final menstrual period) must have a negative pregnancy test within 7 days prior to first dose.
- History of solid organ transplant.
- Other malignant disease diagnosed within the previous 5 years, excluding intra-epithelial

	cervical neoplasia or non-melanoma skin cancer. • Active central nervous system disease.
DESIGN	• An open-label, single-arm, multi-cohort, multicenter, two-stage, Phase 2 study of R1507 for the treatment of patients with recurrent or refractory sarcoma. • Ten cohorts of sarcoma patients defined by histopathologic classification will be studied in parallel: (1) Ewing's sarcoma (Ewing's family of tumors) primary cohort, (2) Ewing's sarcoma (Ewing's family of tumors) non-primary cohort, (3) osteosarcoma, (4) synovial sarcoma, (5) rhabdomyosarcoma and (6) other sarcomas of the following subtypes: alveolar soft part sarcoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, clear cell sarcoma, and myxoid liposarcoma. • All subjects receive R1507 at a dose of 9 mg/kg once weekly until disease progression, unacceptable adverse event, withdrawal or death.
TRIAL STATUS	Open to Accrual. The (2) osteosarcoma arm is closed as it has reached its total accrual. The (3) synovial sarcoma arm is temporarily closed to accrual. All other arms are open to accrual.
REFERRAL	Contact Donna Bernstein (301-435-7804) for evaluation and treatment.

PILOT TRIALS

01-C-0030 K: SHORT-COURSE EPOCH-RITUXIMAB FOR UNTREATED CD-20+ HIV-ASSOCIATED LYMPHOMAS

BACKGROUND

- This is a study to investigate in a preliminary fashion the feasibility of short course chemotherapy to patients with HIV-associated non-Hodglun's lymphoma (HIVNHL). Patients will be treated every three weeks with a combination of EPOCH and rituximab for one cycle beyond CRICRu by CT scan of all detectable tumors for a minimum of three and maximum of six cycles. Following cycle 2, CT, positron emission tomography scans (PET), and bone marrow biopsies (if initially positive) will be performed.
- This study will investigate if the paradigm for treatment can be successfully changed from a standard of 6 cycles to one cycle beyond complete remission with 6 total allowable cycles.
- At the conclusion of the study, we will estimate whether the number of cycles can be reduced using the paradigm. If the cumulative number of patients to relapse exceeds 25% by 6 months, the study will be closed.
- Following the completion of chemotherapy, restaging will be performed 2 months following the end of treatment, then every 3 months for one year, every 6 months for one year, then every 12 months until relapse, death, or loss to follow up. Anti-HIV therapy will be suspended prior to initiation of the chemotherapy and optimum therapy will be reinitiated after all the cycles have been administered.
- To study the effects of treatment approach on parameters of HIV disease, measurements of CD4 cells and viral loads will be made at baseline and at the completion of therapy, and then 2 months following the end of treatment, and then every 3-6 months for a total of 24 months following chemotherapy.

ELIGIBILITY

Inclusion Criteria

Age: Patient must be ≥ 4 years of age.

Diagnosis: Aggressive CD20 positive NHL previously untreated with cytotoxic chemotherapy, and HIV+ serology

Disease Status: All stages (I-IV) of disease

Performance Status: ECOG performance status of 0-4

Hematologic Function: ANC ≥ 1000/mm^3 and platelet ≥ 75,000/mm^3 (unless impairment due to ITP)

Renal Function: Creatinine ≤1.5 mg/dl or creatinine clearance ≥ 50 ml/min; pediatric patients must have age-adjusted normal serum creatinine according to the following table or a creatinine clearance > 60 ml/min/1.73 m^2.

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

Hepatic Function: Bilirubin < 2.0 mg/dl, or total bilirubin ≤ 4.5 mg/dl with direct fraction ≤ 0.3 mg/dl in patients for whom these abnormalities are felt to be due to protease inhibitor therapy; AST and ALT ≤ 3x ULN (AST and ALT ≤ 6x ULN for patients on hyperalimentation for whom these abnormalities are felt to be due to the hyperalimentation)

Informed Consent: Ability of patient or parent/guardian to provide informed consent.

Exclusion Criteria

- Previous rituximab
- Pregnancy or nursing.
- Current clinical heart failure or symptomatic ischemic heart disease.

	• Serious underlying medical condition or infection other than HIV that would contraindicate SC-EPOCH-R (e.g. severe AIDS-related wasting, severe intractable diarrhea, active inadequately treated opportunistic infection of CNS, etc.). • Primary CNS lymphoma. • Adolescents who do not freely assent to treatment.
DESIGN	• Initial evaluation: Patient will be screened for eligibility. • Lymphoma Treatment: 3-6 cycles of EPOCH-R chemotherapy [Etoposide/Doxorubicin/Vincristine continuous IV infusion on days 1 to 4, Prednisone days 1 to 5, Cyclophosphamide day 5, and Rituximab days 1 and 5] followed by Filgrastim daily from day 6 until neutrophil recovery. • CNS Prophylaxis: All patients will receive CNS prophylaxis with intrathecal chemotherapy. • Antiretroviral Therapy: Antiretrovirals will be discontinued prior to starting chemotherapy and will resume after the final cycle of chemotherapy.
TRIAL STATUS	Open to accrual.
REFERRAL	For evaluation and treatment, contact Cindy Love (lovec@mail.nih.gov), or call 301-496-4256.

01-C-0125 H:	A Pilot Study of Non-Myeloablative, HLA-matched Allogeneic Stem cell Transplantation for Pediatric Hematopoietic Malignancies
Background	• Allogeneic blood and marrow stem cell transplantation (BMT) plays an important role in the curative treatment of a number of pediatric malignancies. Unfortunately, the success of conventional allogeneic BMT is limited in part by the multiple toxicities associated with myeloablative preparative regimens. • Non-myeloablative pre-transplant regimens are associated with less toxic side effects than standard BMT. Recently, a novel immunosuppressive, non-myeloablative pre-transplant chemotherapy regimen has been shown to facilitate complete donor engraftment in an adult trial at the NCI. • The primary objective of this protocol is to evaluate the efficacy and safety of this treatment approach in pediatric patients with hematopoietic malignancies.
Eligibility	**Inclusion Criteria** **Age:** Patient must be ≥ 5 years and < 22 years of age. **Diagnosis:** • Hodgkin's and Non-Hodgkin's Lymphoma: Refractory disease or relapse after salvage regimen. • Acute Myelogenous Leukemia: History of bone marrow relapse in remission (CR) #2 or greater. • Acute Lymphocytic Leukemia: History of bone marrow relapse in CR #2 or greater (CR#1 with Philadelphia chromosome positive or prior induction failure). • Acute Hybrid Leukemia including mixed lineage, biphenotypic and undifferentiated: History of bone marrow relapse in CR #2 or greater (CR#1 with Philadelphia chromosome positive or prior induction failure). • Myelodysplastic Syndrome: RAEB or RAEB-t with <10% blasts in marrow and blood. • Chronic Myelogenous Leukemia: Chronic phase or accelerated phase with <10% blasts in marrow and blood. • Juvenile Myelomonocytic Leukemia: <10% blasts in marrow and blood. **Prior Therapy:** Chemotherapy to achieve above criteria allowed. Prior BMT allowed as long as at least day 100+ post-prior BMT, no evidence of GVHD, and no detectable residual donor chimerism. **Donor:** First degree related donors, who are HLA matched (single HLA-A or B locus mismatch allowed), weight ≥ 15 kilograms, and who meet standard donation criteria will be considered. The same donor from a prior BMT is allowed. **ECOG Performance Status:** 0, 1, or 2. and life expectancy: > 3 months. **Liver Function:** Serum direct bilirubin < 2.0 mg/dL and serum ALT and AST values ≤ 2.5x upper limit of normal. (Values above these levels may be accepted if due to malignancy.) **Renal Function:** Age adjusted normal serum creatinine or Cr clearance ≥ 60 mL/min/1.73 m^2. **Pulmonary Function:** DLCO ≥ 50%. **Cardiac Function:** LVEF ≥ 45% by MUGA or LVSF ≥ 28% by ECHO. **Exclusion Criteria** • Active CNS malignancy: Tumor mass on CT or leptomeningeal disease. (Patients with a history of CNS involvement and no current evidence of CNS disease are allowed.) • HIV infection, active hepatitis B or C infection: HbSAg or HCV seropositive and elevated liver transaminases. • Fanconi Anemia. • Lactating or pregnant females.
Design	• Initial evaluation: Patient and donor will be screened for eligibility. G-CSF primed bone marrow derived stem cells will be collected from the donor.

