Cancer Research Consortium of West Michigan
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FAST FACTS

A071401: PHASE II TRIAL OF SMO/AKT/NF2 INHIBITORS IN PROGRESSIVE MENINGIOMAS WITH SMO/AKT/NF2 MUTATIONS

Eligibility Criteria

1. Documentation of Disease
   a. Histologic Documentation: Histologically proven intracranial meningioma as documented by central pathology review.
   b. **Molecular Documentation:** Presence of SMO, PTCH1 or NF2 mutation in tumor sample as documented by central laboratory. See Sections 4.4, 4.5 and Appendix VII for further details.
   c. **Progressive OR residual disease**, as defined by the following:
      a. Residual measurable disease (see also 3.3.2): Residual measurable disease immediately after surgery without requirement for progression. For Grade I disease, progression pre-operatively needs to be documented, with an increase in size of the measurable primary lesion on imaging by 25% or more (bidirectional area). The change must occur between scans separated by no more than 12 months. Residual measurable disease will be defined by bidimensionally measurable lesions with clearly defined margins by MRI scans, with a minimum diameter of 10mm in both dimensions. See Section 11.2.
      b. Progressive measurable disease (see also 3.3.2): Progression defined as an increase in size of the measurable primary lesion on imaging by 25% or more (bidirectional area). The change must occur between scans separated by no more than 12 months.
      c. Post radiation patients: Patients with measurable and progressive meningioma who have received radiation are potentially eligible, but need to show evidence of progressive disease after completion of radiation. At least 24 weeks must have elapsed from completion of radiation to registration. (See Section 3.3.3).
2. Measurable disease
   a. Measurable disease is defined by a bidimensionally measurable main lesion on MRI or CT images (MRI preferred) with clearly defined margins. Multifocal disease is allowed.
   For measurable disease, refer to Section 11.0.
3. Prior Treatment
   a. Prior medical therapy is allowed but not required.
   b. No limit on number of prior therapies.
   c. No chemotherapy, other investigational agents within 28 days of study treatment.
   d. No other concurrent investigational agents or other meningioma-directed therapy (chemotherapy, radiation) while on study.
   e. For patients treated with external beam radiation, interstitial brachytherapy or radiosurgery, an interval > 24 weeks must have elapsed from completion of radiation treatment to registration (See 3.3.1).
   f. Steroid dosing stable for at least 4 days.
   g. Recovered to CTCAE grade 1 or less toxicity from other agents with exception of alopecia and fatigue.
   h. No craniotomy within 28 days of registration.
4. Not pregnant and not nursing
   a. A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months). Please note the information below is strictly for eligibility purposes, please reference section 5.0 (Study calendar) for details on pregnancy monitoring during the duration of the trial. Also see section 3.1 for further details.
5. For patients with NF2 mutation: Age ≥ 18 years

For patients with SMO /PTCH1 mutation: Age ≥ 30 years

6. ECOG Performance Status ≤ 2
7. Patient history:
    a. Patients with history of NF may have other stable CNS tumors (schwannoma, acoustic neuroma or ependymoma) if lesions have been stable for 6 months.
    b. No metastatic meningiomas (as defined by extracranial meningiomas) allowed.
    c. No history of allergic reactions attributed to compounds of similar or biologic composition to assigned study drug.
    d. No Known active hepatitis B or C
    e. No current Child Pugh Class B or C liver disease
    f. No uncontrolled gastric ulcer disease (Grade 3 gastric ulcer disease within 28 days of registration)
    g. No uncontrolled diabetes defined as a known diabetic with HBA1C >7.5 OR fasting glucose > 140.
    h. No uncontrolled hypertension defined as BP > 140/90
    i. No abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to registration
8. Concomitant Medications

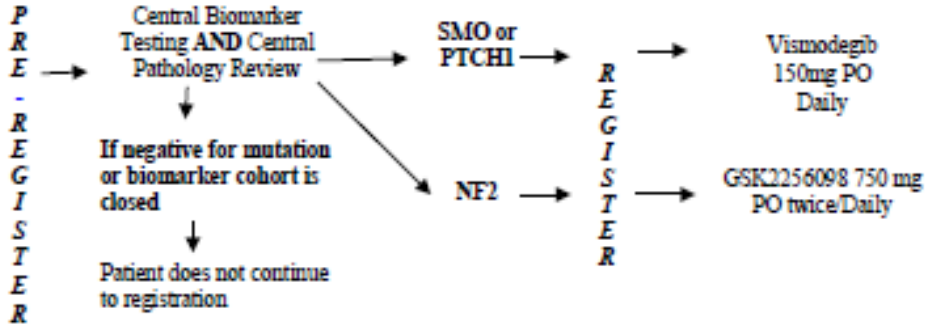
    a. Chronic concomitant treatment with strong inhibitors of CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study for patients with NF2 mutation enrolled to GSK2256098. See Section 7.1 for more information.
    b.
9. Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to registration for patients with NF2 mutation enrolled to GSK2256098. See Section 7.2 for more information. Required Initial Laboratory Values:
    a. Absolute Neutrophil Count (ANC) ≥ 1,500/mm3
    b. Platelet Count ≥ 100,000/mm3
    c. Creatinine OR ≤ 1.5 mg/dl x upper limit of normal (ULN) OR
    d. Calc. Creatinine Clearance > 45 mL/min
    e. UPC ≤ 45mg/mmol*
    f. Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)**
    g. AST / ALT ≤ 2.5 x upper limit of normal (ULN)
    h. Fasting triglyceride ≤ 200mg/dL*
    i. Fasting cholesterol ≤ 240mg/dL*
        QTcF*** ≤ 500 msec*

    * ONLY APPLICABLE for patients with NF2 mutation (GSK2256098).
    ** Except in case of Gilbert's disease
    *** QT calculated using Fridericia formula: QTc = QT/(RR^0.33), where RR = 60/HR

Schema

1 Cycle = 28 Days

Note: Pregnancy prevention must start 4 weeks prior to study drug.



Treatment is to continue until disease progression or unacceptable adverse event. Patients discontinuing treatment for reasons other than progressive disease, will continue following the Study Calendar for disease assessments until progressive disease is documented, for a maximum of 2 years. Patients will be followed for survival up to a maximum of 5 years from registration.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Pre study parameters

- History and physical, weight, height, PS
- Pulse, blood pressure
- Adverse event assessment
- Registration fatigue/uniscale assessment
- CBC
- Basic metabolic panel
- Urine protein
- Serum or urine HCG
- AG and Hepatitis C RNA (physician discretion, not required)
- Fasting cholesterol, triglyerides
- EKG
- MRI/CT brain
- Central review for eligibility