Lorlatinib for Newly-Diagnosed High-Grade Glioma With ROS or ALK Fusion

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 1 year to 21 years old
Healthy Volunteers: This study is also accepting healthy volunteers
Inclusion Criteria:

1. Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment on TarGeT-SCR.
2. Diagnosis:

Patients with newly diagnosed high-grade glioma (HGG), including diffuse intrinsic pontine gliomas (DIPG), whose tumors harbor an ALK or ROS-1 fusion alteration are eligible. Patients must have had histologically verified high-grade glioma from diagnostic biopsy or resection. For the diagnosis of DIPG, patients must have a tumor with pontine epicenter and diffuse involvement of at least 2/3 of the pons, with histopathology consistent with diffuse WHO Grade 2-4. All other HGGs must be Grade 3 or 4.
3. 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 ALK or ROS-1 fusion, must be discussed with the Study Chair on a case-by-case basis.
4. 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.
5. Prior Therapy:

- Patients must not have received any prior anti-cancer chemotherapy.
- Prior use of corticosteroids is allowed (see below Exclusion Criteria)

    1. Organ Function Requirements 6.1 Adequate Bone Marrow Function Defined as:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/µL
- Platelet count ≥ 100,000/µL (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin >8 g/dL (may receive transfusions) 6.2 Adequate Renal Function Defined as:
- Serum creatinine within normal institutional limits OR Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 6.3 Adequate Liver Function Defined as:
- Total bilirubin ≤ 2 × institutional upper limit of normal
- AST(aspartate aminotransferase)/ALT(alanine transaminase) ≤ 2.5 × institutional upper limit of normal 6.4 Adequate Pulmonary Function Defined as: Pulse oximetry > 94% on room air if there is clinical indication for determination (e.g. dyspnea at rest).

6.5Adequate Cardiac Function Defined as: QTc ≤ 470 msec (by Bazett formula) 6.6 Adequate Neurologic Function Defined as: Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.

6.7 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:

1. 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.

Females of reproductive potential must use an effective non-hormonal method of contraception, since lorlatinib can render hormonal contraceptives ineffective, during study treatment and for at least 6 months after the final dose. Males with female partners of reproductive potential must use effective contraception during treatment with lorlatinib and for 3 months after the final dose.
2. Concomitant Medications

- Investigational Agents/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
    1. Infection: Patients must not have any active, uncontrolled systemic bacterial, viral or fungal infection.
    2. Patients who have received prior solid organ transplantation are not eligible.
    3. Patients must not have malabsorption syndrome or other condition affecting oral absorption.

4. Patients must not be receiving any treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor or inducer. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to treatment with loraltinib. Moderate inducers of CYP3A4 should be avoided
5. Avoid concomitant use of lorlatinib with certain CYP3A substrates, for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with approved product labeling.
6. P-glycoprotein (P-gp) substrates: Lorlatinib is considered a moderate P-gp inducer. Co-administration of lorlatinib with P-gp substrates including but not limited to digoxin should be avoided as the concentration of these drugs may be reduced by lorlatinib.
7. 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.
8. Patients with a known personal history of acute or chronic severe psychiatric disorders or current history of suicidal ideation and history of suicide attempt.

Conditions & Interventions

Interventions:
DRUG: Lorlatinib, DRUG: Lorlatinib with chemotherapy1, DRUG: Lorlatinib with chemotherapy 2, DRUG: Lorlatinib post Radiation
Conditions:
High Grade Glioma, Diffuse Intrinsic Pontine Glioma, Anaplastic Astrocytoma, Infant Type Hemispheric Glioma, Glioblastoma, Glioblastoma Multiforme, WHO Grade III Glioma, WHO Grade IV Glioma, Diffuse Midline Glioma, H3K27-altered
Keywords:
ALK fusion, ROS fusion, High Grade Glioma, Diffuse Intrinsic Pontine Glioma

More Information

Description:
The goal of this study is to determine the response of the study drug loratinib in treating children who are newly diagnosed high-grade glioma with a fusion in ALK or ROS1. It will also evaluate the safety of lorlatinib when given with chemotherapy or after radiation therapy.

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