	• Induction/Consolidation chemotherapy: 1 to 3 cycles will be given every 22 days depending on disease response, CD4 count, and toxicities. • Lymphoma: fludarabine, etoposide, doxorubicin, vincristine, cyclophohamide, prednisone, and filgrastim (EPOCH-fludarabine). • Leukemia and MDS: Fludarabine, cytarabine, and filgrastim (FLAG). • Transplantation: Fludarabine and cyclophosphamide will be administered over 4 days followed by bone marrow transplant. Patients will remain hospitalized until bone marrow recovery. Patients will be monitored closely at the NIH for at least 100 days post-BMT. • Post-transplant CNS prophylaxis for ALL: Standard post-transplant CNS prophylaxis will be employed with intrathecal methotrexate to decrease the risk of CNS relapse for all patients with ALL.
TRIAL STATUS	Open to accrual.
REFERRAL	For evaluation and treatment, contact Kelly Richards (krichards@mail.nih.gov), or call 301-496-4256.

02-C-0259 J: Pilot Study of Allogeneic Blood Stem Cell Transplantation in Patients with High-Risk and Recurrent Pediatric Sarcomas

Background

- Treatment of pediatric sarcomas has enjoyed progress in the past 25 years for patients with localized, chemosensitive disease. Prognostic factors are now available to identify subsets of patients who have very dismal prognoses including patients with primary metastatic disease to bone and bone marrow metastases and patients with early recurrence.
- Basic laboratory studies have shown that Ewing's sarcoma is susceptible to immune mediated mechanisms of cytolysis in vitro. Interestingly, for Ewing's sarcoma this appears to be true for both chemosensitive and chemoresistant cell lines.
- Recent progress in the field of bone marrow transplantation has identified approaches that can reproducibly induced allogeneic peripheral blood stem cell engraftment in adults with hematologic malignancies. In some cases, this same approach has shown beneficial effects for patients with solid tumors as a result of the development of allogeneic, immune-mediated graft versus tumor effects.

Eligibility

Inclusion Criteria

Age: Patient age > 4 years and < 35 years at diagnosis and age < 35 at enrollment.

Diagnosis:

- Patients with Ewing's sarcoma family of tumors, or alveolar rhabdomyosarcoma in one of the following categories:
  - Patients who present at the time of initial diagnosis with macrometastatic disease (except patients with Ewing's sarcoma metastatic to lung only) may be enrolled after completion of standard front-line therapy. Standard front line therapy for alveolar rhabdomyosarcoma should include vincristine and cyclophosphamide, plus actinomycin D and/or adriamycin. For patients with Ewings' sarcoma, standard front line therapy should include vincristine, cyclophosphamide, adriamycin, ifosfamide and etoposide.
  - Patients with recurrence of tumor at any site less than one year after completing standard front-line therapy or with a second or subsequent recurrence at any time after completing standard front-line therapy.
  - Patients with progression of disease while receiving standard front-line chemotherapy who cannot achieve a CR with local treatment modalities.
- The following patients with desmoplastic small round cell tumor are eligible after receiving front line standard therapy, which is defined as a regimen containing at least vincristine, cyclophosphamide, and adriamycin:
  - Patients with unresectable disease
  - Patients with metastatic tumor (abdominal and extra-abdominal disease)
  - Patients with progressive disease while receiving standard therapy
  - Patients with recurrence within one year of completing therapy

Evaluable Disease: Patients without evaluable tumor at the time of enrollment are eligible

Prior Therapy: Patients who have previously received high-dose chemotherapy with autologous stem cell rescue are eligible for this trial.

Donor: Availability of a 5 or 6 antigen HLA-matched first-degree relative donor (single HLA-A or B mismatch allowed). Genotypically identical twins may serve as stem cell donors. Genotypic identity must be confirmed by RFLP analysis.

Performance Status: ECOG performance status of 0, 1, or 2 or, for children ≤10 years of age, Lansky ≥ 60.

Life Expectancy: >3 months.

Cardiac Function: Left ventricular ejection fraction $\geq$ 45% by MUGA, fractional shortening ≥28% by ECHO, or left ventricular ejection fraction $\geq$ 55% by ECHO.

Pulmonary Function: DLCO $\geq$ 50% of the expected value corrected for alveolar volume.

Renal Function: Age-adjusted normal serum creatinine according to the following table or a creatinine clearance $\geq$ 60 ml/min/1.73 m^2.

Age (years)	Maximum Serum Creatinine (mg/dl)
≤5	0.8
>5, ≤ 10	1.0
>10, ≤15	1.2
>15	1.5

Liver Function: Serum total bilirubin < 2 mg/dl, serum AST and ALT ≤2.5 x upper limit of normal.

Marrow Function: ANC must be > 750/mm^3 (unless due to underlying disease in which case there is no grade restriction), platelet count must be ≥ 75,000/mm^3 (not achieved by transfusion) unless due to underlying disease in which case there is no grade restriction). Lymphopenia, CD4 lymphopenia, leukopenia, and anemia will not render patients ineligible.

Informed Consent: Ability to give informed consent. For patients <18 years of age, their legal guardian must give informed consent. Pediatric patients will be included in age appropriate discussion in order to obtain verbal assent.

Durable Power of Attorney: form completed (patients ≥ 18 years of age only).

Inclusion Criteria: Donor

- Weight ≥ 15 kilograms.
- First degree relative with genotypic identity at 5 or 6 HLA loci (single HLA-A or B locus mismatch allowed). Genotypically identical twins may serve as stem cell donors. Genotypic identity must be confirmed by RFLP analysis.
- For donors <18 years of age, he/she must be the oldest suitable donor, their legal guardian must give informed consent, the donor must give verbal assent, and he/she must be cleared by social work and a mental health specialist to participate.
- For donors ≥ 18 years of age, ability to give informed consent.
- Adequate peripheral venous access for apheresis or consent to use a temporary central venous catheter for apheresis.
- Donor selection criteria will be in accordance with NIH/CC Department of Transfusion Medicine standards.

Exclusion Criteria: Patient

- Uncontrolled fungal infection.
- History of CNS tumor involvement. Extradural masses which have not invaded the brain parenchyma (as is commonly observed in Ewing's sarcoma family of tumors) or parameningeal tumors (as is commonly observed in rhabdomyosarcoma) without evidence for leptomeningeal spread will not render the patient ineligible.
- Lactating or pregnant females.
- HIV positive (due to unacceptable risk following allogeneic transplantation).
- Hepatitis B surface antigen (HBsAg) positive or hepatitis C antibody positive with elevated liver transaminases. All patients with chronic active hepatitis (including those on treatment) are ineligible.
- High risk of inability to comply with transplant protocol, or inability to give appropriate informed consent in the estimation of the PI, social work, or the stem cell transplant team.
- Fanconi Anemia

Exclusion Criteria: Donor

- History of medical illness which poses a risk to donation in the estimation of the PI or the Department of Transfusion Medicine physician including, but not limited to stroke, hypertension that is not controlled with medication, or heart disease. Individuals with symptomatic angina or a history of coronary bypass grafting or angioplasty will not be eligible.
- History of congenital hematologic, immunologic, oncologic or metabolic disorder, which poses a prohibitive risk to the recipient in the estimation of the PI.
- Anemia (Hb less than 11 gm/dl) or thrombocytopenia (platelets < 100,000/µl).

	• Lactating or pregnant females. Donors of childbearing potential must use an effective method of contraception during the time they are receiving G-CSF. The effects of cytokine administration on a fetus are unknown and may be potentially harmful. The effects upon breast milk are also unknown and may potentially be harmful to the infant. • HIV-positive, hepatitis B surface antigen (HBsAg) positive or hepatitis C antibody positive. Donors are providing an allogeneic blood product and there is the potential risk of transmitting these viral illnesses to the recipient. • High risk of inability to comply with transplant protocol.
DESIGN	**Donor:** *Peripheral Blood Stem Cell Harvest and Donor Lymphocyte Collection:* • Donor lymphocyte apheresis • Filgrastim mobilization, 10 µg/kg per day SQ for 5-7 days until collection completed • Stem cell apheresis **Patient:** *Fludarabine-EPOCH Induction Chemotherapy (1 to 3 cycles; 21 d cycles; Cycles 2 and 3 may dose-modified):* • Fludarabine, 30 minutes daily for 3 days; days 1-3 • Etoposide, continuous IV infusion daily for 4 days; days 1-4 • Doxorubicin, continuous IV infusion daily for 4 days; days 1-4 • Vincristine, continuous IV infusion daily for 4 days; days 1-4 • Cyclophosphamide, IV over 30 minutes; day 5 • Prednisone, daily in 2-4 divided doses PO for 5 days; days 1-5 • Filgrastim, daily SQ from day 6 until ANC >1000/µl x 2 days *Transplant Days -6 to -3:* • Fludarabine, IV over 30 minutes daily for 4 days; days -6, -5, -4, -3 of transplant • Cyclophosphamide, IV over 2 hours daily for 4 days; days -6, -5, -4, -3 of transplant • Melphalan, IV infusion over 1 hour for 1 day; day -2 of transplant • Mesna, continuous IV infusion daily for 4 days; days -6, -5, -4, -3. *Stem Cell Infusion (Transplant Day 0):* • ≥ 3 x 10^6/kg CD34+ stem cells by IV infusion • Filgrastim, SQ from day 0 until ANC >5000/µl x 3 days *GVHD Prophylaxis:* • Tacrolimus: Begin day -1, titrate to maintain a trough level of 5-10 ng/ml • Sirolimus: Begin on day +3, titrate to maintain a trough level of 3-12 ng/ml
TRIAL STATUS	Open to accrual. A total of 28 – 31 donors and 28 –31 recipients will be accrued.
REFERRAL	For evaluation and treatment, contact Cindy Love (lovec@mail.nih.gov), or call 301-496-4256.

