ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A071601

PHASE II TRIAL OF BRAF/MEK INHIBITORS IN PAPILLARY CRANIOPHARYNGIOMAS

Industry-supplied agent(s): Vemurafenib, Cobimetinib (IND EXEMPT)

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[X] Other : Updated CTSU Language	

If your site utilizes the CIRB as your IRB of record
No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

If your site utilizes a local IRB as your IRB of record
Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your local IRB guidelines. The proposed changes in this amendment are minor and do not affect the overall risk/benefit ratio.

UPDATES TO PROTOCOL:

Cover Page (Page 1)

- [redacted]
- [redacted]

Study Resources (Page 2)

CTSU Address and Contact Information (Page 3)
The CTSU Contact Information table has been updated to reflect current CTSU boilerplate language.

Section 4.0 (Patient Registration)
All text in this section has been updated to reflect current CTSU boilerplate language.

Section 6.1 (Data Collection and Submission)
All text in this section has been updated to reflect current CTSU boilerplate language.

Section 6.1.3 (IRB Terminations)
A new section has been added to note institutions must not close a trial with the IRB of record until a formal notice from the Alliance regarding termination to patient follow-up has been received.

Section 6.3.3 (Using TRIAD Image Submission)
All text in this section has been updated to reflect current CTSU boilerplate language.

Section 10.1 (Vemurafenib)
In the 1st sentence of the 1st paragraph in the *Procurement* section, the phrase "RxCrossroads by McKesson" has replaced "Biologics" to accurately reflect the drug distributor.

Section 10.2 (Cobimetinib)
In the 1st sentence of the 1st paragraph in the *Procurement* section, the phrase "RxCrossroads by McKesson" has replaced "Biologics" to accurately reflect the drug distributor.

UPDATES TO CONSENT FORM:

No changes have been made to the informed consent document.

Replacement protocol and model consent documents have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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ALLIANCE A071601

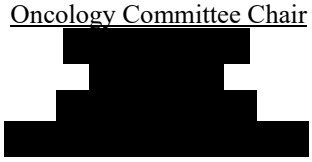
PHASE II TRIAL OF BRAF/MEK INHIBITORS IN PAPILLARY CRANIOPHARYNGIOMAS

Industry-supplied agent(s): Vemurafenib, Cobimetinib (IND EXEMPT)

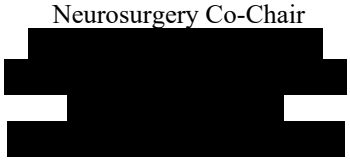
ClinicalTrials.gov Identifier: NCT03224767

Study Chair

Study Co-chair & Neuro-Oncology Committee Chair



Study Co-chair & Neurosurgery Co-Chair



Community Oncology Co-chair

Correlative Co-Chair

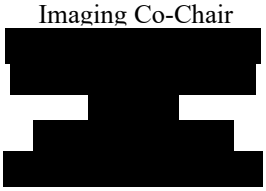
Neuropathology & Correlative Co-chair

Correlative Co-Chair

Correlative Committee Chair

Neuropathology Committee Chair

Imaging Co-Chair

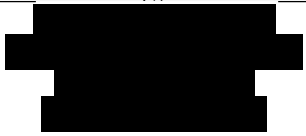


Imaging Co-Chair & Neuro Oncology Imaging Committee Chair

Radiation Oncology Co-Chair

Radiation Oncology Co-Chair

Radiation Oncology Committee Chair



NRG Study Champion

ECOG-ACRIN Study Champion

SWOG Study Champion

Primary Statistician

Secondary Statistician

Protocol Coordinator

Data Manager

Participating NCTN Groups Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN / ECOG-ACRIN Cancer Research Group, NRG / NRG Oncology, SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting

Medidata Rave® iMedidata portal

OPEN (Oncology Patient Enrollment Network)

Biospecimen Management System

Protocol Contacts:

A071601 Nursing Contact

IROC

A071601 Pharmacy Contact

Drug Distribution Contact

Alliance Biorepository at Mayo Clinic

Paraffin-embedded tissue:

Non-paraffin biospecimens:

Central Pathology Review & BRAF IHC Testing

Registration Contact

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review:	Alliance Regulatory Inbox
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox
Questions regarding specimens/specimen submissions:	See Correlative Science Manual, posted on Alliance, CTSU and BioMS websites
Questions regarding drug supply	RxCrossroads by McKesson
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted], and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires logging in with a CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the [redacted] application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

PHASE II TRIAL OF BRAF/MEK INHIBITORS IN PAPILLARY CRANIOPHARYNGIOMAS

Key Pre-Registration Eligibility Criteria (see Section 3.2)

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

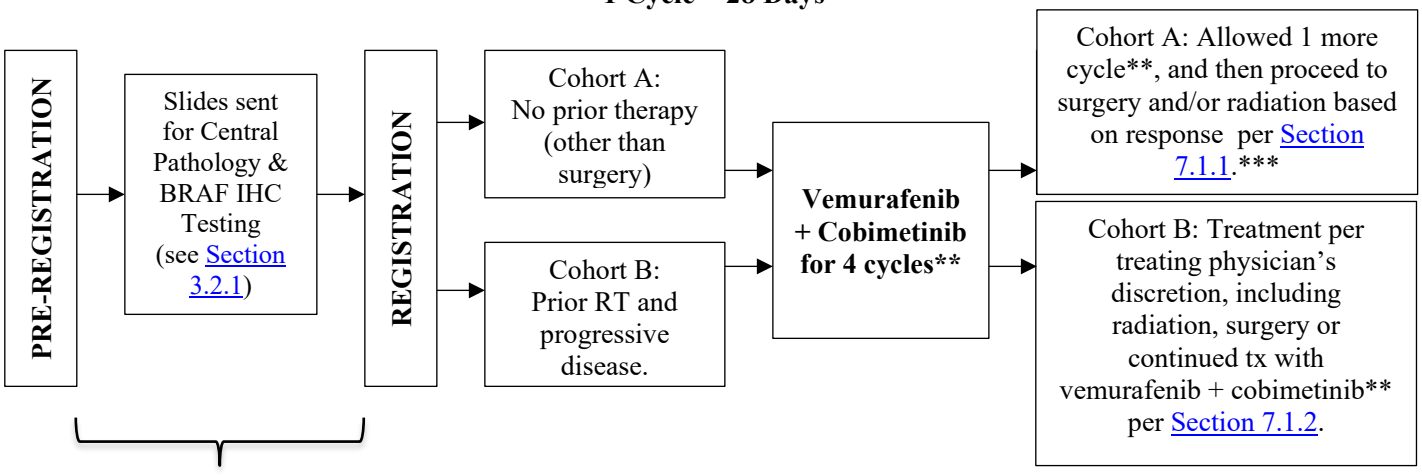
Key Registration Eligibility Criteria (see Section 3.3)

- Histologically proven papillary craniopharyngioma as documented by central path review
- Measureable disease, defined as ≥ 1cm^3 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 Section 3.3.6.
- No CYP3A4 inducers and inhibitors and CYP1A2 substrates within 14 days of registration

Required Initial Laboratory Values (see Section 3.3.8)

ANC	≥ 1500/mm^3
Platelets	≥ 100,000/mm^3
Creatinine	≤ 1.5 mg/dL
OR	
Calc. Creatinine Clearance (see Alliance website)	≥ 45 mL/min
Total Bilirubin	≤ 1.5 x ULN
AST / ALT	≤ 2.5 x ULN

Schema
1 Cycle = 28 Days



* 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 Sections 4.3, 4.4, and 6.2.1 for complete instructions.

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

*** Patients on Cohort A may continue treatment with vemurafenib and cobmetinib beyond 5 cycles in special circumstances with study chair approval. See Section 7.1.1 for more information.

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

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

Study components allowed to be completed at non-registering institutions: Surgery for patients enrolled on Cohort A. Surgery and Radiation for patients enrolled Cohort B. Supporting documentation must be submitted per Section 6.1.1 even if performed at non-registering institution.

Table of Contents

1.0 BACKGROUND

1.1 The natural history of craniopharyngioma

Craniopharyngiomas, which occur at an average age-adjusted incidence rate of 0.18 per 100,000,[1] are epithelial tumors that arise in the pituitary stalk along the path of the craniopharyngeal duct.[2] There are two main subtypes of craniopharyngiomas, the adamantinomatous form that is more common in children and the papillary form that predominantly occurs in adults. Located in or above the sella turcica, these tumors grow adjacent to the optic chiasm and often extend to involve the hypothalamus, cranial nerves, the ventricular system, visual pathways and major blood vessels at the base of the brain. Craniopharyngiomas can cause profound clinical sequelae both in the pediatric and adult populations, both through mass effect at presentation and through morbidity of treatment.[3-5] At initial presentation, a broad range of signs and symptoms can be observed. Visual deficits, neuroendocrine deficiencies and severe headaches are common. Attempted surgical resection is usually the initial treatment of craniopharyngioma, but because these tumors adhere to critical brain and vascular structures, incomplete resection is common. Incompletely excised tumors have a propensity to recur, frequently with cysts, with firm adhesions between the recurrent tumor and the surrounding structures such that curative surgery is exceedingly difficult.[6] Either the cystic, solid or both components, of craniopharyngiomas can cause significant symptomatic mass effect. As a result, most patients suffer lifelong sequelae that include panhypopituitarism, visual defects, impaired intellectual function and wide-ranging hypothalamic dysfunction leading to sleep disorders,[7] abnormal thermo-regulation, and diabetes insipidus as well as hyperphagia and uncontrollable obesity.[3-5] Radiation therapy, often used as an adjunct after surgery, can contribute to these complications. The debilitating long-term morbidities can have significant psychosocial impact on patients. No effective treatment besides surgery and radiation is known for craniopharyngiomas, and incomplete knowledge of the molecular mechanisms that drive craniopharyngiomas has hampered the development of targeted therapies for this tumor.

