

01-C-0222: A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled Trial of the Farnesyltransferase Inhibitor R115777 in Pediatric Patients with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Patients with neurofibromatosis type 1 (NF1) have an increased risk of developing tumors of the central and peripheral nervous system. Plexiform neurofibromas are a major source of morbidity, with no standard treatment options, other than surgery, available. Neurofibromin, the NF1 gene product, contains a domain with significant homology to *ras* GTPase-activating proteins. Patients with NF1 have decreased levels of neurofibromin, which is associated with an activated *ras*-GTP status. Agents directed at inhibiting *ras*, therefore, are a rational choice for trials of potential therapeutic agents in patients with NF1. R115777 is a farnesyltransferase inhibitor that inhibits the post-translational isoprenylation of *ras* and other farnesylated proteins, which is essential for the function of both mutant and non-mutant *ras* proteins. R115777 has completed phase I trials in adults, and in children with solid tumors and NF1. A randomized, cross-over, double-blinded, placebo-controlled pediatric phase II trial of oral R115777 will be performed in children and young adults with NF1 who have progressive, plexiform neurofibroma(s) to determine the effect of this novel anticancer drug on the rate of growth of neurofibromas. The endpoint of the trial is time to disease progression. R115777/placebo will be administered orally at a dose of 200 mg/m² twice daily for 21 days followed by a 7 day rest .

ELIGIBILITY CRITERIA:

Age: ≥3 years and ≤25 years of age

Diagnosis: Patients with NF1 and progressive plexiform neurofibromas 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), 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 plexiform neurofibroma is clinically suspected. In addition to plexiform neurofibroma(s), all study subjects must have at least one other diagnostic criteria for NF1 listed below (NIH Consensus Conference[9]):

- 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

In this study a plexiform neurofibroma is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal plexiform neurofibroma involves two or more levels with connection between the levels or extending laterally along the nerve.

Measurable disease: Patients must have measurable plexiform neurofibroma(s). For the purpose of this study a measurable lesion will be defined as a lesion of at least 3 cm

measured in one dimension. There must be evidence of recurrent or progressive disease as documented by an increase in size or the presence of new plexiform neurofibromas on MRI. Progression at the time of study entry is defined as:

- A measurable increase of the plexiform neurofibroma ($\geq 20\%$ increase in the volume, or a $\geq 13\%$ increase in the product of the two longest perpendicular diameters, or a $\geq 6\%$ 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.
- 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.

Prior therapy:

- Patients with NF1 are eligible at the time of recurrence or progression of inoperable plexiform neurofibroma.
- A surgical consultation should be obtained prior to enrollment on the study to evaluate if tumor resection is a feasible option. Patients 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 progressive plexiform neurofibromas, patients may be treated on this trial without having received prior therapy.
- Patients must have recovered from the toxic effects of all prior therapy before entering this study. The Cancer Therapy Evaluation Program Common Toxicity Criteria (CTC) Version 2.0 will be used for toxicity assessment. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). Recovery is defined as a toxicity grade <2 , unless otherwise specified in the Inclusion and Exclusion Criteria.
- Patients must have had their last dose of radiation therapy at least six weeks prior to study entry, and their last dose of chemotherapy at least four weeks prior to study entry. Patients who received G-CSF after the prior cycle of chemotherapy must be off G-CSF for at least one week prior to entering this study.

Performance Status: Patients should have a life expectancy of at least 12 months and an ECOG performance score of 0, 1, or 2 (see below). Patients who are wheelchair bound because of paralysis should be considered “ambulatory” when they are up in their wheel chair.

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

Hematologic Function: Patients must have an absolute granulocyte count $\geq 1,500/\mu\text{L}$, a hemoglobin ≥ 9.0 gm/dl, and a platelet count $\geq 150,000/\mu\text{L}$ at study entry, and a normal fibrinogen.

Hepatic Function: Patients must have a bilirubin within normal limits and SGPT \leq 2x upper limit of normal. Patients with Gilbert syndrome are excluded from the requirement of a normal bilirubin. (Gilbert syndrome is found in 3-10% of the general population, and is characterized by mild, chronic unconjugated 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 (70 mL/min/1.73 m²).

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

Informed Consent: All patients or their legal guardians (if the patients is <18 years old) must sign an IRB approved document of informed consent indicating their understanding of the investigational nature and the risks of this study 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 discussion 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.

Ability to undergo MRI examinations.

EXCLUSION CRITERIA

- Pregnant or breast feeding females are excluded, because the toxic effects and pharmacology of R115777 in the fetus and newborn are unknown.
- 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 R115777 or are likely to interfere with the study procedures or results.
- Prior treatment with >1 prior myelosuppressive chemotherapy regimen.
- An investigational agent within the past 30 days.
- Patients with a history of malignant peripheral nerve sheath tumor or other cancer.
- 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.
- Prior treatment with R115777.

PRETREATMENT EVALUATION:

- History and physical, including complete neurological exam, Quality of Life Assessment
- Photography of plexiform neurofibromas visible on the body surface
- Laboratory work (within 2 weeks prior to enrollment), including hematology, chemistries, pregnancy test, urinalysis.
- MRI all measurable disease sites within 2 wks of start of therapy, & volumetric (3D) MRI imaging of progressing plexiform neurofibroma

- Ophthalmologic evaluation prior to or within 3 days of starting treatment
- Biopsy of easily accessible discrete neurofibromas or superficial plexiform neurofibromas - not mandatory
- Farnesyl-Protein Transferase (FPTase) activity in peripheral blood mononuclear cells; 10-20 ml blood
- Prelamin A in buccal mucosal cells collected on clean, charged microscope slides
- Nerve Growth Factor (NGF); 3 ml blood sample

GENERAL TREATMENT PLAN:

- Randomization at study entry to receive either R115777 or placebo first (cycles of 200mg/m² q12h for 21 days followed by a 7 day rest period). After documentation of disease progression patients will be crossed over to receive R115777 (if placebo was first given) or placebo (if R115777 was first given). Two week washout period when crossing over. Disease progression is assessed by volumetric MRI measurements that are performed centrally. Patients can expect to stay in the area for approximately 4 days for the initial work-up. Treatment is outpatient unless otherwise clinically indicated.

ACCRUAL:

Open to accrual at the POB, Children's Memorial Hospital of Chicago, Children's Hospital of Philadelphia, and Dana Farber. Other participating institutions will open the trial after final institutional and Army IRB approval