07-C-0206 B: A PILOT STUDY OF TUMOR VACCINATION IN PATIENTS WITH HIGH RISK PEDIATRIC SOLID TUMORS AND ALTERED T CELL HOMEOSTASIS	
BACKGROUND	• Patients with recurrent or metastatic pediatric solid tumors experience low survival rates, but using current standard therapies, many patients with these diseases are rendered into a state of minimal residual disease associated with lymphopenia. • Lymphopenic hosts show augmented immune reactivity, which may be favorable for inducing antitumor immune responses.
ELIGIBILITY CRITERIA	Patients will be enrolled and undergo Apheresis/Tumor Biopsy used to prepare the cell therapy and vaccine product. The patient will then receive standard anti-neoplastic therapy upon the direction of the referring/local physician. Upon completion of standard anti-neoplastic therapy, the patient will be reassessed to confirm eligibility and then receive the protocol directed immunotherapy. **Inclusion Criteria** **Diagnosis** • Rhabdomyosarcoma: embryonal or alveolar • Ewing's sarcoma family of tumors • Neuroblastoma • Synovial cell sarcoma • Desmoplastic small round cell tumor • Undifferentiated or embryonal sarcoma **Extent of Disease/Previous Therapy** • If Initial diagnosis: Stage IV or metastatic disease, enrolled prior to any cytoreductive therapy. • If Late recurrence: Completed all cytotoxic therapy ≥ one year prior to recurrence for patients who are > 5 years of age, or completed all cytotoxic therapy > 6 months prior to recurrence for patients who are ≤ 5 years of age. Multiple recurrences are allowable as long as these treatment-free intervals have been met. At least 4 weeks must have elapsed since last dose of non-cytotoxic therapies (i.e. Avastin, monoclonal antibodies such as anti-IgF1R and anti-TRAIL, immunotherapies, etc). **Age/Weight** • >18 mos. and ≤ 35 years at the time of initial diagnosis • > 10 kg at the time of apheresis. Patients between 10-15 kg. must be approved by the apheresis unit prior to enrollment on protocol. **Laboratory Parameters** • Renal function: creatinine clearance > 60 mL/min/1.73m^2 or normal age adjusted serum creatinine (≤ 5 yrs. ≤ 0.8 mg/ml; 5-10 yrs. ≤1.0 mg/ml; 10-15 yrs. ≤ 1.2 mg/ml; >15 yrs. ≤ 1.5 mg/ml) • Liver function: AST and ALT < 2.5x ULN, bilirubin < 1.5 ULN • Hematologic function: platelets > 75,000 cells/mcl, Hgb > 9.0 gms/dl, PT < 1.5 ULN. Patients may receive transfusion if necessary to reach the pre-apheresis hematology parameters. **Accessibility of Tissue to Generate Tumor Lysates** Patients must have adequate tumor bulk accessible to biopsy in order to generate the tumor lysate (at least 2 cm diameter). Procedures employed to acquire biopsies for tumor lysates will be limited to percutaneous biopsies or open biopsies of readily accessible lesions. For patients with bone marrow involvement, bone marrow aspirates may be used as a source of tumor for tumor lysates. **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). **Exclusion Criteria** • Clinically significant unrelated systemic illness, such as serious infections, autoimmunity or organ dysfunction, which in the judgment of the Principal or Associate Investigators would compromise the patient's ability to tolerate the investigational agents or are likely to interfere with the study procedures or results. • Previous allogeneic stem cell or allogeneic bone marrow transplantation. • Conditions related to tumor, which require emergency treatment (airway compression, spinal cord compression) since enrollment would delay initiation of such therapy. • Women who are pregnant or lactating. • Patients with human immunodeficiency virus infection, hepatitis B, hepatitis C infection due to confounding effects on immune function. • Corticosteroids initiated at the time of tumor diagnosis or recurrence for treatment of nerve compression or other symptoms *are permitted* during period of cell harvest/tumor biopsy, but will not be permitted during the immunotherapy phase, with the exception of a self limited course of steroids. • Patients with a history of CNS metastases from cancer are not excluded provided that the metastatic CNS disease has been effectively treated and there is no evidence of active CNS disease as evidenced by stable clinical findings and stable radiographic findings for a period of 6 weeks. • Patients with human immunodeficiency virus, hepatitis B, or hepatitis C due to confounding effects on immune function.
DESIGN	• Immunotherapy consists of one autologous lymphocyte infusion depleted of CD25+ suppressive T cells and depleted of contaminating tumor cells plus 6 sequential tumor lysate/KLH pulsed dendritic cell vaccines. • Patients will be evaluated for immune responses to tumor lysates using ex vivo assays and DTH. • The trial uses a one-stage design targeting a response rate of 50%. Up to 40 patients will be treated. • Stopping rules will take effect if adequate amounts of tumor lysate cannot be obtained from at least 85% of patient or if excessive toxicity is observed.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Crystal Mackall (301) 402-5940 for evaluation and treatment. A summary of previous evaluation and treatment, most recent laboratory work, copies of most recent radiologic studies and original pathology slides and report should be sent ahead of or with the patient.

08-C-0051 A:	PILOT TRIAL OF WT1 PEPTIDE-LOADED ALLOGENEIC DENDRITIC CELL VACCINE AND DONOR LYMPHOCYTE INFUSION FOR WT1-EXPRESSING HEMATOLOGICAL MALIGNANCIES
BACKGROUND	• Efforts to incorporate anti-tumor immunotherapy at stages of minimal residual disease burden are limited by profound host immune depletion associated with standard anti-cancer therapies. • Allogeneic blood and marrow stem cell transplantation (SCT) can be curative for a number of hematologic malignancies. Part of the success of this approach is an allogeneic immunologic reaction that has been demonstrated to play a role in the eradication of residual malignant disease after transplant in certain cancers (the so-called *graft-versus-leukemia*, GVL, or *graft-versus-tumor*, GVT, effect). Nonetheless, relapse remains the primary cause of treatment failure after allogeneic SCT. • The Wilms' tumor 1 (WT1) gene product is a tumor-associated antigen that represents a potential target for immunotherapy in a wide array of cancers. WT1 is expressed in most cases of acute leukemia and in many cases of chronic myelogenous leukemia and myelodysplastic syndromes. Importantly, WT1 has limited expression in normal tissues beyond embryogenesis. This trial represents an attempt to incorporate antigen-specific immunotherapy in the setting of allogeneic adoptive cell transfer.
ELIGIBILITY CRITERIA	**Inclusion Criteria: Patient (i.e., transplant recipient)** HLA-A2+ patients may be enrolled on this trial if they have relapsed or residual disease following allogeneic SCT for a WT1 expressing hematologic malignancy. **Age** > 1 years and < 75 years. **WT1-expressing hematologic malignancies**: • Acute lymphocytic leukemia (ALL), ≤ 25% marrow blasts • Acute myelogenous leukemia (AML), ≤ 25% marrow blasts • Chronic myelogenous leukemia (CML) o Chronic phase, recurrent after or resistant to DLI or resistant to available *abl* kinase inhibitors o Accelerated phase, < 20% marrow blasts o Blastic phase, ≤ 25% marrow blasts • Myelodysplastic syndrome (MDS), < 20% marrow blasts • Non-Hodgkin's lymphoma (NHL), stage 4, ≤ 25% marrow blasts There will be no restriction on the volume of extramedullary disease, with the exceptions of exclusions for central nervous system involvement or progression deemed unacceptably rapid. **WT1 expression will be confirmed by at least one of the following criteria** • >15% of malignant cells react with anti-WT1 by immunohistochemistry. • Positive quantitative RT-PCR of WT1 compared with a negative control. **HLA-A2+** *(heterozygous expression is acceptable)* **Prior SCT:** Prior HLA-matched (5-6/6 antigen or 8-10/10 allele) related or unrelated allogeneic SCT required. Must be at least 42 days post-transplant, have had recovery of transplant-associated toxicity to < grade 2, and have post-transplant donor engraftment as defined by donor chimerism > 50% (blood), neutrophil recovery to an ANC > 500/μl independent of myeloid growth factors, and platelet recovery to > 20,000/μL independent of transfusion. **Disease status:** Post-transplant residual or relapsed disease. Minimal residual disease (MRD) by PCR or flow cytometry is acceptable in accordance with standard disease-specific diagnostic criteria. **Availability of previous allogeneic donor to donate cells again.** **Prior therapy:** Disease-specific therapy must be stopped at least 14 days prior to protocol Cycle 1 Day 1 (C1D1) and recovery of treatment-associated toxicity to < grade 2 is required prior to initiation of protocol therapy. Patients may have received prior DLI, but the last dose must be at least 28 days prior to C1D1 and there must be no active GVHD > grade 1 acute or extensive chronic. Systemic immunosuppression must be stopped at least 28 days prior to protocol C1D1 and there must be no active GVHD > grade 1 acute or extensive chronic. There is no time restriction in regard to prior intrathecal chemotherapy provided there is complete recovery from any acute toxic effects of such. Patients receiving hydroxyurea are

allowed.