1.2 Genetic characterization of craniopharyngiomas

Genetic analysis of 107 craniopharyngiomas revealed activating beta-catenin mutations in 62/65 (95%) of adamantinomatous craniopharyngiomas and BRAF V600E mutation in 39/42 (93%) of papillary craniopharyngiomas[8] and this finding has been validated in subsequent studies (PMID 26927026, 26156055, 25820214, 25442575). The mutations were mutually exclusive and clonal in the two tumor subtypes. To date, our work and that of others has not detected other recurrent mutations or genomic aberrations in either subtype.

1.3 Promising activity in case reports of patients with craniopharyngioma

We recently treated a patient who presented with multiply recurrent BRAF V600E craniopharyngioma using dabrafenib (150mg, orally twice daily) and trametinib (2mg, orally twice daily)[9]. After 35 days of treatment, tumor volume was reduced by 85%. Mutations that commonly mediate resistance to MAPK pathway inhibition were not detected in a post-treatment sample by whole exome sequencing. A blood-based BRAF V600E assay detected circulating BRAF V600E in the patient's blood. In another recently reported case, a patient with a multiply recurrent papillary craniopharyngioma treated with the BRAF inhibitor vemurafenib also had a dramatic tumor response[10]. Given these promising and unique tumor responses, and the consistent occurrence of the BRAF V600E mutation in nearly all papillary craniopharyngiomas, we propose a Phase II study evaluating the combination of BRAF and MEK inhibition in patients with papillary craniopharyngiomas.

1.4 Clinical experience with vemurafenib in other tumors

Vemurafenib (also known as RO5185426, PLX4032, or RG7204) is a low molecular weight, orally available inhibitor of the activated form of the BRAF serine-threonine kinase enzyme, which is commonly found in melanoma. Vemurafenib selectively inhibits oncogenic BRAF kinase. The rationale for identifying such a compound was first provided in 2002, when the high prevalence of activating mutations in the BRAF gene was identified in a variety of cancers, including melanoma. The high level of selectivity of vemurafenib has been demonstrated in biochemical, cell-based, and in vivo assays (see the Vemurafenib Investigator's Brochure for details).

Summary of clinical efficacy of vemurafenib in melanoma

Phase III, randomized, controlled study (NO25026 [BRIM-3])

In Study NO25026 (BRIM-3), a global, randomized Phase III study, 675 patients with previously untreated, metastatic melanoma harboring the $BRAF^{V600E}$ mutation were randomly assigned to receive either vemurafenib or dacarbazine between January 2010 and December 2010[12]. In the interim analysis for OS and the final analysis for PFS, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine ($P < 0.001$ for both comparisons). In the vemurafenib group, most patients had a detectable decrease in tumor size and 106 of 219 patients (48%; 95% CI: 42%–55%) had a confirmed objective response, including 2 patients with a CR and 104 with a PR. Median time to response was 1.45 months. Ten patients in the vemurafenib group were later found to have $BRAF^{V600K}$ mutations; of these, 4 had a PR (40%). In the dacarbazine group, a minority of patients had a detectable decrease in tumor size, and 12 of 220 patients (5%; 95% CI: 3%–9%) met the criteria for a confirmed response (all PRs). The median time to response was 2.7 months. The difference in confirmed RR between the two study groups (48% vs. 5%) was statistically significant ($P < 0.001$).

In a recent post hoc analysis (data cut 1 February 2012), updated survival data censored at crossover showed a median OS of 13.6 months for the vemurafenib treatment arm and 9.7 months for the dacarbazine treatment arm (HR 0.70 [95% CI: 0.57–0.87] $P < 0.001$). The median PFS was 6.9 months with vemurafenib treatment compared to 1.6 months with dacarbazine treatment (HR 0.38 [95% CI: 0.32–0.46] $P < 0.0010$ (McArthur et al. 2014). This study also assessed efficacy by $BRAF^{V600}$ mutation type (V600E and V600K). Median OS with vemurafenib in the $BRAF^{V600E}$ group ($n = 295$) was 13.3 months compared with 10.0 months in the dacarbazine group ($n = 303$; HR 0.75 [95% CI: 0.60-0.93]). Median PFS was 6.9 months and 1.6 months respectively (HR 0.39 [95% CI: 0.33-0.47]). For the $BRAF^{V600K}$ mutation group median OS was 14.5 months with vemurafenib ($n = 33$) and 7.6 months with dacarbazine ($n = 24$; HR 0.43 [95% CI: 0.21-0.90]). Median PFS was 5.9 months and 1.7 months, respectively (HR 0.30 [95% CI: 0.16-0.56)

1.5 Combined BRAF and MEK inhibition

Based on nonclinical studies to date, multiple mechanisms of acquired resistance to vemurafenib in $BRAF^{V600}$-mutated melanoma have been identified which may account for the majority of disease progression:

- Acquisition of activating RAS (NRAS or KRAS) mutations was reported, which accounts for the reactivation of ERK signaling and increased AKT survival signaling[14,15]
- Spliced isoforms of $BRAF^{V600E}$ were identified which led to enhanced dimerization of $BRAF^{V600E}$ and reactivated the MAPK pathway[16].
- Increased PDGFRb or IGF1R activity was reported, which may enhance signaling through different RAF isoforms and/or the PI3K/AKT pathway to confer resistance [14,17]

- Loss of NF1 leads to RAS activation (PMID 24576830, 23288408)

Based on clinical validation data to date, the most prevalent mechanisms of acquired resistance to vemurafenib appear to be the first two mechanisms described above: the acquisition of activating NRAS mutations and spliced isoforms of $BRAF^{V600E}$, which result in reactivation of ERK signaling in the presence of vemurafenib[18]. The retention of the $BRAF^{V600E}$ mutation in both nonclinical models of vemurafenib resistance and biopsies from patients who progressed on vemurafenib suggests that continued suppression of the pathway by vemurafenib may be required to control tumor cell proliferation; however, reactivation of ERK signaling points to the potential for combination with another agent such as a MEK inhibitor that further inhibits the ERK signaling pathway and, consequently, overcomes the emergence of the pathway-specific resistance in tumors harboring the $BRAF^{V600E}$. Synergistic anti-proliferative activity was observed when vemurafenib was combined with GDC-0973 in multiple $BRAF^{V600E}$ mutant cancer cell lines. The in vivo combination of vemurafenib with GDC-0973 was also tested in the murine xenograft A375 $BRAF^{V600E}$ mutant melanoma model and in a model of A375 that had acquired resistance to vemurafenib[19]. In both models, the combination of vemurafenib and GDC-0973 is efficacious and well-tolerated and shows greater efficacy than either single agent alone at comparable doses.

Phase Ib open-label cobimetinib and vemurafenib study (NO25395; BRIM-7)

Study NO25395 (BRIM-7) was a Phase Ib study designed to assess the safety, tolerability, and pharmacokinetics of combined MEK inhibition with cobimetinib and BRAF inhibition with vemurafenib. This multicenter study had two stages: a dose-escalation stage and a cohort-expansion stage. This study was being conducted in patients with $BRAF^{V600}$ mutation-positive, unresectable locally advanced or metastatic melanoma who were either vemurafenib naïve or had progressed on vemurafenib treatment.

All patients in the dose-escalation stage received vemurafenib (720 mg or 960 mg) twice daily in combination with cobimetinib (60 mg, 80 mg, or 100 mg) administered daily according to one of the following 28-day schedules:

- 14 consecutive days of study drug followed by a 14-day drug holiday (14/14)
- 21 consecutive days of study drug followed by a 7-day drug holiday (21/7)
- Continuous daily dose (28/0).

Each treatment cycle was 28 days. There were 10 dose-escalation cohorts of 3−6 patients per cohort. Patients in Cohort 1 received vemurafenib at a dose of 720 mg BID continuously and cobimetinib 60 mg once daily (QD) for 14 consecutive days of each 28-day cycle of combination dosing (14/14). Dose-escalation used the standard 3 + 3 design and proceeded in increments, taking into account the safety and tolerability of the combination.

Cohorts 1A and 1B were expansion cohorts because both cohorts were declared safe and tolerable after dose escalation; furthermore, they delivered the single-agent maximum tolerated dose and schedule of cobimetinib and, in the case of cohort 1B, the approved dose and schedule of vemurafenib[20].

Randomized phase III study of vemurafenib and cobimetinib (GO28141; CoBRIM)

This randomized, open-label, multicenter, Phase III study assessed previously untreated patients with metastatic melanoma confirmed by histopathology (unresectable stage IIIC or stage IV) and with a $BRAF^{V600}$ mutation[21]. In this study, 495 patients were randomly assigned to receive vemurafenib (960 mg BID PO) and cobimetinib (60 mg QD PO) for the first 21 days of each 28 day cycle (combination group) or vemurafenib and placebo (control group). The primary end point was investigator-assessed PFS according to RECIST version 1.1.

Clinical efficacy of cobimetinib and vemurafenib in melanoma

Study GO28141 (CoBRIM)

Vemurafenib plus cobimetinib was significantly superior to vemurafenib alone: median PFS was 12.3 months in the combination group and 7.2 months in the vemurafenib group (HR 0.58 [95% CI: 0.46-0.72]). The PFS benefit was observed across key subgroups including LDH levels and BRAF mutation type. BORR was 69.9% (95% CI: 63.5-75.3) with 15.8% CRs in the combination arm and 50% (95% CI: 43.6-56.4) with 10.5% CRs in the single-agent arm. OS data are still not mature but interim analysis (data cut-off date of May 2014; [21]) showed 9-month OS rate of 81% (95% CI: 75-87) for the combination group and 73% (95% CI: 65-80) for the monotherapy group and a HR of 0.65 (95% CI: 0.42-1.00).

1.6 Safety

1.6.1 Vemurafenib safety summary

AE data from the clinical trials with vemurafenib include events of arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia, and pruritus. Vemurafenib also has been associated with reports of well-differentiated cuSCC most of which are the keratoacanthoma (KA) sub-type, or with some features of KA (incompletely expressed or with some features unusual in KA). AEs with vemurafenib have been predominantly mild in severity and transient, even with continuous dosing (over 15 months of treatment in 1 patient). At the recommended Phase II and Phase III dose of 960 mg BID, AEs have been consistent with the safety profile observed in the Phase I setting. Treatment-related Grade 3 AEs and dose-limiting toxicities (DLTs) have been successfully managed by a temporary discontinuation of vemurafenib and/or a reduction in dose. Further details can be found in the current Vemurafenib Investigator's Brochure.

