Study of Ribociclib and Everolimus in HGG and DIPG or Ribociclib and Temozolomide in DHG, H3G34-mutant

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 12 months to 39 years old
Healthy Volunteers: This study is NOT accepting healthy volunteers
TarGeT-A study strata definitions Part1: Initial Feasibility Study for the combination of ribociclib PfOS formulation with everolimus: Enrollment on this cohort will be limited to patients aged <21 years with primary intracranial localized HGG and DIPG

Part 2

- Stratum A: Patients with localized, intracranial, non-pontine, and non-thalamic HGG (who do not meet criteria for strata C-D)
- Stratum B: Patients with DIPG
- Stratum C: Patients with primary thalamic, spinal cord, and/or secondary/radiation-related HGG.
- Stratum D: Patients with metastatic/disseminated HGG, multifocal HGG, and/or gliomatosis cerebri who received CSI.

Stratum E

- Stratum E: Patients with localized DHG, H3G34-mutant.

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 months and ≤39 years of age at the time of enrollment on TarGeT-SCR. For the Part 1 Initial Feasibility Cohort (receiving ribociclib and everolimus) only: patients must be <21 years of age at the time of enrollment on this protocol.

1.2) Diagnosis: patients with newly-diagnosed HGG, including DIPG are eligible. All patients must have histologic confirmation 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, with histopathology, consistent with diffuse WHO grade 2-4 glioma
* All other HGGs must be WHO grade 3 or 4.

1.3) Disease status: There are no disease status requirements for enrollment
* Patients without measurable disease are eligible.
* Patients with metastatic or multifocal disease or gliomatosis cerebri who received upfront CSI are eligible
* Patients with a primary spinal HGG are eligible
* Patients with secondary, radiation-related HGG are eligible.
2. Inclusion criteria for assignment to TarGeT-A, for all strata:

2.1) Presence of at least one relevant actionable somatic alteration, detailed here:

- Pathogenic alterations presumed to cause activation of cell cycle:
- Amplification of CDK4 or CDK6
- Deletion of CDKN2A, CDKN2B, or CDKN2C
- Amplification of CCND1 or CCND2
- Pathogenic alterations presumed to cause activation of the PI3K/mTOR pathway:
- Deletion or mutation of PTEN
- Mutation or amplification of PIK3CA
- Mutation of PIK3R1
- Deletion or mutation of TSC1 or TSC2
- Patients with evidence of homozygous (biallelic) RB1 loss by sequencing are excluded from TarGeT-A
- Patients whose tumors harbor other alterations suspected to activate the cell cycle and/or PI3K/mTOR pathway could potentially also be eligible, but only following consensus recommendation by the international multidisciplinary molecular screening committee.
- For Stratum E: H3G34 (R/V) mutation

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

2.3) Prior Therapy for HGG:

- Surgery, RT, dexamethasone are permissible. Temozolomide administered concurrently with RT is permissible. Avastin/bevacizumab use is permitted given the last dose was administered > 21 days prior to enrollment. No other prior anticancer therapy for HGG will be allowed.
- Patients must have received photon or proton RT.
- Patients must have started RT < 42 calendar days from initial diagnosis defined as the date of diagnostic biopsy or resection. If a patient underwent 2 upfront surgeries (e.g., biopsy then resection or debulking), this is the date of the second surgery.
- RT delivered via photon or proton beam, must have been administered at a standard dose including (54 Gy in 30 fractions for DIPG, 54-59.4

Gy in 30-33 fractions), 45 Gy-54 Gy for primary spinal disease, and/or 36 Gy-39.6 Gy craniospinal for patients with spinal or leptomeningeal metastatic disease with supplemental boost to 45-54 Gy for metastasis within the thecal sac and 54 Gy-60 Gy for intracranial metastasis. Any variances in the radiotherapy dose within 10% of the standard doses outlined above will be discussed with the Sponsor-Investigator to confirm eligibility prior to study enrollment.
- Patients must enroll and start treatment No later than 35 calendar days post-completion of RT. The earliest patients can begin protocol treatment is 28 calendar days post-completion of RT.