Performance status of 0, 1, 2, or 3.

Renal function: Patients must have a serum creatinine ≤ 1.5x the upper limit of normal based on age- specific normal range OR a creatinine clearance ≥ 60 mL/min/1.73 m^2.

Hepatic function: Patients must have a total bilirubin ≤ 2.0 mg/dl and ALT ≤ 5x the upper limit of normal based on age-specific normal ranges.

Informed consent: For patients < 18 years of age, their legal guardian must give informed consent. Pediatric patients will be included in age appropriate discussion in order to obtain verbal assent.

Recipients of unrelated donor transplants must sign a release of information form to authorize NMDP transfer of information to the NIH.

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: PATIENT

- Active GVHD > grade 1 acute or extensive chronic
- Breast feeding or pregnant females (due to risk to fetus or newborn).
- Central nervous system (CNS) malignancy by any of the following criteria:
  - Demonstration of malignant cells in the cerebrospinal fluid (CSF) in patients with leukemia or MDS as manifested by CSF WBC >5/µl and confirmation of CSF blasts.
  - Cranial neuropathies deemed secondary to the underlying malignancy.
  - CNS mass lesions deemed secondary to the underlying malignancy.
  - *Note: History of CNS involvement without current evidence of CNS malignancy is NOT an exclusion.*
- Rapidly progressive malignancy and/or clinically significant systemic illness (e.g., severe unstable infections or organ dysfunction) that in the judgment of the Principal Investigator would likely compromise the patient's ability to tolerate this therapy or interfere with the study procedures, including but not limited to a life expectancy of < 3 months.
- High risk of inability to comply with protocol requirements as determined by principal investigator, social work, and primary team.
- HIV infection or HTLV-1 infection (due to associated immune suppression and decreased likelihood of developing an immune response to the vaccine and increased risk of severe infection)
- Active hepatitis B or C infection as defined by seropositive for hepatitis B (HbSAg) or hepatitis C and elevated liver transaminases.
- Patients who require systemic corticosteroid or other immunosuppressive therapy. Immunosuppressive therapy must be stopped at least 28 days prior to protocol Cycle1 Day1. Topical agents and/or inhaled corticosteroids are permitted.

Inclusion Criteria: Donor

Weight ≥ 18 kg, and for unrelated donors only age ≥ 18 years

Previous HLA-matched related or unrelated allogeneic donor. Donors must be 5-6/6 antigen or 8-10/10 allele matched.

HLA-A2+ (heterozygous expression is acceptable)

Adequate venous access for peripheral apheresis, or consent to use a temporary central venous catheter for apheresis.

Donor selection will be in accordance with NIH Department of Transfusion Medicine (DTM) criteria and, in the case of an unrelated donor, the National Marrow Donor Program (NMDP) standards. When a potentially eligible recipient of an unrelated donor product is identified, the recipient will complete an NMDP search transfer request to allow NIH NMDP staff to contact the NMDP Coordinating Center, who will, in turn, contact the donor's prior Donor Center. The NMDP Policy for Subsequent Donation Requests will be followed and the appropriate forms (Subsequent Donation Request form and Therapeutic T Cell Collection) will be submitted as required.

Informed consent: For donors < 18 years of age, their legal guardian must give informed consent. Pediatric donors must give verbal assent and be cleared by social work and a mental health specialist to participate.

	Exclusion Criteria: Donor • History of medical illness that in the estimation of the Principal Investigator or DTM/NMDP physician poses prohibitive risk to donation. • Anemia (Hb < 10 gm/dl) or thrombocytopenia (<100,000/μl). • Breast feeding or pregnant females (due to risk to fetus or newborn). • High risk of inability to comply with protocol requirements as determined by the principal investigator and donor center team. • Positive screening test for transfusion-transmissible infection in accordance with DTM or NMDP donation standards. • Kaposi's sarcoma.
DESIGN	• This is a pilot study, the primary aim of which is to assess safety and feasibility of this novel vaccine strategy aimed to enhance the GVL effect after allogeneic SCT. • Donor-derived dendritic cells prepared from peripheral blood monocytes will be loaded with a combination of three WT1-derived peptides. These peptides are each comprised of one WT1-derived oligomeric epitope known to bind to HLA-A2 and an 11-mer protein transduction epitope known to enhance peptide loading and antigen presentation. • Patients will receive donor-derived dendritic cell vaccines every 14 days for 6 doses. Donor leukocyte infusions (DLI) will also be administered with the vaccine. • Study endpoints will include toxicity, feasibility, antigen-specific immunity, and disease response. • This is an exploratory pilot trial. Up to 12 patients will be treated. • Stopping rules will take effect if excessive toxicity (e.g., GVHD) or inability to generate vaccines are observed.
TRIAL STATUS	Open to accrual.
REFERRAL	For evaluation and treatment, contact Alan Wayne, M.D. (waynea@mail.nih.gov), Cindy (Love) Dellbrook, R.N. (lovec@mail.nih.gov), or Kelly Richards, R.N. (krichards@mail.nih.gov), or call 301-496-4256.

	PILOT STUDY OF INTRATHECAL ANALGESIA VIA AN EXTERNALIZED CATHETER OR IMPLANTABLE DRUG DELIVERY SYSTEM (IDDS) IN CHILDREN AND YOUNG ADULTS WITH REFRACTORY TUMOR-RELATED PELVIC OR LOWER EXTREMITY PAIN
BACKGROUND	• Eighty-nine percent of children with cancer require scheduled pain medications during the terminal stages of their disease and greater than 20% do not receive adequate analgesia. Fifty-five percent of parents of children (n=103) who died of progressive disease or treatment related causes reported their child suffered "a lot" or "a great deal" from pain and greater than 70% reported that treatment for pain was not successful. • Temporary spinal analgesia is often used for pediatric patients after surgical procedures and has been found to be safe and effective. The incidence of infection associated with long-term pediatric epidural catheter use has been reported at 2.4%. • In a randomized comparison of aggressive medical pain management vs. implantable drug delivery system (IDDS) in adults, clinical success was better with IDDS and a significant reduction in opioid side effects was observed.
ELIGIBILITY CRITERIA	**Inclusion Criteria** • AGE: greater than or equal to 4 and less than or equal to 25 years of age • PAIN STATUS: refractory tumor-related pelvic or lower extremity pain (average score ≥6/10 over 24 hours on age-appropriate scale, see appendix 10.1) or intolerable side effects of systemic opioids (i.e. somnolence, constipation, nausea, pruritus, dysphoria—any >grade 2) after at least 5 days of maximal medical management by the pain service. • DIAGNOSIS: Solid tumor of any histology primary or metastatic in the pelvis, sacrum or lower extremities. Patients with neurofibromatosis-1 (NF-1) with pelvic, sacral or lower extremity plexiform neurofibromas will also be eligible. • HEMATOLOGIC FUNCTION: ANC must be above 750/mL (growth factor support may be used). Platelets must be greater than or equal to 75,000/mL. Patients may receive platelet transfusions, but must not be known to be refractory to transfusions. **Exclusion Criteria** • Tumor invasion or impingement into the lumbar spinal cord • Infection at the site of catheter placement or any uncontrolled infection • Need for therapeutic systemic anticoagulation therapy or significant coagulopathy that precludes surgical intervention • Patients receiving or planning to enroll on studies of agents known to inhibit VEGF are excluded (examples include cediranib, sorafinib, sunitinib, bevacizumab; metronomic therapy is not excluded unless it includes a specific inhibitor of VEGF). • Ventriculoperitoneal or ventriculoatrial shunts
DESIGN	• Patients with refractory pain/intolerable side effects of opioid therapy after medical management will have a titration period of spinal analgesia with externalized lumbar spinal catheter. • Age-appropriate pain scales will be used daily to quantify pain scores. Patients who achieve effective intrathecal analgesia as defined by a ≥50% reduction in their pain score, or adequate pain score and reduction in opioids-related side effects for those who entered the study for intolerable opioid side effects, during the intrathecal titration period will be eligible to continue on study. Patients will continue on study with either an IDDS or tunneled externalized catheter. • Pain scores at baseline will be compared to average pain scores after placement of IDDS or tunneled externalized catheter for the duration of the therapy. A Kaplan-Meier analysis will be used to estimate the duration of successful use of intrathecal analgesia. In addition, toxicity of the regimen and changes in systemic opioid use and side effects of systemic pain management therapy will be evaluated.
TRIAL STATUS	Opening Soon
REFERRAL	Contact Dr. Beth Fox (301-402-6641), Dr. Meredith Chuk (301-594-6104), or Dr. Frank Balis (301-496-0085) for evaluation and treatment.