Cutaneous squamous cell carcinoma (cuSCC)

In Studies NO25026, NP22657, and NP25163, 79 (23.5%), 34 (25.8%), and 10 (19.2%) patients developed cuSCC/KA. Most cuSCC cases were keratoacanthomas: 58/79 (73.4%) and 30/34 (88.2%) in Studies NO25026 and NP22657, respectively. In the NP25163 study 4/11 (36%) patients had keratoacanthomas.

Other neoplasms

Non-cutaneous squamous cell carcinoma

Squamous cell carcinoma (SCC) of the head and neck has been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled in clinical trials (NO25026/BRIM-3 and NP25163 a pharmacokinetic/pharmacodynamic study of vemurafenib). A pathology examination of both tumors (both arising in the tonsillar area) revealed the presence of invasive SCC. Of note, one patient's medical history was significant for risk factors for head and neck cancer, and the tumor tissue tested positive for human papillomavirus (HPV). The patient in the second case did not have any risk factors for head and neck cancer, and the tumor tissue preliminarily did not reveal the presence of HPV. Detailed accounts of these events are provided in the current vemurafenib Investigator's Brochure.

Adenomatous colonic polyps

Two cases of adenomatous colonic polyps have been reported in patients who were receiving vemurafenib for over 2 years. The first patient developed an upper gastrointestinal bleed, and on a work up, was found to have duodenal ulceration (non-malignant), hyperplastic gastric polyps, and 5 colonic polyps (3 adenomatous). A previous colonoscopy, performed in 2008 at time of a jejunal resection for recurrent melanoma, documented no prior evidence of colonic polyps. All polyps have been resected, and the patient has subsequently resumed vemurafenib therapy. The second patient was found to have 7 colonic

polyps (5 adenomatous) during elective colonoscopy, and all were detected and removed. The severity and nature of this risk are currently unknown and under investigation. The clinical significance of colonic polyps is uncertain but physicians should be aware that they may occur in patients treated with vemurafenib.

Liver injury

An analysis of liver-related adverse events reported with vemurafenib use showed that 63 cases (out of an estimated 19,926 patients exposed) of medically confirmed serious adverse events were consistent with drug induced liver injury based on clinical chemistry criteria from the DILI Expert Working Group [126]. Of the 63 cases, two were assessed as severe, both reported as hepatic failure. There were no reported deaths among the 63 cases of liver injury; the outcome of both cases of severe liver injury is considered resolved. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to ALP ratio was calculated as 1.5, suggesting a trend towards cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

QT prolongation

The effects of single and multiple doses of vemurafenib (960 mg bid) on ECG measurement, including the QT interval, were evaluated in 132 adult patients with metastatic melanoma in the Phase 2 study, NP22657.

Vemurafenib treatment at 960 mg bid did not appear to have a clinically meaningful effect on heart rate (HR). The study population-specific correction (QTcP) eliminated most of the bias from the QT-RR relationship and was therefore used for the primary statistical analyses of variables related to the QTc interval.

A total of 41 patients (31.1%) exhibited new ECG changes considered to be abnormal and potentially significant. No patients developed new abnormal U waves, and 19 patients (14.4%) had new abnormal T-waves. Vemurafenib did not cause a meaningful change from the time-matched baseline ECG in either the QRS or the PR (PQ) interval.

Two patients (1.5%) developed treatment-emergent QTcP values >500 msec (CTC Grade 3), while 49 (37.1%) and 6 (4.5%) of patients exhibited treatment-emergent, QTcP values > 450 msec and > 480 msec, respectively. No patients had treatment-emergent uncorrected QT values > 500 msec. Maximal, treatment-emergent, individual QTcP changes >30 msec from baseline were observed in 58 (43.9%) patients, but only one patient (0.8%) exhibited a QTcP change >60 msec from baseline.

The pattern of increasing vemurafenib concentration from Days 1 to 15 of vemurafenib treatment appeared to correlate with the increased mean QTcP change observed from Days 1 to 15 and the constant vemurafenib exposures observed in later cycles appeared to correlate with the maintenance of the effect on QTc interval.

Phase I, dose-finding study (PLX 06-02)

Among patients enrolled in the Phase I study PLX 06-02, the most common vemurafenib-related Grade 2 or 3 toxicities observed were arthralgia, rash, nausea, photosensitivity, fatigue, cutaneous SCC, pruritus, and palmar-plantar dysesthesia. In total, 89% of the toxicities were Grade 1 or 2. Rashes were evenly distributed among face/neck, trunk, and extremities. Four patients had a Grade 4 AE: 2 had elevated gamma-glutamyltransferase (GGT) levels; one had fatigue; and one had reversible pancytopenia of uncertain attribution. Thirteen patients out of 32 total (41%) in the extension cohort required a dose reduction (10 patients to 720 mg BID, one patient to 600 mg BID, and two patients to 480 mg BID).[11]

Phase III, randomized, controlled study (NO25026 [BRIM-3])

An overview of AEs and deaths in Study NO25026 is presented in Table 1. Ninety-nine percent and 91% of patients in the vemurafenib and DTIC treatment groups experienced at least one AE. The majority of AEs were of mild or moderate intensity. The most common AEs (reported in ≥ 30% of patients) in the vemurafenib group were in the system organ class of skin and subcutaneous tissue disorders, the most common of which were alopecia, rash, and photosensitivity.

Table 1 NO25026 (BRIM-3): Overview of Adverse Events

	Vemurafenib (N=336)	DTIC [a] (N=282)	DTIC/ Vemurafenib [b] (n=37)
Patients with at least one AE	331 (99)	261 (91)	32 (86)
Treatment-related AEs	325 (97)	201 (70)	26 (70)
AEs of Grade ≥ 3	197 (59)	96 (33)	11 (30)
Treatment-related AEs of Grade ≥ 3	166 (49)	57 (20)	8 (22)
Deaths [c]	63 [d] (19)	99 [d] (34)	0 (0)
Deaths within 28 days of last vemurafenib dose	28 (8)	17 (6)	0 (0)
SAEs	142 (42)	51 (18)	4 (11)
Treatment-related SAEs	104 (31)	15 (5)	1 (3)
AEs that led to treatment discontinuation	24 (7)	12 (4)	1 (3)

AE = adverse event; SAE = serious adverse event.

Clinical cut-off: March 1, 2011.

[a] For DTIC patients who crossed over to vemurafenib, only AEs with an onset date before date of crossover are summarized.

[b] In the subset of DTIC patients who crossed over to receive vemurafenib, only events occurring after crossover to vemurafenib are summarized here.

[c] Deaths were based on the all-treated population: n=293 for DTIC; n=336 for vemurafenib; and n=37 for DTIC/vemurafenib.

[d] In the DTIC arm, 94 of 99 deaths were due to disease progression; in the vemurafenib arm, 53 of 63 deaths were due to disease progression.

1.6.2 Cobimetinib monotherapy safety summary

Study MEK4592g was a multicenter, Phase I, non-randomized, open-label, dose-escalation study. The primary objectives of this study were to evaluate the safety, tolerability, and maximum tolerated dose (MTD) of cobimetinib administered orally as repeated doses in patients with solid tumors. As of the data cutoff date of 11 June 2013, 115 patients were treated across all study stages in Study MEK4592g, including 74 patients treated with cobimetinib 60 mg 21/7

All patients in Study MEK4592g experienced an AE. The most frequent AEs were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea, vomiting (33.9% each), and peripheral edema (28.7%). Other events that occurred in ≥10% of patients included anemia, abdominal pain, constipation, hypokalemia, decreased appetite, headache, dizziness, back pain, increased AST, dermatitis acneiform, pruritus, and dry skin.

Amongst the patients who received cobimetinib 60 mg 21/7, the most frequent treatment-emergent AEs in the cobimetinib 60 mg QD 21/7 group were diarrhea (64.4%),

rash (53.3%), fatigue (48.9%), nausea, edema peripheral (31.1% each), and vomiting (28.9%).

Amongst all cobimetinib-treated patients, 5 patients (4.3%) experienced a Grade 4 AE, and 53 patients (46.1%) experienced a Grade 3 AE. The most frequent Grade 3 and Grade 4 AEs were hyponatremia (9.6%), fatigue (8.7%), anemia (7.8%), diarrhea, and hypokalemia (6.1% each). Grade 5 AEs, which in Study MEK4592g included disease progression reported as an adverse event, are discussed separately below.

As of the clinical-data cutoff date (20 September 2013), a total of 29 patients (25.2%) had died, including 11 patients in the cobimetinib 60 mg QD 21/7 group.

A total of 14 deaths were reported for patients treated in Stage I of the study. With the exception of 1 patient who died of cardiopulmonary arrest secondary to PD, all Stage I deaths occurred because of PD and no death was considered by the investigator to be related to the study drug.

During Stages IA, II, and IIA of the study, 12 deaths were reported, all of which occurred ≤30 days after the last dose of study drug. Of these, 2 deaths were considered by the investigator to be possibly related to study drug. In both cases, the investigator considered the metastatic cancer to be a contributing etiologic factor to the patient's death.

Three deaths were reported in Stage III of this study. None was assessed by the investigator as treatment related. Other contributing etiologic factors to the deaths included the patients' underlying diseases and malignant tumor progression

1.6.3 Combined vemurafenib and cobimetinib safety summary

Study NO25395 (BRIM-7)

In Study NO25395, similar types of AEs occurred among the BRAF inhibitor-naïve (BRAFi-naïve) patients and vemurafenib-PD patients, however, AEs were less frequently reported in vemurafenib-PD than in BRAFi-naïve patients. This difference was also apparent for Grade ≥ 3 AEs and SAEs with lower rates of incidence in vemurafenib-treated patients with PD, and may reflect that vemurafenib-treated patients with PD had previously demonstrated ability to tolerate vemurafenib, as well as had shorter duration of exposure to study drugs.

