Alliance A071601: Phase II Trial of BRAF/MEK Inhibitors in Papillary Craniopharyngiomas

Priscilla K. Brastianos, MD, Evanthia Galanis, MD and Frederick G Barker, II, MD

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Rationale

Based on our biomarker work, we have designed a phase 2 study of BRAF and MEK inhibition in papillary craniopharyngiomas. We propose two cohorts, one with newly diagnosed craniopharyngiomas and the second with recurrent craniopharyngiomas. For the newly diagnosed cohort, patients will go on to receive definitive therapy with radiation or surgery after treatment with 4 months. For the recurrent cohort, given that patients have progressed after prior therapies and their treatment options are more limited, patients will be allowed to continue BRAF and MEK inhibition if they are responding to BRAF and MEK inhibitors. This study represents a novel therapeutic approach in craniopharyngioma, a disease with a critical need for effective therapy.

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Objective

Co-Primary

- To determine the activity of BRAF and MEK inhibitor combination in untreated papillary craniopharyngiomas as measured by best response at any time during the first four cycles of BRAF and MEK inhibitor treatment.
- To determine the activity of BRAF and MEK inhibitor combination in papillary craniopharyngiomas that have progressed after prior radiation treatment with or without surgical resection as measured by best response at any time during the first four cycles of BRAF and MEK inhibitor treatment.

Secondary

- To determine the progression-free survival of patients with papillary craniopharyngiomas receiving BRAF and MEK inhibitors.
- To determine the toxicity of BRAF/MEK inhibitors in patients with papillary craniopharyngiomas.
- To determine the activity of BRAF and MEK inhibitor combination in papillary craiopharyngiomas as measured by response of enhancing volume of craniopharyngioma.
- To determine the activity of BRAF and MEK inhibitor combination in papillary craiopharyngiomas as measured by response of nonenhancing volume of craniopharyngioma.
- To determine the overall survival of patients with papillary craniopharyngiomas receiving BRAFand MEK inhibitors.
- To determine the duration of response in patients with papillary craniopharyngiomas receiving BRAF and MEK inhibitors.

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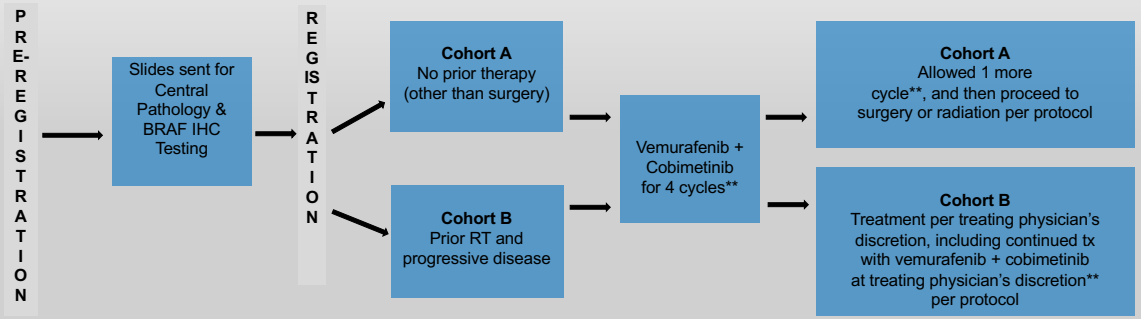
Study Schema



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* Submit slides for Central Pathology BRAF IHC within 28 days after pre-registration. Once slides are received at BWH/DFCI, results will be returned within 14 days. Register patient within 21 days of result notification. See protocol for complete instructions.

** Discontinue vemurafenib + cobimetinib at progression, unacceptable adverse event, or drug hold >28 days. Subsequent treatment is at the discretion of the treating physician.

Patients will be followed for 5 years from study registration (Step 1) or until death, whichever comes first.

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Treatment Plan

Protocol treatment is to begin ≤ 10 days of registration. EKG, Echo (or MUGA), O2 Saturation, and skin exam must be perfo rmed prior to initiation of treatment for safety as required in the protocol.

Each cycle will consist of 28 days. Patients will be treated with vemurafenib 960mg po twice daily for 28 days, and cobimetinib 60mg po once daily for 21 days, followed by 7 days off.

Vemurafenib + Cobimetinib

Agent	Dose	Route	Administration Days	Frequency
Vemurafenib	960 mg	P.O.	Days 1-28	Twice daily for 28 days
Cobimetinib	60 mg	P.O.	Days 1-21	Once daily for 21 days, followed by 7 days off

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Key Eligibility Criteria

Key Pre-Registration Eligibility Criteria

- Local diagnosis of papillary craniopharyngioma
- Tissue slides available for central path review

Key Registration Eligibility Criteria

- Histologically proven papillary craniopharyngioma as documented by central path review - Measureable disease, defined as ≥ 1cm3 present on imaging
- Surgery completed ≥ 21 days from registration.
  - Cohort A: No prior therapy other than surgery. Progressive disease allowed but not required.
  - Cohort B: Prior radiation therapy and progressive disease required. Completion of RT ≥ 14 days from registration.-No prior treatment with BRAF or MEK inhibitors
  - Steroid dosing stable for ≥ 4 days-Non pregnant and non nursing-Age ≥ 18 years - ECOG Performance Status < 2
  - No comorbid conditions as outlined in the protocol.
- No CYP3A4 inducers and inhibitors and CYP1A2 substrates within 14 days of registration

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Contact Us

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