

v2.0, 4.0

## Protocol Abstract and Schema

**Description:** Children with newly diagnosed, diffuse, intrinsic pontine gliomas will be eligible for this study. Patients are to receive R115777 concurrently with radiation therapy and subsequent to radiation in the absence of dose limiting toxicity or disease progression. The dose escalation phase of the study has been completed and the maximum tolerated dose (MTD) of R115777 with concurrent radiation therapy has been established as 125 mg/m<sup>2</sup>/dose BID.

In the Phase II portion of this study, patients will continue to receive R115777 after radiation therapy and a two-week rest period at the previously established MTD (single agent without concurrent irradiation) of 200 mg/m<sup>2</sup>/dose BID. Efficacy of this treatment in patients with diffuse intrinsic pontine gliomas will be investigated with progression-free survival and survival distribution as the primary outcomes.

### **Primary Objectives:**

1. To estimate the MTD of R115777 administered concurrently with radiation therapy to pediatric patients with non-disseminated, diffuse, intrinsic brainstem gliomas who are not receiving enzyme-inducing anti-convulsant drugs (EIACD).
2. To assess the efficacy of R115777 treatment in combination with radiation therapy for patients with non-disseminated, diffuse, intrinsic pontine gliomas as measured by progression-free survival and survival distributions.

### **Secondary Objectives:**

3. To characterize toxicities associated with R115777 treatment in combination with and post radiation therapy.
4. To characterize radiographic changes in brainstem gliomas treated with radiation and R115777 using MRI, MRS, perfusion and diffusion imaging and PET scans.

### **Eligibility Criteria:**

- **Age:** Patient must be  $\geq 3$  and  $\leq 21$  years of age.
- **Tumor:** Newly diagnosed non-disseminated intrinsic diffuse brainstem glioma.
- **Performance Score:** Karnofsky Performance Scale (KPS for  $> 16$  yrs of age) or Lansky Performance Score (LPS for  $\leq 16$  years of age)  $\geq 50$  assessed within two-weeks prior to registration.
- **Prior/ Concurrent Therapy:**
  - Chemo: No prior therapy allowed.
  - XRT: No prior therapy allowed.
  - Bone Marrow Transplant: None prior.
  - Anti-convulsants: Patients receiving EIACD will not be eligible and patients must be off EIACD for a minimum of 7 days prior to registration. However, patients may switch from EIACDs to non-EIACDs and must then be on non-EIACDs.
  - Growth factors: Off all colony forming growth factor(s)  $> 2$  weeks prior to registration (G-CSF, GM-CSF, erythropoietin).

- The following laboratory values must be assessed within two (2) weeks prior to registration and again within seven (7) days prior to the start of therapy.
  - Absolute neutrophil count  $\geq 1,000/\text{mm}^3$
  - Hemoglobin  $\geq 8 \text{ gm/dL}$  (transfusion independent)
  - Platelets  $\geq 100,000/\text{mm}^3$  (transfusion independent)
  - Renal: Serum creatinine less than upper limit of institutional normal for age or  $\text{GFR} > 70 \text{ ml/min/1.73m}^2$ .
  - Hepatic: Bilirubin  $\leq 1.5$  times upper limit of normal for age; SGPT (ALT) and SGOT (AST)  $< 2.5$  times institutional upper limit of normal.
- Female patients of childbearing potential must have negative serum or urine pregnancy test. Patient must not be pregnant or breast-feeding.
- 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.
- Signed informed consent according to institutional guidelines must be obtained.

#### ***Exclusion Criteria***

- Patients must not have any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy. Patients must not have any disease that will obscure toxicity or dangerously alter drug metabolism.
  - Patients with disseminated intrinsic diffuse brainstem glioma
  - Patients taking enzyme-inducing anticonvulsant drugs.
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- Patients with known allergy to topical or systemic imidazoles (e.g., clotrimazole, ketoconazole, miconazole, econazole).
  - Patients receiving any other anticancer or experimental drug therapy.
  - Patients with uncontrolled infection.

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***Schema:***

R115777 (Zarnestra) will be given twice a day, starting one to two days prior to the start of radiation therapy. Concurrent initiation of R115777 and radiation therapy is acceptable. Patients will take R115777 continuously during radiation therapy with no breaks during weekends. After completion of radiation, patients will stop taking R115777 for a two-week rest period. At approximately week 9, patients will resume taking R115777 at 200 mg/m<sup>2</sup>, the previously established MTD in the absence of radiation therapy, or at one dose level lower than the initially assigned dose for patients who experience a DLT during the DLT observation period. R115777 will be administered twice a day on a 28-day schedule consisting of three weeks on drug followed by a one-week rest period. Each 28-day period is defined as a course. R115777 therapy will continue for up to 26 courses (104 weeks) in the absence of disease progression or toxicity inconsistent with treatment.

<b><i>Schedule</i></b>		
<b><i>Course</i></b>	<b><i>Weeks</i></b>	<b><i>Protocol Therapy</i></b>
Course 1	Weeks 1 through 4	RT + R115777
Course 2	Weeks 5 through 6 Weeks 7 through 8	RT + R115777 None
Course 3	Weeks 9 through 11 Week 12	R115777 None
Course 4	Weeks 13 through 15 Week 16	R115777 None
Course 5	Weeks 17 through 19 Week 20	R115777 None
Course 6	Weeks 21 through 23 Week 24	R115777 None
Course 7	Weeks 25 through 27 Week 28	R115777 None
Course 8	Weeks 29 through 31 Week 32	R115777 None
Course 9	Weeks 33 through 35 Week 36	R115777 None
Course 10	Weeks 37 through 39 Week 40	R115777 None
Course 11	Weeks 41 through 43 Week 44	R115777 None
Course 12	Weeks 45 through 47 Week 48	R115777 None
Course 13	Weeks 49 through 51 Week 52	R115777 None
Therapy will continue on the same 4 week schedule up through Course 26 (through Week 104)		