NEUROFIBROMATOSIS TYPE-1 TRIALS

08-C-0180:	A Phase I trial of the Raf Kinase and Receptor Tyrosine Kinase Inhibitor Sorafenib (BAY 43-9006, Nexavar®) in Children and Young Adults with Neurofibromatosis Type 1 and Inoperable Plexiform Neurofibromas
Background	• Patients with Neurofibromatosis 1 (NF1) have an increased risk of developing tumors of the central and peripheral nervous system, including plexiform neurofibromas (PN), which are benign nerve sheath tumors that are among the most debilitating complications of NF1. Plexiform neurofibromas may be congenital and appear to have the fastest growth rate in young children. There are no standard treatment options for PN other than surgery, which is often difficult due to the extensive growth and invasion of surrounding tissues. • Plexiform neurofibromas are composed of neoplastic Schwann cells that lack NF1 gene expression resulting in upregulation of Ras, which initiates several signaling cascades regulating cell proliferation. In addition, PN over express epidermal and platelet derived growth factor receptor and vascular endothelial growth factors, which may promote angiogenesis. • Sorafenib, a novel orally bioavailable, bi-aryl urea, is a potent inhibitor of raf kinase and a number of receptor tyrosine kinases, which is currently undergoing evaluation in adult cancers, and may mediate anti-tumor effects in PN by several mechanisms.
Eligibility	**Inclusion Criteria** **Age:** ≥3 years and ≤18 years of age at the time of study enrollment. The upper age limit is in place because early childhood and puberty are considered to be the greatest risk for disease progression, and where sorafenib may have the most benefit. In addition, an important objective of this study is to characterize the pharmacokinetics of sorafenib in the pediatric population since it has been well studied in adults. **Diagnosis:** Patients with NF1 and inoperable PNs that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or significant cosmetic problems, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. **Histologic confirmation** of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected. A **PN** is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with connection between the levels or extending laterally along the nerve. In addition to PN, all study subjects must have either positive genetic testing for NF1 or have at least one other diagnostic criterion for NF1 listed below (NIH Consensus conference: • Six or more café-au-lait spots (≥0.5cm in prepubertal subjects or ≥1.5 cm in post pubertal subjects) • Freckling in axilla or groin • Optic glioma • Two or more Lisch nodules • A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex) • A first-degree relative with NF1 **Measurable disease**: Patients must have at least one measurable PN, defined as a lesion of at least 3 cm measured in one dimension. Patients who underwent surgery for resection of a PN are eligible provided the PN was incompletely resected and is measurable as per criteria above.

Prior Therapy: Patients with NF1 will only be eligible if complete tumor resection is not feasible, or if a patient with a surgical option refuses surgery.

- Since there is no standard effective chemotherapy for patients with NF1 and PN, patients may be treated on this trial without having received prior medical therapy directed at their PN.
- May have received ≤ 1 myelosuppressive regimen for PN or other tumor manifestations associated with NF1 such as optic glioma.
- Patients who have received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, or other VEGFR inhibitors are eligible for enrollment.
- Growth factors that support platelet or white cell number or function must not have been administered within the past 7 days.
- Patients who received prior medical therapy for their PN must have recovered from the toxic effects of all prior therapy before entering this study.

Performance status: Patients >10 years of age must have a Karnofsky performance level of ≥50%, and children ≤10 years old must have a Lansky performance of ≥50% (Appendix I).

Hematologic Function: Patients must have an absolute neutrophil count ≥1500/µl, hemoglobin ≥9g/dl, and platelet ≥100,000/µl.

Coagulation: Patients must have adequate hemostatic function defined as PT and PTT ≤ 1.5 X ULN. Patients receiving prophylactic anticoagulation for thrombosis are eligible if they meet criteria for adequate hemostatic function (PT and PTT ≤ 1.5 x ULN) and thrombotic episode occurred 3 months prior to enrollment. Use of anticoagulants or thrombolytics for care and maintenance of central venous catheters is acceptable.

Hepatic Function: Patients must have bilirubin ≤1.5x upper limit of normal for age, with the exception of Gilbert syndrome, and ALT ≤2.5x upper limit of normal for age.

Serum lipase and amylase within upper limits of normal.

Renal Function: Patients must have a creatinine clearance or radioisotope GFR ≥60ml/min/1.73 m^2 or a normal serum creatinine based on age described in the table below.

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

Blood pressure: Patients must have a systolic and diastolic blood pressure < 95th percentile for age and gender (Appendix II) measured as described in section 2.2.

Informed Consent: Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent from all patients or their legal guardians (if the patient is <18 years old). When appropriate, pediatric patients will be included in all discussions. This can be accomplished through one of the following mechanisms: a) the NCI, POB screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

Durable Power of Attorney (DPA): All patients ≥18 years of age will be offered the opportunity to assign DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.

	Exclusion Criteria • Pregnant or breast-feeding females are excluded due to risks of fetal and teratogenic adverse events as seen animal studies. Pregnancy tests must be obtained prior to enrollment on this study in girls, age 9 or older. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method. Abstinence is an acceptable method of birth control. • Sorafenib is predominantly metabolized via CYP3A4, and patients who take cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine or Phenobarbital), rifampin, grape fruit, or St. Johns Wort will not be eligible for the trial. Patients must have discontinued these medications at least 7 days prior to enrollment of trial. • Patients who have had major surgery with in the past 3 months are excluded. Patients having minor surgery (i.e., central line placement) within the past 2 weeks are excluded. • An investigational agent within the past 30 days. • Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, immunotherapy, or biologic therapy. • Clinically significant uncontrolled unrelated systemic illness such as serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction. • Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study. • Inability to swallow tablets, since tablets cannot be crushed or broken. • Inability to undergo MRI and/or contraindication for MRI examinations following the MRI protocol (Appendix III). Prosthesis or orthopedic or dental braces that would interfere with volumetric analysis of target PN on MRI. • Prior treatment with sorafenib. • Evidence of an optic glioma, malignant glioma, malignant peripheral nerve sheath tumor, or other cancer requiring treatment with chemotherapy or radiation therapy. • Patients with a history of arterial or venous thrombosis with in the prior 3 months. • Patients who experienced significant hemorrhage (hemoptysis, melena, or hematemesis) within the past 2 weeks or with a history of bleeding diathesis. • Patients with a history of NF1 related cerebral vascular anomaly. • Patients requiring systemic full dose anticoagulation with systemic thrombolytics, heparin, coumadin, or low molecular weight heparin or other anticoagulants for therapy of active thrombosis within the prior 3 months. • Patients on anti-hypertensive medications and patients with baseline hypertension (≥95th % for age and gender, see Appendix II) (treated or untreated).
DESIGN	• Sorafenib will be administered orally BID on a continuous dosing schedule (28 days = 1 treatment cycle). Limited dose escalations will be performed to define the MTD based on tolerability of sorafenib during the first three treatment cycles. • Disease status will be evaluated using volumetric MRI analysis at regular intervals. • The plasma pharmacokinetics and pharmacodynamics of sorafenib will be evaluated. • Cognitive function and quality of life outcomes will also be assessed in a pilot fashion to define measures to be used in subsequent phase II trials.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Brigitte Widemann (301-496-7387) or Dr. Aerang Kim (301-451-7025) for evaluation and treatment.

