Study of Cabozantinib With Selumetinib for Plexiform Neurofibromas

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 16 years and over
Healthy Volunteers: This study is NOT accepting healthy volunteers
1.0 INCLUSION CRITERIA

1.1. All participants must have a diagnosis of NF1 based on the 2021 revised consensus criteria.

1.2. Participants must have PN(s) that are progressive OR are causing significant morbidity, such as (but not limited to) head and neck lesions that are compromising the airway or great vessels, brachial or lumbar plexus lesions that are causing nerve compression and loss of function, lesions causing significant disfigurement (e.g., orbital lesions), lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Participants with paraspinal PN will be eligible for this trial. Histologic confirmation of tumor is not necessary but should be considered if there are clinical or radiographic findings concerning for malignant transformation of a PN.

1.2.1. For participants enrolled for tumor progression, progression is defined as: Presence of new PN on MRI or CT (documented by comparison with prior MRI or CT), OR A measurable increase in PN size (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) documented by comparison of two scans (MRI or CT) in the time period of 18 months or less prior to evaluation for this study.

1.2.2. For participants enrolled for tumors causing "significant disfigurement" without meeting another criterion (i.e., not progressive or causing other significant morbidity), eligible tumors will be limited to tumors of the head & neck or those on other areas of the body that are unable to be concealed by standard garments. In order to enroll a participant with PN for these indications, photographs must be reviewed by a Study Chair and/or Co-Chair for decision regarding participant eligibility prior to enrollment.

1.3. Disease status: Measurable disease: Participants must have measurable PN(s) amenable to volumetric MRI analysis. For the purpose of this study, the target lesion must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest. Tumors must be at least 3 mL in volume (most PN 3 cm in longest diameter will meet this criteria). If the tumor is <3 cm in longest diameter, the participant may still be eligible. Central review of the MRI of the target PN is required prior to enrollment to ensure that the tumor is measurable and amenable to volumetric analysis.

1.4. Age: Participants must be ≥16 years of age at the time of study entry.

1.5. Performance Level: Participants must have Karnofsky ³ 50%. Note: Participants who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for assessing the performance score.

1.6. Body Surface Area (BSA): Participants must have a BSA of 1.0 m2 or greater.

1.7. Organ Function Requirements:

1.7.1. Adequate Bone Marrow Function Defined as: Absolute neutrophil count (ANC) ≥ 1500/µL without granulocyte colony-stimulating factor support.

White blood cell count ≥ 2500/µL Platelet count ³ 100,000/mL without transfusion Hemoglobin ³10.0 gm/dL (>5 days between enrollment and last RBC transfusion)

1.7.2. Adequate Renal Function Defined as: Maximum serum creatinine based on age/gender as per institutional standards OR a creatinine clearance, radioisotope GFR, or calculated creatinine clearance using the Cockcroft-Gault equation ³70ml/min/1.73 m2.

Cockcroft-Gault equation:

- Males: (140 - age) x weight (kg)/(serum creatinine [mg/dL] × 72)
- Females: [(140 - age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85 Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.2 mg/mmol), or 24-h urine protein ≤ 1 g.

1.7.3. Adequate Liver Function Defined as: Total bilirubin (sum of conjugated + unconjugated) £ 1.5x upper limit of normal (ULN) for age (for participants with Gilbert's disease ≤3x ULN), and Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) < 2.5x the upper limit of normal (ULN).

Serum albumin ³ 2.8 g/dL. PT/INR and partial thromboplastin time (PTT) test < 1.3x the laboratory ULN

1.7.4. Adequate Thyroid Function Defined as: ≤ Grade 1 or adequately managed asymptomatic Grade 2 hypothyroidism.

1.7.5. CPK level within normal limits within 14 days from the start of treatment.

1.7.6. Normal pancreatic function: amylase and lipase levels ≤ 1.5 x ULN

1.7.7. Blood pressure within upper limit of normal as defined below. Antihypertensives are permissible to achieve blood pressure within ULN, however must be on stable antihypertensive regimen with no adjustments within 30 days of enrollment.

In adolescents, a blood pressure (BP) ≤ 90th percentile for age, height, and sex.

In adults (³18 years of age), a systolic blood pressure ≤130 mmHg and a diastolic pressure of ≤80 mmHg.

1.8. Major surgery: Only participants who are not anticipated to need major surgery within 3 months after enrollment are eligible.

1.9. Sexually active fertile participants and their partners must agree to use effective methods of contraception e.g., hormonal oral contraception, injectables, intrauterine device, surgical sterilization including vasectomy, or hormonal implant with barrier methods (male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment. Barrier methods alone are insufficient. True sexual abstinence is an acceptable method of birth control for both men and women. Persons of childbearing potential will be given a pregnancy test within 7 days prior to first dose of study treatment and must have a negative urine or serum pregnancy test.