The most common AEs (≥ 10%) are summarized by group in Table 2.

Table 2 Treatment-Emergent Adverse Events That Occurred in 10% or More of Patients in Study NO25395NO25395 (BRIM-7)

MedDRA System Organ Class MedDRA Preferred Term	BRAFinhibitor-naive n=63	Vemurafenib-PD n=66	All patients n=129
Any Adverse Events	63 (100.0%)	61 (92.4%)	124 (96.1%)
Gastrointestinal Disorders	56 (88.9%)	44 (66.7%)	100 (77.5%)
Diarrhea	52 (82.5%)	31 (47.0%)	83 (64.3%)
Nausea	36 (57.1%)	22 (33.3%)	58 (45.0%)
Vomiting	27 (42.9%)	13 (19.7%)	40 (31.0%)
Abdominal Pain	12 (19.0%)	10 (15.2%)	22 (17.1%)
Constipation	10 (15.9%)	9 (13.6%)	19 (14.7%)
Skin and Subcutaneous Tissue Disorders	62 (98.4%)	33 (50.0%)	95 (73.6%)

MedDRA System Organ Class MedDRA Preferred Term	BRAFinhibitor-naive n=63	Vemurafenib-PD n=66	All patients n=129
Photosensitivity Reaction	42 (66.7%)	10 (15.2%)	52 (40.3%)
Rash	32 (50.8%)	18 (27.3%)	50 (38.8%)
Pruritus	18 (28.6%)	7 (10.6%)	25 (19.4%)
Dermatitis Acneiform	19 (30.2%)	5 (7.6%)	24 (18.6%)
Rash Maculopapular	19 (30.2%)	2 (3.0%)	21 (16.3%)
Dry Skin	15 (23.8%)	2 (3.0%)	17 (13.2%)
Alopecia	9 (14.3%)	7 (10.6%)	16 (12.4%)
Erythema	14 (22.2%)	2 (3.0%)	16 (12.4%)
Actinic Keratosis	11 (17.5%)	2 (3.0%)	13 (10.1%)
General Disorders and Administration Site Conditions	53 (84.1%)	32 (48.5%)	85 (65.9%)
Fatigue	44 (69.8%)	18 (27.3%)	62 (48.1%)
Pyrexia	27 (42.9%)	11 (16.7%)	38 (29.5%)
Edema Peripheral	26 (41.3%)	11 (16.7%)	37 (28.7%)
Chills	17 (27.0%)	10 (15.2%)	27 (20.9%)
Investigations	48 (76.2%)	22 (33.3%)	70 (54.3%)
Blood Creatine Phosphokinase Increased	27 (42.9%)	10 (15.2%)	37 (28.7%)
Blood Alkaline Phosphatase Increased	21 (33.3%)	10 (15.2%)	31 (24.0%)
Aspartate Aminotransferase Increased	22 (34.9%)	6 (9.1%)	28 (21.7%)
Alanine Aminotransferase Increased	23 (36.5%)	4 (6.1%)	27 (20.9%)
Blood Creatinine Increased	20 (31.7%)	6 (9.1%)	26 (20.2%)
Blood Bilirubin Increased	8 (12.7%)	6 (9.1%)	14 (10.9%)
Musculoskeletal and Connective Tissue Disorders	36 (57.1%)	23 (34.8%)	59 (45.7%)
Arthralgia	30 (47.6%)	8 (12.1%)	38 (29.5%)
Myalgia	15 (23.8%)	4 (6.1%)	19 (14.7%)
Back Pain	7 (11.1%)	10 (15.2%)	17 (13.2%)
Pain In Extremity	10 (15.9%)	4 (6.1%)	14 (10.9%)
Nervous System Disorders	22 (34.9%)	18 (27.3%)	40 (31.0%)
Headache	17 (27.0%)	13 (19.7%)	30 (23.3%)
Dizziness	8 (12.7%)	9 (13.6%)	17 (13.2%)
Metabolism and Nutrition Disorders	22 (34.9%)	17 (25.8%)	39 (30.2%)
Decreased Appetite	15 (23.8%)	14 (21.2%)	29 (22.5%)

MedDRA System Organ Class MedDRA Preferred Term	BRAFinhibitor-naive n=63	Vemurafenib-PD n=66	All patients n=129
Hypokalemia	10 (15.9%)	4 (6.1%)	14 (10.9%)
Injury, Poisoning and Procedural Complications	20 (31.7%)	15 (22.7%)	35 (27.1%)
Sunburn	20 (31.7%)	15 (22.7%)	35 (27.1%)
Blood and Lymphatic System Disorders	20 (31.7%)	10 (15.2%)	30 (23.3%)
Anemia	20 (31.7%)	10 (15.2%)	30 (23.3%)
Vascular Disorders	17 (27.0%)	6 (9.1%)	23 (17.8%)
Hypertension	17 (27.0%)	6 (9.1%)	23 (17.8%)
Infections and Infestations	14 (22.2%)	6 (9.1%)	20 (15.5%)
Upper Respiratory Tract Infection	14 (22.2%)	6 (9.1%)	20 (15.5%)
Respiratory, Thoracic and Mediastinal Disorders	12 (19.0%)	6 (9.1%)	18 (14.0%)
Cough	12 (19.0%)	6 (9.1%)	18 (14.0%)
Eye Disorders	11 (17.5%)	2 (3.0%)	13 (10.1%)
Vision Blurred	11 (17.5%)	2 (3.0%)	13 (10.1%)

Multiple occurrences of a specific adverse event for a patient were counted once at the highest NCI CTCAE grade of these occurrences. For example, if a patient experienced two events with a specific preferred term, one Grade 3 and one Grade 4, the patient would be counted only once in the Grade 4 row. Similarly, in the 'Any adverse events' and the 'Overall' rows, if a patient experienced, for example, three separate events of Grade 1, 3, and 4, the patient would be counted only once in the Grade 4 row.
Source: Table 21 in CSR NO25395.Data cutoff: 1 October 2013.

In Study NO25395, 62.0% of patients experienced at least one Grade ≥ 3 AE; 52.7% experienced a Grade 3 AE, 9.3% a Grade 4 AE, and there were no AEs of Grade 5.

Among the BRAFi-naive patients, the most common Grade ≥ 3 (occurring in ≥ 5% of patients) were anemia, diarrhea, fatigue, increased blood ALP, increased ALT, increased AST, hypophosphatemia, arthralgia, SCC, maculopapular rash, and hypertension. Among the vemurafenib-PD patients, the most common Grade ≥ 3 AEs (occurring in ≥ 5% of patients) were SCC and anemia.

Twelve BRAFi-naive patients (19%) and 45 vemurafenib-PD patients (68.2%) had died as of the clinical cutoff date. All 12 deaths in BRAFi-naive patients and 43 of the 45 deaths in the vemurafenib-PD population were attributed to disease progression, and the majority of deaths occurred > 30 days after last study drug administration. Two vemurafenib-PD patients (3%) died from unknown causes after being off the study for disease progression. No deaths in Study NO25395 were attributed to Grade 5 AEs.

Study GO28141 (CoBRIM)

Most patients in both treatment arms experienced at least one AE. The most common AEs, by system organ class, reported in the cobimetinib + vemurafenib arm were: skin and

subcutaneous tissue disorders (83.3%), GI disorders (78%), investigations (68.1%), and general disorders and administrative site conditions (66.9%).

Table 3 tabulates the most common AEs occurring in 20% or more of patients in either study arm by preferred term. The most common AEs that occurred with greater frequency in the cobimetinib plus vemurafenib arm were diarrhea (56.7% vs. 28%), rash (39% vs. 35.6%), nausea (39% vs. 23.8%), blood creatine phosphokinase increased (29.9% vs. 2.9%), photosensitivity reaction (28.3% vs. 15.9%), pyrexia (26% vs. 22.2%), alanine aminotransferase (ALT) increased (23.6% vs. 18%), aspartate aminotransferase (AST) increased (22% vs. 12.6%), and vomiting (21.3% vs. 12.1%).

Table 3 Most Common Adverse Events (Occurring in >20% of Patients) in Study GO28141

	Vemurafenib n=	Vemurafenib + cobimetinib n=
Diarrhea	67 (28%)	144 (56.7%)
Rash	85 (35.6%)	99 (39%)
Arthralgia	96 (40.2%)	83 (32.7%)
Fatigue	74 (31%)	82 (32.3%)
Nausea	57 (23.8%)	99 (39%)
Pyrexia	53 (22.2%)	66 (26%)
Photosensitivity	38 (15.9%)	72 (28.3%)
Alopecia	70 (29.3%)	35 (13.8%)
ALT increase	43 (18%)	60 (23.6%)
Hyperkeratosis	68 (28.5%)	26 (10.2%)
AST increase	30 (12.6%)	56 (22%)
CPK increase	7 (2.9%)	76 (29.9%)
Vomiting	29 (12.1%)	54 (21.3%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase.

At least one Grade > 3 AE was reported in 65% of patients treated with cobimetinib + vemurafenib and 59% of patients treated with placebo + vemurafenib. Table 3 tabulates the Grade >3 AEs occurring in at least 2% of patients in either arm. The most common Grade >3 AEs in patients treated with cobimetinib + vemurafenib than in patients treated with placebo + vemurafenib were ALT increased (11.4% vs. 6.3% of patients), blood creatine phosphokinase increased (10.2% vs. 0%), AST increased (8.3% vs. 2.1%), diarrhea (6.3% vs. 0%), blood alkaline phosphatase increased (4.3% vs. 1.7%), hyponatremia (2.4% vs. 0.4%), photosensitivity reaction (2.4% vs. 0%), and retinal detachment (2.4% vs. 0%). Serious adverse events (SAEs) occurred in 75 patients (29.5%) treated with cobimetinib + vemurafenib, of which, 46 SAEs were considered related to study treatment. SAEs occurred in 60 patients (25.1%) treated with placebo + vemurafenib, of which, 35 SAEs were considered related to study treatment.

