Cancer Research Consortium of West Michigan
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FAST FACTS

A071601 - PHASE II TRIAL OF BRAF/MEK INHIBITORS IN PAPILLARY CRANIOPHARYNGIOMAS

Pre-registration eligibility criteria (step 0)
Central pathology review and BRAF testing submission
This review is mandatory prior to registration to confirm eligibility. Patients must have local diagnosis of papillary craniopharyngioma and have tissue slides available for submission to central pathology review. Central pathology review will include IHC testing for BRAF V600E mutation (VE1 clone) and beta-catenin IHC (membranous, non-nuclear pattern) if needed to confirm diagnosis of papillary craniopharyngioma. See Sections 4.4, 4.5, and 6.2.1 for complete details.

Registration eligibility criteria (step 1)
When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.
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).

1. Documentation of disease:
   Histologically proven papillary craniopharyngioma as documented by central pathology review with positive BRAF V600E mutation by IHC.
2. Measurable disease as defined in Section 11.0.
   • Measurable disease, defined as bidimensionally measurable lesions with clearly defined margins by MRI scans, with a minimum diameter of 10mm in both dimensions.
   • Progressive disease required in cohort B, defined as any progressive measureable disease after surgery and radiation. Progressive or recurrent disease is not required in cohort A, but is allowed provided it is a new diagnosis and patient has not received prior treatment.
3. Prior treatment
   • Cohort A: No prior therapy received other than surgery.
   • Cohort B: Prior radiation therapy required (any type of prior radiation is allowed) - For patients treated with external beam radiation therapy, interstitial brachytherapy or radiosurgery, an interval of ≥ 3 months must have elapsed from completion of radiation therapy to registration
      - Recovered to CTCAE grade 1 or less toxicity attributed to radiation with exception of alopecia and fatigue.
   • For patients enrolling on Cohort A or Cohort B: - For patients treated with surgery, an interval of ≥ 21 days must have elapsed prior to registration.
      - No prior treatment with BRAF or MEK inhibitors.
      - Steroid dosing stable for at least 4 days prior to registration.
4. Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.
   Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.
5. Age ≥ 18 years
6. ECOG performance status < 2
7. Comorbid conditions
   • No evidence of active bleeding, bleeding diathesis, or hemoptysis (≥ ½ teaspoon of red blood) ≤ 8 weeks prior to registration
   • No evidence of intracranial hemorrhage ≤ 4 weeks prior to registration
   • Patients who have experienced thromboembolic event within 6 months prior to registration must be on stable therapeutic anticoagulation for at least 4 weeks prior to registration.
   • No symptomatic congestive heart failure (New York Heart Association Class II, III, or IV) within 6 months prior to registration.
   • No current unstable angina or uncontrolled arrhythmia.

• No uncontrolled hypertension at time of registration (BP > 150/95 despite antihypertensive therapy).
• No known history of prolonged QT syndrome.
• No known history of ventricular arrhythmia within 6 months of registration.
• No known history of uveitis or iritis ≤ 4 weeks prior to registration.
• No evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO, central serous chorioretinopathy, or neovascular macular degeneration within 12 months of registration.

8. Concomitant medications
• Chronic concomitant treatment with strong CYP3A4 inducers or CYP3A4 inhibitors is not allowed. Patients must discontinue the drug at least 14 days prior to study registration. See Sections 8.1.9 and 8.1.10 for more information.
• Chronic concomitant treatment with CYP1A2 substrate is not allowed. Patients must discontinue the drug at least 14 days prior to study registration. See Section 8.1.11 for more information.

9. Required initial laboratory values:
• Absolute Neutrophil count ≥ 1500/mm3
• Platelets ≥ 100,000/mm3
• Creatinine ≤ 1.5 mg/dL OR Creatinine Clearance ≥ 45mL/min
• Bilirubin ≤ 1.5 ULN
• AST/ALT ≤ 2.5 ULN

- No comorbid conditions as outlined in Section 5.3.6.
- No CYP3A4 inducers and inhibitors and CYP1A2 substrates within 14 days of registration

Schema
1 Cycle = 28 Days