Study of Olutasidenib and Temozolomide in HGG

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 12 years to 39 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
Criteria TarGeT-D study strata definitions

- Stratum A: Patients with localized, intracranial, non-pontine, and non-thalamic IDH 1 mutant Astrocytoma, CNS WHO Grade 3.
- Stratum B: Patients with localized, intracranial, non-pontine, and non-thalamic IDH 1 mutant Astrocytoma, CNS WHO Grade 4.
- Stratum C: Patients with IDH-1 mutant DIPG, primary thalamic and spinal cord IDH-1 mutant HGG.

Inclusion Criteria:

1. Inclusion criteria already met to enroll on TarGeT-SCR (central molecular and histopathologic screening) based on:

1.1) Age: patients must be ≥12 years and ≤39 years of age at the time of enrollment on TarGeT-SCR 1.2) Diagnosis:
* Patients with a newly-diagnosed IDH1-mutant HGG including DIPG are eligible. All patients must have tumor tissue from diagnostic biopsy or resection, without exceptions. The diagnosis of HGG, including DIPG, must have been confirmed through TarGeT-SCR.
* For the diagnosis of DIPG, patients must have a tumor with pontine epicenter and diffuse involvement of at least 2/3 of the pons, and histopathology consistent with diffuse WHO Grade 2-4 glioma.
* All other HGG must be WHO Grade 3 or 4.

1.3) Disease status: There are no disease status requirements for enrollment
* Measurable disease is not required. Patients without measurable disease are eligible.
* Primary spinal tumor: Patients with a primary spinal HGG are eligible.
* Patient must not have metastatic disease.
2. Inclusion criteria for assignment to TarGeT-D, for all strata:

2.1 Presence of at Least One Relevant Actionable Somatic Mutation in IDH1 Gene, Detailed Here:

- R132H, R132C, R132S, R132G or R132L.
- Patients whose tumors harbor other alterations in addition to IDH1 mutation will potentially be eligible following consensus recommendation by the international multidisciplinary molecular screening committee.
- Patients with IDH2 mutations are not eligible.
- Patients with oligodendroglioma, IDH-mutant and 1p/19q-codeleted are not eligible.

2.2 Weight: Patients must weigh ≥35 Kg (77 lbs) at the time of enrollment on TarGeT-D.

2.3 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age. 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.

2.4 Prior Therapy 2.4.1 Surgery, radiation, and/or dexamethasone are permissible. Temozolomide administered concurrently with radiotherapy is permissible. Prior administration of bevacizumab is allowed, given at least 42-day washout period is completed prior to beginning treatment on TarGeT-D. No other prior anticancer therapy for HGG will be allowed.

2.4.2 Radiation therapy requirements: RT, delivered via photon or proton beam, must have been administered at a standard dose including 54 Gy in 30 fractions for DIPG, 55-59.4 Gy in 30-33 fractions for other HGG or 45-54 Gy for primary spinal cord HGG. Any variances in the radiotherapy dose within 10% of the standard doses outlined above will be discussed with the Study Chair to confirm eligibility prior to study enrollment.

2.4.3 Timing between diagnosis and start of RT: Patients must have started RT < 42 calendar days of initial diagnosis defined as the date of diagnostic biopsy or resection; if a patient underwent two upfront surgeries (e.g., biopsy then resection or debulking), this is the date of the second surgery.

- Patients in pre-maintenance phase must enroll and start treatment no later than 21 calendar days post-completion of RT.
- Patients not in pre-maintenance phase must enroll and start treatment no later than 35 calendar days post-completion of RT.

2.5 Organ Function Requirements 2.5.1 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 be transfused). 2.5.2 Adequate Renal Function Defined as
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 OR
- Maximum serum creatinine based on age/gender as follows: 10 to < 13 yrs=1.2 mg/dL for males and females. 13 to < 16 yrs=1.5 mg/dL for males and 1.4 mg/dL for females.

2.5.3 Adequate Liver Function Defined as:

- Total bilirubin must be ≤ 1.5 × institutional ULN.
- AST(SGOT)/ALT(SGPT) < 3 × institutional ULN.
- Alkaline Phosphatase < 3 × institutional ULN. 2.5.4 Adequate Neurologic Function Defined as:
    - Patients with seizure disorder may be enrolled if well-controlled on anticonvulsants that are not a strong inducer or inhibitor of CYP3A4/5.
    - Patients must be able to swallow oral medications to be eligible for study enrollment.