The three most common SAEs in patients treated with cobimetinib+vemurafenib were pyrexia (2.4% of patients), dehydration (2.0%), and rash (1.6%). The three most common

SAEs in patients treated with placebo + vemurafenib were pyrexia, keratoacanthoma, and pleural effusion (1.3% each).

As of the clinical cutoff date, 36 of 254 patients (14.2%) who received cobimetinib + vemurafenib and 48 of 239 patients (20.1%) who received placebo + vemurafenib had died. In most cases, the primary cause of death was attributed to disease progression.

Six patients in the cobimetinib + vemurafenib arm and 3 patients in the placebo+vemurafenib arm were reported to have Grade 5 AEs. There were no patterns with respect to the type of Grade 5 events reported, and for most events the patient's underlying disease was considered to contribute to the cause of the event.

Of the 6 patients with Grade 5 AEs in the cobimetinib + vemurafenib arm, the AE was recorded as the primary cause of death for 2 patients ("cardiac arrest" and "pneumonia", respectively). An additional 2 patients with reported Grade 5 events ("unexplained death", and "asthenia and fatigue") had primary cause of death recorded as "other." The remaining 2 patients with reported Grade 5 events ("hemiparesis" and "cerebral hemorrhage") had disease progression recorded as the primary cause of death.

Of the 3 patients with AEs graded 5 in the placebo plus vemurafenib arm, 1 patient was reported to have died from "cardiac failure" while 2 patients with Grade 5 AEs of "fatigue" and "pulmonary embolism", respectively were reported to have died from PD.

1.7 Clinical pharmacokinetics

1.7.1 Phase I dose-finding and pharmacokinetics of vemurafenib

A total of 55 patients were enrolled in the dose-escalation phase of study PLX06-02, including patients with metastatic melanoma (n = 50), thyroid cancer (n = 3), rectal carcinoma (n = 1), and ovarian cancer (n = 1). Twenty-six patients received doses of vemurafenib ranging from 160 mg to 1120 mg BID using the optimized drug formulation (referred to as micro-precipitated bulk powder [MBP] formulation) with greater bioavailability. With this optimized formulation, minimum efficacious exposures above the exposure identified in the preclinical models (≥400 μM • h) were achieved at 240 mg BID. Vemurafenib MBP formulation has shown dose proportional increases in exposure across all cohorts, particularly from 240 to 960 mg BID. Mean steady state exposure levels of vemurafenib (area under the plasma concentration-time curve, $AUC_{0\text{-}24h}$) in these dose cohorts ranged from 467.1 μM • h to 1324.6 μM • h. The 960 mg BID dose of vemurafenib achieved mean steady state exposure levels of 69.6 μM and 1324.6 μM • h, for maximum plasma concentration (C_{max}) and $AUC_{0\text{-}24h}$, respectively.

An apparent mean half-life of approximately 90 hours (range, 30 to 145 hours) following multiple doses in patients receiving 960 mg BID in the melanoma extension cohort was determined based on the mean accumulation ratio of vemurafenib exposure between Day 1 and Day 15. With the twice-daily dosing regimen, all patients were exposed to relatively constant daily levels of the drug at steady state.

Dose-limiting toxic effects were not observed until a dose of 720 mg BID. At the next highest dose given to one group of patients (1120 mg BID), 4 of 6 patients developed non-life threatening DLT: 3 patients with Grade 3 rash (2 of whom also had Grade 3 fatigue) and one patient with Grade 3 arthralgia. All events resolved with temporary drug interruption. In all cases, patients resumed treatment at lower doses of 720 mg BID. One DLT, Grade 4 pancytopenia, was observed at 720 mg BID. Upon resolution of the pancytopenia after 9 days of vemurafenib interruption, the patient was re-challenged with vemurafenib at a lower

dose of 360 mg BID without recurrence of the pancytopenia. No new occurrence of pancytopenia was observed in the 1120 mg BID dose cohort or since in the extension cohort.

The dose of 960 mg BID orally was determined to be tolerated in the first 6 patients given the dose. This dose level of 960 mg BID was established as the recommended Phase II dose for the extension cohort (these 6 patients were included as the first 6 patients in the extension cohort) and for future Phase II and III studies.

1.7.2 Clinical pharmacokinetics of cobimetinib

Cobimetinib pharmacokinetics has been characterized in cancer patients following oral administration after single and multiple dosing in the Phase Ia dose-escalation study (MEK4592g). Cobimetinib has a moderate rate of absorption (median tmax of 1 to 3 hours). Exposure increased with increasing doses and was dose-proportional from 0.05 mg/kg (approximately 3.5 mg for a 70 kg adult) to 80 mg (clinically relevant dose range). The cobimetinib mean terminal half-life following single-agent administration was 48.8 hours (range: 23.1 to 80.0 hours). Plasma samples were also analyzed for EXEL-0382, a metabolite of cobimetinib. Since the metabolite concentrations were less than 10% of the parent drug and showed no dose proportional increase in exposure, further analysis of the metabolite was not conducted in subsequent studies. Overall, cobimetinib demonstrates dose proportional and time independent pharmacokinetics with a moderate rate of absorption and a mean half-life of 48.8 hours. In vitro studies showed that cobimetinib is a time-dependent inhibitor of CYP3A and a competitive inhibitor of CYP2D6. In vitro studies also show that cobimetinib is a substrate of CYP3A and UGT2B7. Given the potential to inhibit CYP3A and CYP2D6, Study MEK4592g was amended to add a cohort of patients for evaluation of the drug interaction potential of cobimetinib with a CYP3A4 substrate (i.e., single dose of midazolam) and a CYP2D6 substrate (i.e., single dose of dextromethorphan).

Cobimetinib showed high variability in pharmacokinetic parameters during the dose-escalation phase of the study, MEK4592g.

Pharmacokinetics of vemurafenib and cobimetinib in combination

Preliminary data from study N025395 show that cobimetinib and vemurafenib pharmacokinetics are not significantly altered when administered in combination.

Study NO25395

Pharmacokinetics of vemurafenib in study NO25395

Generally, the mean vemurafenib exposures on Day -1 (in the absence of cobimetinib) were similar to or slightly lower than the steady-state exposure observed in a previous single-agent vemurafenib study (NP25163). In study NP25163, the steady-state (Day 15) vemurafenib C_{max} and AUC from 0 to 8 hours (AUC_{0-8h}) values were 52.7 μg/mL (range 18.5−77.8 μg/mL) and 343.3 μg h/mL (range 103.2−504.8 μg h/mL), respectively, for 720 mg BID dosing; C_{max} and AUC_{0-8h} values were 61.4 μg/mL (range 31.2−106.0 μg/mL) and 392.2 μg h/mL (range 217.3−575.8 μg h/mL), respectively for the 960 mg BID dose. In study NO25395, the first vemurafenib and cobimetinib combination study, the mean values of the exposure (C_{max} and AUC_{0-8h}) ratios (Day 14/Day -1) ranged between 0.83 and 1.4, except for Cohorts 1B and 2. The mean exposures on Day -1 and Day 14 indicated that the vemurafenib exposures when vemurafenib was co-administered with cobimetinib were comparable to the data previously reported for vemurafenib monotherapy.

Pharmacokinetics of cobimetinib in study NO25395

Cobimetinib had a median t_{max} of 2-6 hours similar, to the t_{max} observed in study MEK4592g, the single agent cobimetinib study in cancer patients. On the 14-day-on/ 14-day-off schedule, plasma concentration data were collected during the dosing holiday to allow

estimation of half-life. For the 21/7 schedule, data were not collected to allow estimation of $t_{1/2}$. The half-life in study NO25395 ranged from 32.9-96 hours and was similar to the half-life (range, 23-80 hours) in study MEK4592g. The apparent clearance in this study was also consistent with the apparent clearance in MEK4592g (geometric mean, 12.5 L/h).

1.8 Impact of the trial

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.

2.0 OBJECTIVES

2.1 Co-primary objectives

2.1.1 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.

2.1.2 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.

2.2 Secondary objectives

2.2.1 To determine the progression-free survival of patients with papillary craniopharyngiomas receiving BRAF and MEK inhibitors.

2.2.2 To determine the toxicity of BRAF/MEK inhibitors in patients with papillary craniopharyngiomas.

2.2.3 To determine the activity of BRAF and MEK inhibitor combination in papillary craniopharyngiomas as measured by response of enhancing volume of craniopharyngioma.

2.2.4 To determine the activity of BRAF and MEK inhibitor combination in papillary craniopharyngiomas as measured by response of nonenhancing volume of craniopharyngioma.

2.2.5 To determine the overall survival of patients with papillary craniopharyngiomas receiving BRAF and MEK inhibitors.

2.2.6 To determine the duration of response in patients with papillary craniopharyngiomas receiving BRAF and MEK inhibitors

2.3 Exploratory objectives

2.3.1 To evaluate visual fields in patients with papillary craniopharyngiomas who have received BRAF/MEK inhibitors.

2.3.2 To evaluate pituitary hormone replacement over time in patients with papillary craniopharyngiomas who have received BRAF/MEK inhibitors.

2.3.3 To evaluate the time to response in patients with papillary craniopharyngiomas receiving BRAF and MEK inhibitors

2.3.4 To assess toxicity that may be associated with radiotherapy in patients with papillary craniopharyngiomas who have received BRAF/MEK inhibitors.

2.4 Correlative science objectives

2.4.1 To evaluate molecular biomarkers of response in papillary craniopharyngiomas.

2.4.2 To evaluate circulating tumor cells and cell-free circulating DNA in patients with papillary craniopharyngiomas.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-study guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agents.

In addition:

- As there is evidence that vemurafenib and cobimetinib may decrease the concentration of hormonal contraceptives (such as birth control pills), women and men of reproductive potential should agree to use two methods of birth control throughout their participation in this study (and for six months after discontinuation of study drugs) due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Physicians should discuss the appropriate methods of birth control, or pregnancy prevention, with the patient prior to study enrollment.

3.2 Pre-registration eligibility criteria (step 0)

___ 3.2.1 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 4.3, 4.4, and 6.2.1 for complete details.

3.3 Registration eligibility criteria (step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

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).