1.10. Written informed consent must be obtained from all participants (>18 years of age) or their legal guardians (if the participant is <18 years of age). Participants or legal guardians must be capable of understanding and complying with the protocol requirements and must have signed the informed consent document. Participants unable to provide informed consent/assent will NOT be enrolled on this study.

1.11. Willingness to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.

1.12. Willingness to avoid the ingestion of grapefruit and Seville oranges (as well as other products containing these fruits, e.g., grapefruit juice or marmalade) during the study, as these may affect selumetinib metabolism.

2.0 EXCLUSION CRITERIA

2.1. Evidence of an optic pathway or other low-grade glioma, high-grade glioma, malignant peripheral nerve sheath tumor, or other cancer/tumor requiring treatment with chemotherapy, biologic therapy or radiation therapy.

2.2. Patients with high-grade glioma, atypical or malignant peripheral nerve sheath tumor, or other malignancy who received treatment in the last 12 months. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that have undergone potentially curative therapy.

2.3. Dental braces or prosthesis that interfere with volumetric analysis of the neurofibroma(s).

2.4. Prior Therapy: Participants may have received treatment for a PN or other tumor/malignancy but must have fully recovered to baseline or CTCAE ≤ Grade 1 from acute toxicities from prior therapies except alopecia.

Myelosuppressive chemotherapy: Must not have received within 28 days of entry onto this study.

2.5. Hematopoietic growth factors: Must not have received a growth factor that supports platelet, red or white cell number or function within 14 days of initiation of therapy.

2.6. Biologic (anti-neoplastic agent): At least 28 days (or 5 half-lives whichever is longer) since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 28 days after administration (or 5 half-lives whichever is longer), this period must be extended beyond the time during which adverse events are known to occur. These participants must be discussed with the Study Chair on a case-by-case basis.

2.7. Investigational Drugs: At least 28 days (or 5 half-lives whichever is longer) since the completion of therapy with an investigational drug or systemic anticancer treatment. For agents that have known adverse events occurring beyond 28 days after administration (or 5 half-lives whichever is longer), this period must be extended beyond the time during which adverse events are known to occur. These participants must be discussed with the Study Chair on a case-by-case basis.

- Prior treatment with cabozantinib or selumetinib is permitted for participants on Phase 1 of this study only (not Phase 1b/2). Participants may have previously received cabozantinib and/or a MEK inhibitor but not simultaneously. If participants have received either cabozantinib or selumetinib previously, they must have tolerated either medication at the recommended entry doses for this study or greater and must not have discontinued therapy due to toxicity. Participants who have received the combination of cabozantinib with any MEK inhibitor previously will not be eligible. Prior treatment with cabozantinib and/or selumetinib will not be permitted for participants on Phase 1b or Phase 2.

2.8. Radiation therapy: 6 months from involved field radiation to index PN(s) must have elapsed prior to study entry; ³ 6 weeks must have elapsed if participant has received radiation to areas outside index PN(s) Participants who received radiation to the orbit at any time previously are not eligible.

>12 weeks must have elapsed between systemic treatment with radionuclides and first dose of study treatment.

Participants with clinically relevant ongoing complications from prior radiation therapy are not eligible.

2.9. Surgery:

2.9.1. Participants are not eligible if complete resection of a PN with acceptable morbidity is feasible, or if a participant with a feasible surgical optior with minimal risk for surgical morbidity refuses surgery. Participants who underwent surgery for a progressive PN will be eligible to enter the study after the surgery, provided the PN was incompletely resected and is measurable.

2.9.2. Any major surgery within 3 months before first dose of study treatment.

2.9.3. Any minor surgeries (e.g., the placement of an implanted vascular device, tooth extractions, biopsy, or an invasive operative procedure for procurement of tissue samples or body fluids using a needle or trocar, other than routine peripheral venous access) within 1 month before first dose of study treatment.

2.9.4. Participants must have complete wound healing from major surgery or minor surgery before first dose of study treatment. Participants with clinically relevant ongoing complications from prior surgery are not eligible.

2.10. Concomitant anticoagulation with coumarin agents (e.g., warfarin), low molecular weight heparins, direct thrombin inhibitors (e.g.,

dabigatran), direct factor Xa inhibitor betrixaban, or platelet inhibitors (e.g., clopidogrel). Allowed anticoagulants are the following: Prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines)

2.11. Clinically significant hematuria, hematemesis, or hemoptysis of >0.5 teaspoon (2.5ml) of red blood, or other history of significant bleeding (e.g., pulmonary hemorrhage) within 12 weeks before first dose of study treatment.