2.6. 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. Pregnancy or Breast-Feeding: Pregnant or breast-feeding women will not be entered on this study due to unknown potential risks of fetal and teratogenic adverse events as seen in animal studies. Pregnancy tests must be obtained in girls who are post-menarchal. Patients of childbearing or child fathering potential must agree to use one highly effective method of contraception while being treated on this study and for 3 months after completing therapy. A woman is considered of childbearing potential if she is fertile, following menarche and until becoming post-menopausal unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy. Male participants should refrain from sperm donation throughout the duration of treatment and for 3 months after completion of therapy.

A highly effective contraception method is defined as one that results in a low failure rate (<1% per year) when used consistently and correctly. The following are considered highly effective contraception methods:
* Combined estrogen and progesterone containing hormonal contraception associated with inhibition of ovulation.
* Progesterone-only hormonal contraception associated with inhibition of ovulation.
* Intra Uterine Device (IUD).
* Intra uterine hormone releasing system.
* Bilateral tubal occlusion.
* Vasectomized partner.
* Sexual abstinence (avoiding heterosexual intercourse).
* The following contraceptive measures are NOT considered effective:

* Progesterone-only hormonal contraception (birth control pill) that that does NOT stop ovulation.
* Male or female condom with or without spermicide.
* Cap, diaphragm, or sponge with spermicide.

1. Using the following types of concomitant medications:

- Corticosteroids: Patients receiving corticosteroids are eligible. The use of corticosteroids must be reported.
- Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
- Anti-cancer Agents: Concurrent anti-cancer agents are not allowed with the exception of temozolomide given concurrently with RT and as protocol-instructed post RT maintenance therapy after enrollment on TarGeT-D.
- Anticonvulsants: Patients who are receiving enzyme inducing anticonvulsants that are strong inducers of CYP3A4/5 are not eligible.
- Strong CYP3A4/5 inducers: Patients who are receiving strong inducers of CYP3A4/5 are not eligible. Strong inducers of CYP3A4/5 should be avoided from 14 days prior to or 5 half-lives (whichever is longer) enrollment to the end of the study.
- Patients who are receiving medications known to prolong QTc interval are not eligible
- Selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft) should be used with caution but are not contraindicated.

    1. Other Criteria
- Infection: Patients who have an uncontrolled infection are not eligible.
- 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.
- Patients with known clinically significant active malabsorption syndrome or other condition that could affect absorption are not eligible.
- Patients with malignancy related to HIV or solid organ transplant: known history of HIV, HBV surface antigen positivity or positive HCV antibody are not eligible. Viral testing is not required unless clinically indicated in patients without a known history.
- Patients with prior or ongoing clinically significant illness, medical or psychiatric condition, that, in the investigator's opinion, could affect the safety of the participant, or could impair the assessment of study results are not eligible.
- Patients with any prior solid organ transplant are not eligible.
- Patients with secondary/radiation-related HGG are not eligible.
- Patients with metastatic/disseminated HGG who have received CSI are not eligible.

Conditions & Interventions

Interventions:
DRUG: Olutasidenib + TMZ
Conditions:
High Grade Glioma, Astrocytoma, Astrocytoma, Grade III, Astrocytoma, Grade IV, Diffuse Intrinsic Pontine Glioma, WHO Grade III Glioma, WHO Grade IV Glioma, Metastatic Brain Tumor, Diffuse Midline Glioma, H3 K27M-Mutant, Thalamus Tumor, Spinal Tumor, IDH1 Mutation, IDH1 R132, IDH1 R132C, IDH1 R132H, IDH1 R132S, IDH1 R132G, IDH1 R132L, Oligodendroglioma

More Information

Description:
The goal of this study is to determine the efficacy of the study drug olutasidenib to treat newly diagnosed pediatric and young adult patients with a high-grade glioma (HGG) harboring an IDH1 mutation. The main question the study aims to answer is whether the combination of olutasidenib and temozolomide (TMZ) can prolong the life of patients diagnosed with an IDH-mutant HGG.

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