___ **3.3.1 Documentation of disease:**

Histologically proven papillary craniopharyngioma as documented by central pathology review with positive BRAF V600E mutation by IHC.

___ **3.3.2 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.

___ **3.3.3 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.

___ **3.3.4 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.

___ **3.3.5 Age ≥ 18 years**

___ **3.3.5 ECOG performance status ≤ 2**

___ **3.3.6 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.

___ **3.3.7 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.

___ **3.3.8 Required initial laboratory values:**

- Absolute Neutrophil count ≥ 1500/mm^3
- Platelets ≥ 100,000/mm^3
- Creatinine ≤ 1.5 mg/dL OR Creatinine Clearance ≥ 45mL/min
- Bilirubin ≤ 1.5 ULN
- AST/ALT ≤ 2.5 ULN

4.0 PATIENT REGISTRATION

4.1 Investigatior and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] Investigators and clinical site staff who are significant contributors to research must register in the [redacted] (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) – MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) – clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) – other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) – individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users) is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;

- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email at [redacted]

4.2 Cancer Trials Suport Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the [redacted] application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading site registration documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A071601*.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol-Specific Requirements for A071601 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at [redacted] Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to

participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

4.2.3 Checking site's registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the sites 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support.

4.3 Patient pre-registration (step 0) requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

  Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

- **Central pathology review & BRAF testing:** Patients must be pre-registered to this study in order to undergo central pathology review and BRAF testing which will be performed by IHC on each case. Tissue must be submitted per Section 6.2.1 and must be accompanied by a completed "Central Pathology and BRAF Results Form" found on the A071601 study page on the CTSU and Alliance web sites. Failure to submit this form with the specimens will delay turnaround time for central review and BRAF testing. Sites will be notified via e-mail whether or not the patient is eligible based on central pathology & BRAF IHC testing within 14 days of specimen receipt at Brigham and Women's Hospital (BWH)/Dana-Farber Cancer Institute (DFCI).

  For local site HIPAA documentation, please note that the following personal health information (PHI) may be released outside of the Alliance: tumor block or slides for central review will be labeled with patient initials and date of collection.

4.4 Patient registration requirements

- **Receipt of "Central Pathology and BRAF Testing Results Form" by institution**: Upon the completion of testing, the results section of the "Central Pathology and BRAF Testing Results Form will be completed by the pathologists, scanned and sent via e-mail to the responsible CRP listed on the form.
- **Receipt of "Central Pathology and BRAF Testing Results Form" by Alliance Patient Registration Office:** After receiving the results form via e-mail, the institution must forward the form to the Alliance Patient Registration office at [redacted] in order to register the patient.
- **Registration must occur within 21 days of the date that the e-mail containing the Results Form.** Once the form is forwarded to the Alliance Patient Registration Office and the Registration Eligibility Criteria have been met, the patient can be registered using the OPEN system (see below). The same patient ID number obtained at pre-registration from the OPEN system must be used to register the patient. Please contact the Alliance Patient Registration office at [redacted] if registration problems occur.

4.5 Patient registration/randomization procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

4.6 Registration to substudies described in Section 14.0

There is one substudy within Alliance A071601. This correlative science study must be offered to all patients enrolled on Alliance A071601 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A071601 is:

- Identification of blood and tissue-based molecular biomarkers, Alliance A071601 (Section 14.1)

If a patient answers "yes" to Question #1 in the model consent ["I agree to have my blood collected and tissue submitted, and I agree that my specimen sample(s) and related information may be used for the laboratory study described above"], they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A071601-ST1 at the same time they are registered to the treatment trial (A071601). Samples should be submitted per Section 6.2.

4.7 Treatment assignments

Patients will be assigned to an arm of the trial based on whether they have received radiation. Cohort A will enroll newly diagnosed craniopharyngiomas that have not received radiation. Cohort B will enroll recurrent craniopharyngioma patients that have recurred after radiation.

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 28 DAYS before registration:
  - All laboratory studies, history and physical, eye exam
  - Any scan which is utilized for tumor measurement per protocol.
- To be completed ≤ 60 DAYS before registration: Any baseline exams used for screening that are not utilized for tumor measurement.

	Prior to Registration*	Day 1 of each cycle (cycle is 28 days)*	Weekly on treatment	Every 2 cycles	Monthly on treatment	Post treatment followup**	Clinical & survival follow-up ***
Tests & Observations							
History and physical, weight, PS	X(1)	X(1)				X(1)	X(1)
Height	X						
Pulse, Blood Pressure	X	X					X
Registration Fatigue/Uniscale Assessment	X(2)						
Adverse Event Assessment	X(3)	X(3)				X(3)	X(3)
EKG		B					
Echo or MUGA		C					
O2 Saturation		X(8)					
Eye exam	A	A				A	
Skin Exam		D					D
Patient Medication Diary		X(9)					
Laboratory Studies							
Complete Blood Count, Differential, Platelets	X	X					
Electrolytes, Creatinine (BMP)			X (10)				
Endocrine evaluation (with labs as necessary per endocrine evaluation)					X		
Chemistry	X(4)	X(4)				X(4)	
Serum or Urine HCG	X(5)						
Staging							
Central review for eligibility (pathology/BRAF)	X(6)						
MRI/CT Brain	X (7)			E(7)		E(7)	E(7)

Correlative studies: For paients who consent to participate in A071601-ST1				
Tissue block or slides				Archival tissue at baseline, recurrence and progression for banking and correlative science, see Section 6.2.
Whole blood samples				Whole blood at prior to treatment, Day 1 of Cycle 3 (+/- 3 days), end of treatment, recurrence and progression, see Section 6.2.

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, tests and observations may be obtained +/- 3 days from scheduled day of assessment. Radiographic windows are +/- 7 days from scheduled day of assessment (except prior to registration). A new cycle is defined by day 1 on which the patient starts drug for that cycle.

** Physical examination, adverse event assessment, medication diary, and chemistry are required 4 weeks (+/- 7 days) after the end of treatment. End of treatment is considered 4-5 cycles of treatment, or end of treatment with vemurafenib + cobimetinib.

*** Patients who progress or who do not progress within 2 years from registration, will be followed for survival every 6 months, for a maximum of 5 years from registration (step 1). Patients discontinuing for reasons other than progressive disease will be followed for progression every 16 weeks (+/- 4 weeks) until they have reached 2 years post-registration or until documented progression (whichever comes first), then followed for survival every 6 months, for a maximum of 5 years from registration (Step 1). See also Section 12.0.

1 History & physical should include neurologic exam and assessment of endocrine therapy (including dosage and type the patient is receiving).

2 To be completed after pre-registration and ≤ 21 days prior to treatment, see Appendix I.

3 Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration. See Sections 9.1 and 9.2. See also AEs of special interest in Section 9.3. See Section 9.4 for expedited reporting of SAEs.

4 Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium and CPK. Glucose must be fasting (i.e., 8 hours or more fast).

5 For women of childbearing potential. Must be done ≤ 7 days prior to registration and ≤ 7 days prior to initiation of vemurafenib and cobimetinib

6 See Sections 4.3, 4.4 and 6.2 for central review submission.

7 Scans can include either: 1) MRI Brain or 2) CT Brain. CT should ONLY be used for patients unable to undergo MR imaging because of non-compatible device or life-threatening gadolium allergy. Also see Section 11.0. Supporting documentation is to be submitted, per Section 6.1.1. **All MRIs must be performed per Appendix II and submitted to IROC Ohio**. **Response assessment should include assessment of all sites of disease.** Baseline scan should be submitted to IROC within 14 days after patient registration per Section 6.3. Any images required per footnote E or that are part of clinical care should be submitted to IROC Ohio within 14 days after acquisition per Section 6.3.

8 Oxygen saturation should be assessed at rest and after 1 minute walk. Dose modifications for hypoxia should be followed per Section 8.2.2.15.

9 Medication diaries should be completed by the patient throughout treatment, and should be collected at day 1 of every cycle starting with day 1 cycle 2. Please use Appendix III and IV.

10 It is suggested that the treating physician communicate with the endocrinologist to make any adjustments to the endocrine medications that the patient is on.

A Eye exam that includes retinal exam, slit lamp exam, and visual fields (preferably Goldmann Visual Field testing if available) required prior to registration, then every 2 months (+/- 1 month) for 1 year, then every 6 months (+/- 2 months) while on protocol treatment, and within 28 days after completion of treatment (ONLY if an eye exam has NOT been performed within 28 days prior to last dose of vemurafenib.) Visual field testing reports must be submitted as supporting documentation for each timepoint specified in this footnote. See Section 8.2.2.7 for dose modifications.

B Required prior to treatment, then performed every 28 days (+/- 7 days) for 3 months, then every 3 months (+/- 1 month) while on vemurafenib. See Section 8.2.2.6 for instructions regarding initiation of treatment and dose modifications.

C Echo or MUGA should be performed prior to treatment, after 1 month (+/-5 days) of treatment, and every 3 months (+/- 1 month) while on cobimetinib. See Section 8.2.2.5 for instructions regarding initiation of treatment and dose modifications.

D Skin exam (preferably by dermatology) to screen for malignancy required prior to treatment, then every 6 months (+/- 3 months) while on protocol treatment, then at discretion of treating physician once off protocol treatment. Skin exam should look for: rash, pruritis, dry skin, keratoachanthoma, squamous cell carcinoma, Hyperkeratosis, hand-foot syndrome.