08-C-0096:	A Phase II Study of the mTOR Inhibitor Sirolimus in Neurofibromatosis Type 1 Related Plexiform Neurofibromas
Background	• Patients with Neurofibromatosis 1 (NF1) have an increased risk of developing tumors of the central and peripheral nervous system, including plexiform neurofibromas (PN), which are benign nerve sheath tumors that are among the most debilitating complications of NF1. Plexiform neurofibromas appear to have the fastest growth rate in young children. There are no standard treatment options for PN other than surgery, which is often difficult due to the extensive growth and invasion of surrounding tissues. • Mammalian Target of rapamcyin (mTOR), a serine/threonine kinase regulated by the phosphoinositol 3 kinase (PI3K), acts as a master switch of cellular catabolism and anabolism and controls protein translation, angiogenesis, cell motility, and proliferation. • The NF1 tumor suppressor, neurofibromin, regulates the mTOR pathway activity, with increased mTOR activation observed in *NF1*-deficent cells and tumors from NF1 patients. • Sirolimus is a macrolide antibiotic that inhibits mTOR activity, preventing phosphorylation (and activation) of p70S6K, 4E-BP1, and other proteins involved in cell motility, angiogenesis, and cell growth control.
Eligibility	**Inclusion Criteria** All patients must have the clinical diagnosis of NF1 using the NIH Consensus Conference criteria. In addition to a plexiform neurofibroma, one or more of the following diagnostic criteria for NF1 must be present: • Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects) • Freckling in the axilla or groin • Optic glioma • Two or more Lisch nodules • A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex) • A first-degree relative with NF1 Patients must have plexiform neurofibroma(s) that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or significant cosmetic problems, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Patients with paraspinal plexiform neurofibromas will be eligible for this trial. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a plexiform neurofibroma is clinically suspected. **Age:** Patients must be ≥ 3 years of age at the time of study entry. **Durable Power of Attorney:** Adults evaluated for this study will be offered a durable power of attorney. Adults who are unable to provide informed consent will have to have a durable power of attorney in order to participate in this trial. **Disease status:** Measurable disease: Patients must have measurable plexiform neurofibroma(s) amenable to volumetric MRI analysis. For the purpose of this study, a measurable lesion will be defined as a lesion of at least 3 cm measured in one dimension. **Performance Level:** Karnofsky ≥ 50% for patients > 10 years of age and Lansky ≥ 50 for patients ≤ 10 years of age. Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score. **Prior Therapy & Concurrent Medication Restrictions**

- Patients who underwent surgery for a progressive plexiform neurofibroma will be eligible to enter the study after the surgery, provided the plexiform neurofibroma was incompletely resected and is measurable.
- Patients are only eligible if complete resection of a plexiform neurofibroma with acceptable morbidity is not feasible, or if a patient with surgical option refuses surgery.
- Patients may have been previously treated for a plexiform neurofibroma but must have fully recovered from the acute toxic effects of all prior chemotherapy or radiotherapy prior to entering this study.
- **Myelosuppressive chemotherapy:** Must not have received within 4 weeks of entry onto this study.
- **Hematopoietic growth factors:** At least 7 days since the completion of therapy with a growth factor that supports platelet, red or white cell number or function.
- **Biologic (anti-neoplastic agent):** At least 14 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 14 days after administration, this period must be extended beyond the time during which adverse events are known to occur. These patients must be discussed with the Study Chair on a case-by-case basis.
- **Investigational Drugs:** Patients must not have received investigational drug within 4 wks
- **Steroids:** Patients with endocrine deficiencies are allowed to receive physiologic or stress doses of steroids if necessary.
- **CYP3A4 inhibitors:** Patients may not be currently receiving strong inhibitors of CYP3A4, and may not have received these medications within 1 week of entry. These include:
  - Macrolide Antibiotics: clarithromycin, telithromycin, erythromycin, troleandomycin.
  - Gastrointestinal prokinetic agents: cisapride, metoclopramide.
  - Antifungals: itraconazole, ketoconazole, fluconazole, voriconazole, clotrimazole
  - Calcium channel blockers: verapamil, diltiazem, nicardipine
  - Other drugs: rifampin, bromocriptine, cimetidine, danazol, cyclosporine oral solution.
  - Grapefruit juice.
- **CYP3A4 inducers:** Patients must also avoid strong inducers of CYP3A4, and may not have received these medications within 1 week of entry. These include:
  - Anticonvulsants: carbamazepine, phenobarbital, phenytoin
  - Antibiotics: rifabutin, rifapentine.
  - Herbal preparations: St. John's wort (*Hypericum perforatum, hypericine)*.
- **Enzyme inducing anticonvulsants**: 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)
  - Phenobarbitol
  - Phenytoin (Dilantin)
  - Primidone (Mysoline)
  - Oxcarbazepine (Trileptal)
- **XRT:** ≥ 6 months from involved field radiation to index plexiform neurofibroma(s); ≥ 6 weeks must have elapsed if patient has received radiation to areas outside index plexiform neurofibroma(s).
- **Surgery:** At least 2 weeks since undergoing any major surgery.

Organ Function Requirements

Adequate Bone Marrow Function Defined as:

- Peripheral absolute neutrophil count (ANC) ≥ 1500/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 10.0 gm/dL (may receive RBC transfusions)

Adequate Liver Function Defined As:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age,
- SGPT (ALT) ≤ 5 x upper limit of normal (ULN) for age, and
- Serum albumin ≥ 2 g/dL.
- Fasting LDL Cholesterol: Patients must have a fasting LDL cholesterol of < 160 mg/dL
- Patients taking a cholesterol lowering agent must be on a single medication and on a

stable dose for at least 4 weeks

Adequate Renal Function Defined as: A serum creatinine based on age as follows:

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

OR a creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2

Exclusion Criteria

- Chronic treatment with systemic steroids or another immunosuppressive agent. Patients with endocrine deficiencies are allowed to receive physiologic or stress doses of steroids if necessary.
- Evidence of an active optic glioma, malignant glioma, malignant peripheral nerve sheath tumor, or other cancer requiring treatment with chemotherapy or radiation therapy. Patients not requiring treatment are eligible for this protocol.
- Dental braces or prosthesis that interfere with volumetric analysis of the neurofibroma(s).
- Other concurrent severe and/or uncontrolled medical disease which could compromise participation in the study (e.g. uncontrolled diabetes, uncontrolled hypertension, severe infection, severe malnutrition, chronic liver or renal disease, active upper GI tract ulceration)
- A known history of HIV seropositivity or known immunodeficiency. HIV testing will not be required as part of this trial, unless HIV is clinically suspected.
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of sirolimus (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection). A nasogastric tube (NG tube) is allowed.
- Women who are pregnant or breast feeding.
- Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during the period they are receiving the study drug and for 3 months thereafter. Abstinence is an acceptable method of birth control. Women of childbearing potential will be given a pregnancy test within **7 days** prior to administration of sirolimus and must have a negative urine or serum pregnancy test.
- Patients who have received prior treatment with an mTOR inhibitor.
- History of noncompliance to medical regimens
- Patients unwilling to or unable to comply with the protocol, or who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study
- Patients who have an uncontrolled infection.

DESIGN

- Sirolimus oral solution will be administered orally BID on a continuous dosing schedule (28 days = 1 treatment course) with pharmacokinetically-guided dosing.
- Disease status will be evaluated using volumetric MRI analysis at regular intervals.
- The plasma pharmacokinetics and pharmacodynamics of sirolimus will be evaluated, as will pharmacogenetic polymorphisms and their influence on the metabolism of sirolimus in this patient population.
- Pain reduction and quality of life outcomes will also be assessed.
- Toxicity of chronic sirolimus administered will be evaluated using physical and laboratory evaluations.

TRIAL STATUS

Open to accrual.

REFERRAL

Contact Dr. Brigitte Widemann (301-496-7387) for evaluation and treatment.

08-C-0130:	A PHASE II TRIAL OF PEGINTERFERON ALFA-2B (PEGINTRON) FOR NEUROFIBROMATOSIS TYPE 1 RELATED UNRESECTABLE, SYMPTOMATIC OR LIFE-THREATENING PLEXIFORM NEUROFIBROMAS
BACKGROUND	• Neurofibromatosis 1 (NF1) is a common autosomal dominant neurogenetic disorder characterized by diverse cutaneous, neurological, skeletal and neoplastic manifestations. • Approximately 25% of individuals with NF1 develop plexiform neurofibromas (PN), which are benign nerve sheath tumors that are among the most debilitating complications of NF1. • Plexiform neurofibromas may be congenital and appear to have the fastest growth rate in young children. • There are no standard treatment options for PN other than surgery, which is often difficult due to the extensive growth and invasion of surrounding tissues. Interferon-α has shown immune modulatory and antiproliferative effects in a variety of malignancies, and also inhibits angiogenesis. • The pegylated preparation, peginterferon alfa-2b (Pegintron) lengthens the plasma half-life and allows for administration once a week. • A phase I trial of Pegintron for children and young adults with NF1and PN was completed, and defined the maximum tolerated dose (MTD) as 1 µg/kg by subcutaneous (SC) injection once weekly for a maximum duration of 2 years. • At this dose level, Pegintron was well tolerated, and disease stabilization and minor PN shrinkage by volumetric MRI analysis were observed in several patients. • At doses exceeding the MTD fatigue and behavioral changes were dose limiting. • A phase II trial of Pegintron will be performed to define the activity of Pegintron for inoperable PN in NF1.
ELIGIBILITY	**Inclusion Criteria** All patients must have the clinical diagnosis of NF1 using the NIH Consensus Conference criteria. Patients without biopsy-proof of a plexiform neurofibroma must have at least one or more of the following diagnostic criteria for NF1 must be present: • Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects) • Freckling in the axilla or groin • Optic glioma • Two or more Lisch nodules • A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex) • A first-degree relative with NF1 Patients must have plexiform neurofibroma(s) that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or significant cosmetic problems, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but if any clinical observation or scan suggests possible malignant transformation, the tumor should be biopsied prior to therapy. **Age:** Patients must be ≥18 months to 21 years of age at the time of study entry. **Durable Power of Attorney:** Adults evaluated for this study will be offered a durable power of attorney. Adults who are unable to provide informed consent will have to have a durable power of attorney in order to participate in this trial. **Disease status:** Measurable disease: Patients must have measurable plexiform neurofibroma(s) amenable to volumetric MRI analysis. For the purpose of this study, a measurable lesion will be defined as a lesion of at least 3 cm measured in one dimension. **Stratum 1:** • Radiographic disease progression as defined for stratum 3 (below) is not required for

trial entry.
- Patient does not have clinical symptoms from the plexiform neurofibroma (as defined in section 7.4).