2.12. Known cavitating pulmonary lesion(s) or known endotracheal or endobronchial disease manifestation.

2.13. Cardiovascular disorders: 2.13.1. Congestive heart failure New York Heart Association Class 2-4, unstable angina pectoris (Canadian Cardiovascular Society grade II-IV despite medical therapy), prior or current cardiomyopathy, or severe valvular heart disease, baseline left ventricular ejection fraction (LVEF) below the LLN or <55% measured by echocardiography or institution's LLN for MUGA, serious cardiac arrhythmias including atrial fibrillation.

2.13.2. Stroke (including transient ischemic attack [TIA]), acute coronary syndrome or myocardial infarction (MI), or other ischemic event, or thromboembolic event (e.g., deep venous thrombosis, pulmonary embolism) within 6 months before first dose of study treatment.

2.13.3. Participants with a diagnosis of incidental, subsegmental PE or DVT within 6 months are allowed if stable, asymptomatic, and treated with a stable dose of permitted anticoagulation (aspirin) for at least 1 week before first dose of study treatment.

2.13.4. Baseline QTc interval >450 msec

2.14. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:

2.14.1. The participant has evidence of tumor invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (e.g., Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis, acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction.

2.14.2. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before first dose of study treatment.

Note: Complete healing of an intra-abdominal abscess must be confirmed before first dose of study treatment.

2.15. Ophthalmologic conditions:

2.15.1. Current or history of central serous retinopathy

2.15.2. Current or history of retinal vein occlusion

2.15.3. Known intraocular pressure (IOP) >21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP). Participants with known glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) and are not experiencing pain related to the glaucoma, may be eligible after discussion with the study chair. Participants with orbital plexiform neurofibromas should have IOP measured prior to enrollment.

2.15.4. Participants with any other significant abnormality on ophthalmic examination should be discussed with the Study Chair for potential eligibility.

2.15.5. Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study.

2.16. Other clinically significant disorders that would preclude safe study participation, including:

2.16.1. Serious non-healing wound, ulcer, or bone fracture.

2.16.2. Uncompensated/symptomatic hypothyroidism.

2.16.3. Moderate to severe hepatic impairment (Child-Pugh B or C).

2.16.4. Active infection

2.16.5. A known history of HIV seropositivity or known immunodeficiency. HIV testing will not be required as part of this trial, unless HIV is clinically suspected.

2.16.6. Uncontrolled diabetes, severe malnutrition, chronic liver or renal disease

2.16.7. History of organ transplant

2.17. Pregnant or lactating women.

2.18. Inability to swallow tablets.

2.19. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

2.20. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of cabozantinib or selumetinib (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

2.21. Participants who require chronic concomitant treatment of moderate/strong CYP3A4 inducers or inhibitors (Appendix XIII). While not an exclusion criterion, unless clinically indicated, participants should avoid taking other additional non-study medications that may interfere with the study medications. Participants should avoid medications that are known to either induce or inhibit the activity of hepatic microsomal isoenzymes CYP1A2, and CYP2C19, as this may interfere with the metabolism of selumetinib (Appendix XIII).

2.22. Participants with a history of significant noncompliance to medical regimens, are unwilling to or unable to comply with the protocol, or who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study.

Conditions & Interventions

Interventions:
DRUG: Cabozantinib Oral Tablet, DRUG: Selumetinib Oral Capsule
Conditions:
Neurofibromatosis 1, Plexiform Neurofibroma
Keywords:
adolescents, adults

More Information

Description:
Based on the clinical activity of both selumetinib and cabozantinib as monotherapies in clinical trials, the demonstrated activity of these agents in reduced doses in preclinical studies, and the non-overlapping toxicity profiles, the study will assess the tolerability and efficacy of selumetinib and cabozantinib in combination in participants with NF1 ≥16 years old with progressive and/or symptomatic PN in a phase 1/1b/2 clinical trial. Trial Design Phase 1 This will be an open label, dose escalation phase. Dose level escalation will be determined by a rolling six design. In this design, up to 6 participants can be enrolled at a given dose level and then evaluated for dose limiting toxicity (DLT) within the DLT window. The DLT window is defined as 16 weeks in this study based on the long half-life of cabozantinib and the desire to have maximum confidence about long-term tolerability of the combination prior to proceeding to the next dose level. Phase 1b Once the recommended phase 2 dose has been determined in phase 1, an expanded cohort of 12 participants will be enrolled in phase 1b portion of the study. Phase 2 This will be an open label, single-arm phase using the recommended phase 2 dose.

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