E Every 2 cycles (+/- 7 days) from baseline scan while receiving cobimetinib and vemurafenib. Patients who are noted to have PR or CR should have a confirmation scan performed 4-8 weeks (+/- 7 days) after the scan demonstrating response. Once patients on Cohort A complete treatment, staging scans must be performed every 16 weeks (+/- 4 weeks) (from last scan performed during treatment) until they have reached 2 years post-registration or until documented progression. Patients on Cohort B who receive surgery or radiation at investigator discretion must submit initial post-operative/post-RT scan, 1 year (+/- 14 days) post-op/post-RT scan and any other scans done as part of clinical care after surgery and radiation. Of note, surgery can be delayed by not more than 4 weeks to obtain a confirmatory scan to document a response. Patients discontinuing for reasons other than progressive disease will have staging scans every 16 weeks (+/- 4 weeks) until they have reached 2 years post-registration or until documented progression, whichever comes first.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data collection and submission

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in the [redacted] application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under Data Management > Rave Home and click to accept the invitation in the Tasks pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the [redacted] application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at [redacted]

6.1.1 Supporting documentation

This study requires supporting documentation for diagnosis, response and progression. Supporting documentation must be deidentified and submitted via Rave at the timepoints below:

Baseline: Imaging report, pathology report, operative report, clinic note, standard visual field report, and Central Pathology & BRAF Results Form

During Treatment & Follow-up: Visual field testing reports must be submitted at each timepoint specified in Section 5.0. For any subsequent treatment received for patients on Cohort A and Cohort B, surgical, radiation planning and radiology reports must be submitted.

Response: Imaging report

Progression: Imaging report, and pathology report if applicable

6.1.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.1.3 IRB Terminations

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at [redacted] with any questions.

6.2 Specimen collection and submission

6.2.1 Real time histopathology review and BRAF IHC testing (mandatory for all patients)

Real-time histopathology review and BRAF IHC testing will be conducted on tissue from the diagnostic or recurrent biopsies and/or surgery at Dana-Farber Cancer Institute/BWH (CLIA-certified laboratory, #22D0705149). **The submission of these samples for**

histopathology review is required for all patients pre-registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy. Beta-catenin IHC will testing will also be performed for eligibility screening on the BRAF IHC inconclusive cases. Slides must be shipped within 28 days after patient pre-registration.

Slides must be accompanied by a completed "Central Pathology and BRAF Results Form" found on the A071601 study page on the CTSU and Alliance web sites. Failure to submit this form with the specimens will delay turnaround time for central review and biomarker testing. See Section 4.3 and 4.4 for specific instructions and process for central review results/registration reporting.

Please note that slides must also be accompanied by a de-identified surgical pathology report.

6.2.2 A071601-ST1 (optional for patients)

All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A071601-ST1, although patient participation is optional. For patients who consent to participate (model consent question, "I agree to have my blood collected and tissue submitted, and I agree that my specimen sample(s) and related information may be used for the laboratory study described above"), 1 FFPE tumor block (or slide alternatives) and will be submitted from surgeries performed prior to treatment and at recurrence and progression. Paraffin blocks or slides comprised of primary and, when available, metastatic tissue should be submitted. Whole blood will also be collected and submitted. Blocks/slide and whole blood to be used for biomarker studies as described in Section 14.1.

6.2.3 Correlative Science Manual (CSM)

The Alliance A071601 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS, CTSU, and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

6.2.4 Overview of specimen requirements

	≤ 28 days after pre-registration	**Prior to Protocol Tx**	**Day 1 of Cycle 3 (+/- 3 days)**	**End of Protocol Tx**	**At recurrence and progression**
Mandatory for all patients pre-registered to A071601:					
1 H&E slide and 2 unstained slides for histopathology review & BRAF IHC testing	X				
For patients registered to A071601-ST1[A], submit the following:					
Paraffin block or alternative from surgery[1]		X[2]			X[2]
Whole blood [1] (EDTA/lavender top)		10 mL			
Whole Blood[1]		20 mL	20 mL	20 mL	20 mL

(EDTA/lavender top)					

1 For patients who consent to question "I agree to have my blood collected and tissue submitted, and I agree that my specimen sample(s) and related information may be used for the laboratory study described above." Blocks/slide and whole blood to be used for biomarker studies as described in Section 14.1.

2 Paraffin block or alternatives may be sent up 6 months after registration (for pre-tx specimen) and up to 6 months after progression (for progression/recurrent specimens).

6.2.5 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

6.3 MR/CT data submission requirements

6.3.1 Overview

For all patients enrolled, images will be acquired per Appendix II and transmitted electronically from each participating site to the Imaging and Radiation Oncology Core QA center at The Ohio State University (IROC Ohio).

Images and local interpretation reports will be collected digitally and submitted for centralized, retrospective re-review. Images will be collected locally and submitted within 14 days of image acquisition.

Images must be submitted for all MRI/CTs required at timepoints outlined in Section 5.0 (baseline, during treatment, survival and clinical follow up, confirmation of response and progression, or for patients on Cohort B, any scans related to clinical care or follow-up post-surgery or radiation).

6.3.2 Imaging submission instructions

Complete data sets in digital DICOM format should be submitted to IROC Ohio within 14 days of image acquisition.

BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by IROC. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number and protocol number. The de-identified digital images may be temporarily burned to a CD or transferred to a PC based system.

Data should be transferred electronically (recommended) to IROC as follows:

1) TRIAD based data transfer (see Section 6.3.3)

The standard TRIAD based data transfer approach will be provided separately through IROC efforts per the request by participating sites before their first data submission.

2) Web Transfer [redacted]

   Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

3) FTP Transfer

   Any FTP software can be used to initiate access to the secure FTP Server of IROC. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

4) Mail/CD Shipment

   Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

   Submit these data to:

[redacted]

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email [redacted] to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number
2) Scan time point (i.e., baseline)
3) Date of scans
4) Institution name

IROC will acknowledge receipt of the imaging data via email confirmation to the institution within 1 business day of receipt, and will notify the institution and Alliance imaging committee of the quality check report within 3 business days.

6.3.3 Using TRIAD image submission

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);

- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at [redacted]

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email [redacted]

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 10 days of registration. **EKG, Echo (or MUGA), O2 Saturation, and skin exam must be performed prior to initiation of treatment for safety as required in Section 5.0. See Dose Modifications in Section 8.2 prior to initiating treatment.** For questions regarding treatment, please see the study contacts page.

Prior to initiating treatment, physicians must discuss caffeine limitation while on this study with the patient. See Section 8.1.11 for more information.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

7.1 Vemurafenib + cobimetinib

Each cycle will consist of 28 days.

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

For both arms, a cycle will be 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. Dose modifications will be instituted for toxicity as per Section 8.0. Contrast- MRI (or CT, see Section 5.0) will be performed every 8 weeks as outlined in Section 5.0. See Section 11.0 for response criteria.

If a dose of vemurafenib is missed, it can be taken up to 4 hours prior to the next scheduled dose. If a dose of cobimetinib is missed (i.e. 6 hours or more late), do not make up that dose; resume dosing with the next scheduled dose.

If cobimetinib meets criteria to be discontinued due to protocol dose modifications and vemurafenib does not, cobimetinib may be discontinued and patient may continue on single agent vemurafenib therapy.

If vemurafenib meets criteria to be discontinued due to protocol dose modifications and cobimetinib does not, vemurafenib may be discontinued and patient may continue on single agent cobimetinib therapy.

See complete dose modifications in Section 8.0.

7.1.1 Cohort A

For Cohort A, patients should receive treatment for up to 4 cycles with vemurafenib + cobimetinib (unless progression, unacceptable toxicity, or patient withdrawal from study occurs). See Section 12.0 for additional information. After 4 cycles of vemurafenib and cobimetinib, surgery or radiation for definitive therapy should be performed. Continuation of vemurafenib and cobimetinib beyond 4 cycles in cohort A will require approval from the radiation oncology chair and study chair. If patient stays on study for longer than 4 cycles, visits and labs at the beginning of every cycle are still required with scans every 2 cycles, as per the study calendar.

- **For patients that achieve CR**, they will undergo definitive radiation.
- **For patients with any response that is not CR or better**, the decision of therapy between surgery, or radiation, or both, is at the discretion of the treating physician.

For patients who go on to receive radiation, the pre-treatment scan would be used as a guide for radiation planning. See Section 7.2 for radiation guidelines. Vemurafenib and cobimetinib need to be stopped at least two weeks prior to initiation of radiation therapy. For purposes of radiation planning, if duration of BRAF/MEK inhibitor treatment needs to be extended this will be allowed, for a maximum length of 4 additional weeks (i.e., 5 cycles maximum).

In special cases, if radiation or surgery are not recommended for the patient because of potential risks, then the patient may continue on cobimetinib and vemurafenib past 4 cycles, until disease progression or unacceptable adverse events. **However, continuation of treatment can only be granted with approval from the radiation oncologist and study chair.** A request, with accompanying rationale, must be sent to the radiation oncologist and protocol coordinator. Approval must be obtained via email prior to Cycle 5 drug shipment. The email containing the approval must also be submitted via Rave as supporting documentation.

7.1.2 Cohort B

For Cohort B, patients will receive 4 cycles of study drug therapy (unless progression, unacceptable toxicity, or patient withdrawal from treatment occurs). After 4 cycles of vemurafenib + cobimetinib, the patient may go on to receive treatment per the discretion of the treating physician, including radiation, surgery or continued treatment with vemurafenib + cobimetinib. Treatment with vemurafenib + cobimetinib can be continued until CR, PR, or SD but must be discontinued with PD. The BRAF and MEK inhibitors need to be stopped at least two weeks before initiation of radiation therapy.

7.2 Radiotherapy guidelines for Cohort A

7.2.1 Definition of target volumes

The pre-surgical and most recent pre-irradiation scans performed no greater than one month prior to the CT simulation scan should be used to guide radiation planning. Target volume should include any radiographically visible residual disease and surfaces to which the tumor was previously adherent to that may be at risk for harboring residual microscopic disease.

- GTV = Gross target volume, interpreted as any residual tumor (residual enhancing nodules and cysts)
- CTV = Clinical target volume, should encompass the GTV plus surgical bed/any areas of microscopic residual (surfaces of pre-op tumor contact) adjusting for post-operative anatomic shifts. Often 0-5 mm nonuniform expansion may be added per clinician discretion to capture additional microscopic disease although typically expansion into brain parenchyma is not needed.
- PTV = Planning target volume, as standard for immobilization choice and institutional practice, typically range of 3-5 mm should be employed. Daily image-guided radiation therapy (IGRT) is recommended.
- Because 15% of cystic tumors can enlarge during RT, weekly verification CT or MR is recommended.