Stratum 2:
- Radiographic disease progression as defined for stratum 3 (below) is not required for trial entry.
- Patient has clinical symptoms from the plexiform neurofibroma (as defined in section 7.4).

Stratum 3:
- Patients must have a radiographically progressive plexiform neurofibroma(s) with or without clinical symptoms. Progression at the time of study entry is defined as:
- Presence of new plexiform neurofibromas on MRI within the last 12 months OR
- A measurable increase of the plexiform neurofibroma (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) over the last two consecutive scans (MRI or CT), or over the time period of approximately one year prior to evaluation for this study.

Performance Level: Patients should have a life expectancy of at least 12 months and a Karnofsky ≥ 50% for patients > 10 years of age and Lansky ≥ 50 for patients ≤ 10 years of age. Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

Surgery/Residual disease: Patients are only eligible if complete tumor resection is not feasible, or if a patient with a surgical option refuses surgery. Patients must have measurable residual tumor present. For the purpose of this study a measurable lesion will be defined as a lesion of at least 3 cm measured in one dimension. Evidence of recurrent or progressive disease is NOT necessary. Patients must be at least 21 days from surgery, if performed, prior to receiving their first dose of study drug.

Prior Therapy: Since there is no standard effective chemotherapy for patients with progressive plexiform neurofibromas, patients may be treated on this trial without having received prior therapy. If patients have received prior therapy, they must have recovered from all toxic effects prior to entering this study.

Organ Function Requirements

Adequate Bone Marrow Function Defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 1500/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 10.0 gm/dL (may receive RBC transfusions)

Adequate Liver Function Defined As:
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 mg/dl,
- SGPT (ALT) ≤ 2 x upper limit of normal (ULN) for age, and

Adequate Renal Function Defined as:

A serum creatinine based on age as follows:

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

OR a creatinine clearance ≥ 70ml/min/1.73 m^2

Baseline Clinical and Radiographic Evaluations: MRI scan of the target plexiform

	neurofibroma(s), performed according to study requirements, including axial and coronal STIR images (see Appendix E) within 4 weeks of enrollment on study. Patients with orbital PNF's must have a baseline ophthalmologic evaluation as per Appendix G performed prior to study enrollment by an ophthalmologist familiar with the protocol guidelines. Patients with pain associated with the target PNF must be able to fill out the Pain Medication Diary with at least one week of documentation prior to study enrollment. **Exclusion Criteria** • Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate Pegintron or are likely to interfere with the study procedures or results. • An investigational agent within the past 30 days • Evidence of an optic glioma requiring treatment with chemotherapy or radiation therapy at the time of study entry • History of malignant peripheral nerve sheath tumor or other cancer other than surgically cured non-melanoma skin cancer or cervical carcinoma in situ • Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, or immunotherapy • Inability to return for follow-up visits or obtain follow-up studies required to assess toxicity and response to therapy • Severe cardiovascular disease, i.e., arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease • Pre-existing severe psychiatric condition or a history of a psychiatric disorder requiring hospitalization or a history of suicidal ideation or attempt • Thyroid dysfunction not responsive to therapy • Uncontrolled diabetes mellitus • History of seropositivity for HIV • Subjects who are pregnant, lactating, or of reproductive potential and not practicing an effective means of contraception • Subjects with a medical condition requiring chronic systemic corticosteroids • Subjects who are known to be actively abusing alcohol or drugs • Subjects who have not recovered from the effects of recent surgery • Prior administration of interferon alfa-2b or Pegintron

DESIGN	• Patients will be enrolled on one of three strata depending on disease status.
	  • Stratum 1: Radiographic progression at trial entry cannot be documented. Patient has no clinical symptoms from the PN. Radiographic response (PN volume decrease ≥ 20%) will be the primary endpoint.
	  • Stratum 2: Radiographic progression at trial entry cannot be documented. Patient has clinical symptoms from the PN, such as pain, or decrease in function. Radiographic response (PN volume decrease ≥ 20%), and clinical response rate will be the primary endpoint.
	  • Stratum 3: Patient has a progressive PN. Time to progression (TTP) (PN volume increase ≥20%) will be the primary endpoint, and activity will be defined by comparing TTP on Pegintron to TTP on the placebo arm of the R115777 phase II trial for NF1 PN (01-C-0222) performed at the NCI, POB.
	• Pegintron will be administered SC at a dose of 1.0 mcg/kg/week until disease progression, or development of unacceptable toxicity. In addition, treatment for patients on stratum 1 and 2 will be limited to a maximum of 1 year unless they respond to treatment with Pegintron (partial or complete response), in which case they can continue treatment for a maximum of two years.
	• Tumor evaluation for volumetric MRI analysis will be performed pre treatment, and prior to months 4, 8, 12, and then after every six months on treatment with Pegintron. Response analysis will be performed centrally at the NCI, POB.

TRIAL STATUS	Open to accrual.

REFERRAL	Contact Dr. Brigitte Widemann (301-496-7387) for evaluation and treatment.

08-C-0079:	NATURAL HISTORY STUDY AND LONGITUDINAL ASSESSMENT OF CHILDREN, ADOLESCENTS, AND ADULTS WITH NEUROFIBROMATOSIS TYPE-1
BACKGROUND	Neurofibromatosis Type 1 (NF1) is an autosomal dominant, progressive genetic disorder characterized by diverse clinical manifestations. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas (PN), dermal neurofibromas, optic pathway tumors, brain tumors, malignant peripheral nerve sheath tumors (MPNST), juvenile myelomonocytic leukemia, and pheochromocytomas. In addition, NF1 manifests in essentially every organ system, with for example, skeletal and vascular abnormalities, and cognitive deficits. Thus, the care for individuals with NF1 requires a multidisciplinary approach. The natural history of NF1 related tumor and other manifestations is poorly understood, and for most NF1 related tumor manifestations the only standard treatment option is surgery. The NIH Clinical Center provides the ideal infrastructure for evaluation of the natural history of rare diseases. A better understanding of the natural history of NF1 related tumor and other manifestations will be helpful for the design of treatment studies. The NCI, POB has an active clinical trials program for NF1 related tumor manifestations including PN, MPNST, and in collaboration with Dr. Douglas Stewart from the NHGRI, dermal neurofibromas. Unlike individuals with refractory solid cancers, individuals with NF1 have near normal life expectancy, and their benign tumors progress more slowly than solid cancers. Individuals with NF1 may thus participate in multiple treatment trials.
ELIGIBILITY	**Inclusion Criteria** **Age:** ≤ 35 years of age for new patients evaluated at NIH No upper age limit for patients previously enrolled on clinical trials at NIH or for patients diagnosed with MPNST or with infrequent or unusual NF1 related manifestations. **Diagnosis:** Patients who are diagnosed with NF1 using the NIH Consensus Conference criteria or have a confirmed *NF1* mutation with analysis performed in a CLIA-certified laboratory. *NF1* mutation testing to confirm eligibility will not be performed on this protocol, but as part of a separate screening study. Histologic confirmation of NF1 related benign tumors is not necessary in the presence of consistent clinical and radiographic findings, but is required for individuals with MPNST who enroll on this study. Fore the clinical diagnosis of NF1 all study subjects must have at two or more diagnostic criteria for NF1 listed below (NIH Consensus Conference): • Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects) • ≥ 2 neurofibromas or 1 plexiform neurofibroma • Freckling in the axilla or groin • Optic glioma • Two or more Lisch nodules • A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex) • A first-degree relative with NF1 **Prior and current therapy:** For NF1 related benign tumor manifestations there is no standard effective medical treatment, and surgery is the only standard treatment. Chemotherapy and radiation therapy are additional treatment options for malignant NF1 related tumors. For the purpose of this study subjects who have not previously received medical or surgical treatment, patients, who have previously received medical or surgical treatment, and subjects who are currently receiving medical treatment and or radiation for a NF1 related manifestation will be eligible. Prior and current treatment for NF1 related manifestations will be recorded at trial entry and throughout the study. **Performance Status:** ECOG ≤ 3. Subjects who are wheelchair bound because of paralysis will be considered “ambulatory” when they are up in their wheelchair. Subjects have to be able to travel to the NIH for evaluations.