2.4) Organ Function Requirements

2.4.1) 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)

2.4.2) Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 OR
- Maximum serum creatinine based on (Schwartz et al. J. Peds, 106:522, 1985) age/gender as follows: 1 to < 2 years=0.6 mg/dL for males and females; 2 to < 6 years=0.8 mg/dL for males and females; 6 to < 10 years= 1.0 mg/dL for males and females; 10 to < 13 years=1.2 mg/dL for males and females. 13 to < 16 years=1.5 mg/dL for males and 1.4 mg/dL for females.

2.4.3) Adequate Liver Function Defined as:

- Total bilirubin must be ≤ 1.5 times institutional upper limit of normal for age
- AST(SGOT)/ALT(SGPT) ≤ 3 times institutional upper limit of normal
- Serum albumin ≥ 2g/dL

2.4.4) Adequate Cardiac Function Defined as:

- Ejection fraction of ≥ 50% by echocardiogram
- QTc ≤ 450 msec (by Bazett formula)

2.4.5) Adequate Neurologic Function Defined as: Patients with seizure disorder may be enrolled if well-controlled on anticonvulsants that are not strong inducers or inhibitors of CYP3A4/5.

2.4.6) Adequate Pulmonary Function Defined as: No evidence of dyspnea at rest, and a pulse oximetry >94% on room air if there is clinical indication for determination.

2.5) Ability to take medications by mouth: For ribociclib and everolimus strata, patients must be able to take study medications by mouth as administration via NG/NJ/G tube is not allowed.

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

2.7) Contraception: Male and female patients of childbearing potential must be willing to use a highly effective contraception method.

Exclusion Criteria

1. Pregnant or Breast-Feeding Pregnant or breast-feeding women will not be entered on this study due to known potential risks of fetal and teratogenic adverse events as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. Patients of childbearing or child fathering potential must agree to use at least 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 having 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
2. Concomitant Medications

- Patients receiving corticosteroids are eligible. The use of corticosteroids must be reported.
- Patients who are currently receiving another investigational drug are not eligible.
- Patients who are currently receiving other anti-cancer agents are not eligible, with the exception of temozolomide given concurrently with RT only.
- Patients who are receiving enzyme-inducing anticonvulsants that are strong inducers or inhibitors of CYP3A4/5 are not eligible.

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- Patients who are receiving strong inducers or inhibitors of CYP3A4/5 are not eligible and should be avoided from 14 days prior to enrollment to the end of the study.
- Patients who are receiving medications known to prolong QTc interval are not eligible.
- Patients who are receiving therapeutic anticoagulation with warfarin or other coumadin-derived anticoagulants are not eligible. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed as long as the patient has adequate coagulation defined as aPTT < 1.5Xs ULN and INR < 1.5.
    1. Patients who have an uncontrolled infection are not eligible.
    2. 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.
    3. Patients with known clinically significant active malabsorption syndrome or other condition that could affect absorption are not eligible.
    4. Patients with prior or ongoing clinically significant medical or psychiatric condition that, in the investigator's opinion, could affect the safety of the subject, or could impair the assessment of study results are not eligible.

Conditions & Interventions

Interventions:
DRUG: Ribociclib, DRUG: Everolimus, DRUG: Temozolomide (TMZ)
Conditions:
High Grade Glioma, Diffuse Intrinsic Pontine Glioma, Anaplastic Astrocytoma, Glioblastoma, Glioblastoma Multiforme, Diffuse Midline Glioma, H3 K27M-Mutant, Metastatic Brain Tumor, WHO Grade III Glioma, WHO Grade IV Glioma, Diffuse Hemispheric Glioma, H3 G34-Mutant

More Information

Description:
The goal of this study is to determine the efficacy of the 1) ribociclib and everolimus to treat pediatric and young adult patients newly diagnosed with a high-grade glioma (HGG), including DIPG, that have genetic changes in pathways (cell cycle, PI3K/mTOR) that these drugs target or 2) ribociclib and temozolomide to treat pediatric and young adult patients newly diagnosed with diffuse hemispheric glioma (DHG), H3G34-mutant. The main question the study aims to answer is whether the combinations of ribociclib and everolimus or ribociclib and temozolomide can prolong the life of patients diagnosed with HGG/DIPG or DHG H3G34-mutant.

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