A Pilot Study of Larotrectinib for Newly-Diagnosed High-Grade Glioma With NTRK Fusion

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: Up to 21 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

- Age: Patients ≤ 21 years of age (birth to 21 years of age) at the time of study enrollment will be eligible.
- Diagnosis: Patients with newly-diagnosed high-grade (HGG), including diffuse intrinsic pontine gliomas (DIPG), whose tumors are documented in a CLIA/CAP certified lab (or clinically equivalent method considered standard in non-US sites) to harbor an NTRK fusion alteration by FISH, PCR, or next generation sequencing are eligible. Patients must have had histologically verified high-grade glioma such as anaplastic astrocytoma, glioblastoma, or H3 K27-mutant diffuse midline glioma verified at a CONNECT site.

For sites that do not have CLIA-certified equivalent (certified laboratory) to assess NTRK fusion, testing will be conducted centrally at NCH. NTRK testing will be performed by NGS using targeted RNA-sequencing (Archer Solid Tumor analysis) Please submit 10 unstained sections on charged slides at 10uM thickness, or 10 scrolls cut at 10uM thickness, along with submission of an H&E slide. Formalin-fixed paraffin embedded (FFPE) tissue block and FFPE tissue scroll specimens must contain minimum of 25% tumor Snap-frozen tissue specimens are also acceptable and they must contain a minimum of 10% tumor. Please note that turn-around time for this test is up to 21 days.

- Disease Status: Patients with disseminated DIPG or HGG are eligible only if the patient is to receive chemotherapy only, i.e. no craniospinal RT is intended to be given. MRI of spine must be performed if disseminated disease is suspected clinically by the treating physicians. Patients with primary spinal tumors are eligible only if the patient is to receive either chemotherapy or focal radiation therapy, i.e. no craniospinal RT is intended to be given. Patients with leptomeningeal disease only, with no definitive identifiable primary tumor, and documented NTRK fusion, must be discussed with the Study Chair on a case-by-case basis.
- Surgical Cohort ONLY: Patients with newly-diagnosed HGG with NTRK fusions who have undergone prior biopsy and for whom further resection is indicated for a more definitive surgery at an enrolling site will be eligible to enroll onto the surgical study. DIPG patients are not eligible for the surgical cohort.
- Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). 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: Patients must not have received any prior anti-cancer chemotherapy. Prior use of corticosteroids are allowed (see below Exclusion Criteria)
- Organ Function Requirements: Adequate Bone Marrow Function Defined as:

Peripheral absolute neutrophil count (ANC) ≥ 1000/mm3 Platelet count ≥ 100,000/mm3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment) Hemoglobin >8 g/dL (may receive transfusions)

- Adequate Renal Function Defined as: Serum creatinine within normal institutional limits, or Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2

- Adequate Liver Function Defined as: Total bilirubin ≤ 2.5 × institutional upper limit of normal AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional upper limit of normal

- Adequate Pulmonary Function Defined as: Pulse oximetry > 94% on room air if there is clinical indication for determination (e.g. dyspnea at rest).

- Adequate Neurologic Function Defined as: Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled. See Section 5.5.2 and Appendix III for EIAED guidelines.

- Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

Exclusion Criteria:

- Pregnancy or Breast-Feeding: Pregnant or breast-feeding women will not be entered on this study due to unknown risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.
- Concomitant Medications Investigational Drugs: Patients who have previously received or are currently receiving another investigational drug are not eligible.

Anti-cancer Agents: Patients who have previously received or are currently receiving other anti-cancer agents, including chemotherapy, immunotherapy, monoclonal antibodies, biologic or targeted therapy, are not eligible

- Infection: Patients must not have any active, uncontrolled systemic bacterial, viral or fungal infection.
- Patients who have received prior solid organ transplantation are not eligible.
- Patients must not have malabsorption syndrome or other condition affecting oral absorption.
- Patients must not be receiving any treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor or inducer. (See Appendix III.) Strong inducers or inhibitors of CYP3A4 should be avoided from 7 days prior to enrollment to the end of the study

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- Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

Conditions & Interventions

Interventions:
DRUG: Larotrectinib, PROCEDURE: Larotrectinib surgical
Conditions:
High Grade Glioma, Diffuse Intrinsic Pontine Glioma
Keywords:
NTRK gene fusion, BABYPOG, HIT-SKK, Larotrectinib

More Information

Description:
This is a pilot study that will evaluate disease status in children that have been newly diagnosed high-grade glioma with TRK fusion. The evaluation will occur after 2 cycles of the medication (Larotrectinib) have been given. The study will also evaluate the safety of larotrectinib when given with chemotherapy in your children; as well as the safety larotrectinib when given post-focal radiation therapy.

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