	Informed Consent: All patients or their legal guardians (if the patients is <18 years old) must sign an IRB-approved document of informed consent to demonstrate their understanding of the investigational nature and the risks of this study before any protocol-related studies are performed. When appropriate, pediatric subjects will be included in all discussions. **Durable Power of Attorney (DPA):** All subjects ≥18 years of age will be offered the opportunity to assign DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired. In addition, subjects participating in evaluation for variation in gene expression must: • Have at least 1 plexiform neurofibroma and be able to undergo MRI analysis of the plexiform neurofibroma(s). • If possible, but not absolutely required, have one ore both biologic parents (NF1 affected or not) willing to donate a blood or cheek swab, or mouthwash sample for DNA extraction. A separate informed consent will be obtained from biologic parents. **Exclusion Criteria** • In the opinion of the investigator the patient is not able to return for follow-up visits or obtain required follow-up studies. • In the opinion of the investigator the patient is not able to obtain an MRI scan. • Individuals who are pregnant or breast feeding or who become pregnant while enrolled on this trial will not be excluded from participation, but will not undergo radiographic evaluations or MRI scans requested for research purposes, or other studies which might negatively impact on the pregnancy.
DESIGN	Attempts will be made to have all individuals undergo a comprehensive baseline evaluation including clinical phenotyping, genotyping, imaging of tumor manifestations, and pain, quality of life, neuropsychological, motor, and endocrine evaluations. The NF1 manifestations will be longitudinally monitored with a frequency of every six months to every three years, with the extent and timing of follow-up evaluations depending on the findings at baseline.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Brigitte Widemann (301-496-7387) or Ms Andy Gillespie (301-402-1848) for evaluation and treatment.

OTHER TRIALS

03-C-0278 F:	A Comparative Study of Pediatric CNS Tumor Activity as Assessed by [^{18}F]-DG PET maging and Proton Magnetic Resonance Spectroscopic Imaging (^{1}H-MRSI)
Background	• Children with brain tumors are generally followed for response or progression by imaging studies, such as CT or MRI. While these imaging studies help delineate the anatomical location and extent of a tumor within the CNS, they give no information regarding the biologic or metabolic activity of the lesion. • Proton Nuclear Magnetic Resonance Spectroscopic Imaging (^{1}H-MRSI) is a non-invasive method of detecting and measuring cellular metabolites in vivo, providing biochemical information in conjunction with the spatial information obtained by MRI. • Positron Emission Tomography (PET) is a technique that also provides data on metabolic activity of brain lesions. However, a comparison of these two methods in determining a lesion's metabolic activity has not been reported in children with brain tumors. • This study will be conducted to compare biologic or metabolic activity of brain tumors in pediatric patients as determined by ^{1}H-MRSI and [^{18}F-]-FDG PET scanning and to correlate results of ^{1}H-MRSI and ^{18}F-FDG PET imaging with outcome.
Eligibility	**Inclusion Criteria** **Age:** ≥ 1 years and ≤ 21 years **Diagnosis:** Patients must have a brain tumor (including, but not limited to high grade gliomas, low-grade gliomas, primitive neuroectodermal tumors, ependymomas) or residual abnormality (e.g. post-operatively or post-radiation) that is measurable or evaluable on standard MRI or CT. **Informed Consent:** All patients or their legal guardians (if the patient is < 18 years of age) must sign a document of informed consent indicating their awareness of the investigational nature and the risks of this study. When appropriate, the minor patient will be asked for oral assent. **Durable Power of Attorney (DPA):** A DPA will be offered to all patients 18-21 years of age. **Prior Therapy:** Patients will be eligible for this study regardless of prior treatment, as long as they meet other eligibility criteria. Therefore, patients who are newly diagnosed, post-operative, post-radiation or post-chemotherapy are eligible. **Exclusion Criteria** • Patients under age 18 years who weigh >70 kg are excluded because they would exceed the standard allowable dosimetry for pediatric patients (effective dose > 0.5 REM/year). Patients >136 kg are excluded, as this is the maximum weight allowable on PET scanner tables. • Pregnant women are excluded because the effects from the magnet on the fetus are unknown. In addition, gadolinium is not approved for use in pregnant women, because its teratogenic effects have not been studied. • Any patient who is unable (either because of physical or psychological factors) to undergo imaging studies without sedation but is not considered an anesthesia candidate. • Any patient with a metallic MRI incompatible implant, including cardiac pacemakers, neural pacemakers, aneurysmal clips, shrapnel, cochlear implants or ferrous surgical clips. • Any patient with a history of a severe reaction to Gadolinium or other contrast agents. • Any patient with Diabetes mellitus or steroid-induced hyperglycemia (fasting glucose >150) because this may interfere with the interpretation of the [^{18}F]-FDG PET scan. • Any patient with permanent braces, permanent retainers or nonferrous implant that, in the judgment of the Principal Investigator, would interfere with obtaining spectroscopy in the area of the tumor.
Design	Patients referred for this study will have both ^{1}H-MRSI and ^{18}F-FDG PET imaging performed within 2 weeks of each other at the NCI. Patients will have no more than one ^{18}F-FDG PET scan per year, but more frequent ^{1}H-MRSI scans may be performed at the discretion of the PI if the patient requires standard MRIs for clinical reasons.
Trial Status	Open to accrual.
Referral	Contact Dr. Kathy Warren (301-435-4683) or Robyn Bent (301-496-8009) for evaluation and treatment.

06-C-0219 C:	AN EXPLORATORY STUDY OF BIOLOGIC AND PATHOPHYSIOLOGIC EFFECTS OF RADIATION THERAPY IN PEDIATRIC PATIENTS WITH CENTRAL NERVOUS SYSTEM TUMORS
BACKGROUND	This exploratory study will be performed in pediatric patients with CNS tumors who are undergoing radiation therapy to investigate pathophysiologic effects of radiation on the CNS. The study includes the analysis of blood, urine, and CSF (if available) to measure biological markers involved with angiogenesis, blood: brain barrier integrity, and neurotoxicity. It also entails comprehensive MR imaging techniques and neuropsychological testing in an effort to correlate changes with biomarker measurements.
ELIGIBILITY CRITERIA	**Inclusion Criteria** **Age:** Patients must be ≤21 yrs of age **Tumor**: Any primary CNS tumor **Performance Score**: any **Prior/Concurrent therapy**: Patients will be eligible if they have not received prior radiation. **Other**: • Referred for radiation therapy at NCI • Signed informed consent by patient, parent or legal guardian • Patients who have undergone prior surgery or who have received chemotherapeutic regimens are eligible. **Exclusion Criteria** • Patients who have received prior radiation • Patients who are unable to have MRI performed for any reason
DESIGN	This minimally invasive study is designed to explore various biologic effects of radiation on the pediatric CNS in an attempt to 1) obtain information on the pathophysiology of radiation-induced damage, 2) explore the association of neuropsychological deficits with biologic markers and neuroimaging abnormalities, 3) document changes in neurobehavioral functioning through longitudinal comprehensive neuropsychological assessments with comparison of various radiation therapy techniques, 4) describe changes in quality of life in pediatric patients who have received radiation therapy, and 5) attempt to identify children at increased risk of radiation-induced neurotoxicity.
TRIAL STATUS	Open to accrual.
REFERRAL	Contact Dr. Kathy Warren (301-435-4683) or Robyn Bent (301-496-8009) for evaluation and treatment.

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COG PHASE I CONSORTIUM TRIALS AVAILABLE AT THE POB

06-C-0233 C: **A PHASE I STUDY OF THE RAF KINASE AND RECEPTOR TYROSINE KINASE INHIBITOR BAY 43-9006 (SORAFENIB) IN CHILDREN WITH REFRACTORY SOLID TUMORS OR REFRACTORY LEUKEMIAS (COG PROTOCOL NO. ADVL0413)**

07-C-0166: **A PHASE I STUDY OF BMS354825 (DASATINIB) IN CHILDREN WITH RECURRENT/REFRACTORY SOLID TUMORS OR IMATINIB RESISTENT PH+ LEUKEMIA (COG PROTOCOL NO. ADVL0516)**

07-C-0220 A: **A PHASE I STUDY OF SUNITINIB (SU11248), AN ORAL MULTI-TARGETED TYROSINE KINASE INHIBITOR, IN CHILDREN WITH REFRACTORY SOLID TUMORS**

08-C-0179 A: **A PHASE I TRIAL OF VEGF TRAP (AFLIBERCEPT) IN CHILDREN WITH REFRACTORY SOLID TUMORS (COG ADVL0714)**

08-C-0223: **ADVL08N1: A Pharmacokinetic Participation Questionnaire Study**

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