7.2.2 Dose prescription

The recommended radiation therapy regimen is 54 Gy at 1.8 Gy per fraction delivered daily, Monday

through Friday, utilizing image guidance (IGRT). If able to safely meet normal tissue constraints:

- GTV

  ≥99% of the GTV should receive 54 Gy

  Dmax GTV <59 Gy
- CTV

  ≥99% of the CTV should receive ≥95% prescription dose

  Dmax CTV <59 Gy
- PTV

  ≥95% of the PTV should receive ≥95% prescription dose

  Dmax PTV <59 Gy

7.2.3 Normal tissue constraints

Normal Structure Constraints

Name of Structure	Dosimetric parameter	
SpinalCord	D_{max}	≤50 Gy
BrainStem	D_{max}	≤55 Gy
OpticChiasm	D_{max}	≤55 Gy
OptNrv_L_ and OptNrv_R_	D_{max}	≤55 Gy
Retina_L or Retina_R	D_{max}	≤45 Gy
Brain	$D_{5\%}$	≤57 Gy
Lens_L or Lens_R	D_{max}	≤7 Gy

D_{max} defined for a volume less than or equal to 0.03cc.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 **Patients should not receive any other agent** which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 **Patients should receive full supportive care while on this study.** This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 **Treatment with other chemotherapeutic agents may not be administered** except for steroids given for adrenal failure or pituitary hormone replacement therapy; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic.

8.1.4 **Antiemetics** may be used at the discretion of the attending physician.

8.1.5 **Diarrhea management is per the discretion of the treating physician.** Diarrhea could be managed conservatively with medications such as loperamide. Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 **Palliative radiation therapy may not be administered** except for radiation therapy given for patients on Cohort B as outlined in Section 7.2.

8.1.7 Alliance policy concerning the use of growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

8.1.8 Hypersensitivity reactions

Treat hypersensitivity reactions to vemurafenib and cobimetinib as per institutional standards.

8.1.9 CYP3A4 inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with vemurafenib and cobimetinib.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

If concurrent short term (≤to 14 days) use of a moderate CYP3A4 inhibitor is unavoidable, reduce the cobimetinib dose to 20 mg. After discontinuation of the moderate CYP3A inhibitor, resume cobimetinib at the previous dose.

Investigators may provide patients with the wallet handout card provided Appendix V.

8.1.10 CYP3A4 inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with vemurafenib and cobimetinib.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

Investigators may provide patients with the wallet handout card provided Appendix V.

8.1.11 CYP1A2 substrates

Chronic concomitant treatment with substrate of CYP1A2 with a narrow therapeutic index or sensitive substrate is not allowed on this trial. The following drugs are EXAMPLES of substrates of CYP1A2 with a narrow therapeutic index or sensitive substrate and are not allowed during treatment with vemurafenib:

- Caffeine: Limit to 200 mg/day. It is important that you discuss this limit with your patient prior to initiating treatment. We recommend that you discuss the patient's typical daily food and beverage intake to determine their average caffeine consumption, as well as to discuss strategies and best practices for limiting caffeine to 200 mg/day.
- Tizanidine
- Duloxetine
- Melatonin

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to be CYP1A2 substrate. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA website, or your local institution's pharmacist.

Investigators may provide patients with the wallet handout card provided Appendix V.

8.1.12 QT prolongation: Chronic concomitant treatment with drugs that are known to prolong the QT interval/are associated with Torsades should be avoided, as vemurafenib can cause QT prolongation and arrhythmia. See [redacted] (registration required but is free).

8.1.13 Radiation recall: Vemurafenib has been reported to cause radiation recall. For patients who develop CNS toxicity and were previously irradiated for craniopharyngioma, consider performing MRI brain to evaluate.

8.1.14 Malignancy: Both vemurafenib and cobimetinib are associated with skin malignancies. Patients should report any new or suspicious skin lesions promptly, and have skin exams per Section 5.0. In addition, vemurafenib is associated with RAS-related malignancies, and any suspicious symptoms should undergo prompt workup. In addition, vemurafenib is associated with the formation of colon polyps, and patients should follow national guidelines for colon screening.

8.1.15 Rash: Both agents are associated with rash and cobimetinib is associated with photosensitivity. Patients should avoid sun exposure and practice good skin care. Consider dermatology consult as needed in the setting of rash**.**

8.1.16 Ocular toxicity: Vemurafenib is known to cause uveitis, and cobimetinib is known to cause retinopathy. In addition, due to the location of the tumor, patients with craniopharyngioma are known to have visual field defects. Regular eye exams should be performed as per Section 5.0, and patients should report any visual changes promptly. Consider treatment with steroids for uveitis. Serous retinopathy may be treated with topical corticosteroid eye drops.

8.1.17 Bleeding: Cobimetinib leads to an increased bleeding risk. Hemorrhage, including major hemorrhages, defined as symptomatic bleeding in a critical area or organ, can occur with cobimetinib. In clinical studies with cobimetinib, events of cerebral hemorrhage, GI tract hemorrhage, reproductive tract hemorrhage, and hematuria have been reported. Patients on anticoagulation should undergo increased frequency of monitoring while on treatment.

8.1.18 Pneumonitis: Cobimetinib has been associated with pneumonitis. In the setting of suspected pneumonitis, consider CT scan, PFTs, pulmonary consult, and bronchoscopy, and consider treatment with steroids or referral to pulmonary and infectious disease specialists.

8.2 Dose modifications

- If multiple adverse events are seen, administer dose based on greatest modification required for any single adverse event observed.
- Modifications apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If study agent is held for >28 days, study agent will be discontinued.
- Dose modifications can be communicated to patients taking oral agents at home at any point in the cycle (i.e. if there is Grade III diarrhea at home).
- If cobimetinib meets criteria to be discontinued due to protocol dose modifications and vemurafenib does not, cobimetinib may be discontinued and patient may continue on single agent vemurafenib therapy.
- If vemurafenib meets criteria to be discontinued due to protocol dose modifications and cobimetinib does not, vemurafenib may be discontinued and patient may continue on single agent cobimetinib therapy.
- Descriptors below utilize CTCAE version 4.0. See Sections 9.1, 9.2 and 9.3 for routine AE reporting requirements. Expedited reporting via CTEP-AERS may be required for some adverse events (See Section 9.3). CTCAE version 5.0 must be used for serious adverse event reporting through CTEP-AERS.
- Please see IB for vemurafenib and cobimetinib or contact study chair for additional guidance.

8.2.1 Dose levels

Dose Level	Drug Name	Dose
0*	Vemurafenib	960 mg twice/day
-1	Vemurafenib	720 mg twice/day
-2	Vemurafenib	480 mg twice/day

*Dose level 0 refers to the starting dose.

Dose Level	Drug Name	Dose
0*	Cobimetinib	60 mg once/day
-1	Cobimetinib	40 mg once/day
-2	Cobimetinib	20 mg once/day

8.2.2 Dose modifications for vemurafenib and cobimetinib:

8.2.2.1 Gastrointestinal toxicity

- For **grade 2 or 3 diarrhea**, delay cobimetinib and vemurafenib until grade ≤ 1, then resume vemurafenib at same dose and cobimetinib at 1 dose level decreased.
- For **grade 4 diarrhea**, discontinue cobimetinib and vemurafenib.
- For **grade 3 or 4 nausea or grade 3 vomiting**, delay cobimetinib and vemurafenib until grade ≤ 2, then resume vemurafenib at same dose and cobimetinib at 1 dose level decreased.
- For **grade 4 vomiting**, discontinue cobimetinib and vemurafenib.

8.2.2.2 Hepatic toxicity

- For **grade 3 transaminase increased and/or blood bilirubin increased**, delay cobimetinib and vemurafenib until grade ≤ 1, then resume cobimetinib at same dose and vemurafenib at 1 dose level decreased
- For **grade 4 transaminase increased and/or blood bilirubin increased,** discontinue vemurafenib and cobimetinib.

8.2.2.3 Renal toxicity

- For **grade 3 acute kidney injury or hematuria**, delay vemurafenib until

grade ≤ 1, then resume at 1 dose level decreased.
- For **grade 4 acute kidney injury, hematuria, or grade 4 creatinine increase**, discontinue vemurafenib and cobimetinib.

8.2.2.4 Skin toxicity

- For **grade 3 maculopapular rash and/or grade 3 pruritus**, delay vemurafenib until grade ≤ 1, then resume at 1 dose level decreased.
- For **grade 4 maculopapular rash**, discontinue vemurafenib and cobimetinib.
- For **grade 3 acneiform rash**, delay cobimetinib until grade ≤ 1, then resume at 1 dose level decreased.
- For **grade 4 acneiform rash**, discontinue cobimetinib.
- For **grade 3 pruritus or photosensitivity**, delay cobimetinib and vemurafenib until grade ≤ 1, then resume at cobimetinib at same dose and vemurafenib at 1 dose level decreased.
- For **grade 4 pruritus or photosensitivity**, discontinue cobimetinib and vemurafenib.
- For **Stevens Johnson syndrome**, discontinue vemurafenib and cobimetinib.

8.2.2.5 Cardiac toxicity:

- **Prior to initiation of treatment (i.e. after registration but prior to C1D1), for left ventricular ejection fraction (LVEF) below the institutional LLN or below 50%**, whichever is lower, treatment is not recommended. Consult with study chair prior to initiating treatment with vemurafenib and cobimetinib.
- For **grade 1 heart failure with EF ≤40%,** delay cobimetinib until EF ≥ 40% and then resume at 1 dose level decreased
- For **grade 2 heart failure,** delay cobimetinib until grade ≤1 and EF ≥ 40%, and then resume at 1 dose level decreased.
- For **grade ≥ 3 heart failure**, discontinue cobimetinib.
- For **grade 2 ventricular arrhythmia**, delay vemurafenib until grade ≤ 1 then restart at 1 dose level decreased.
- For **grade ≥ 3 ventricular arrhythmia**, discontinue vemurafenib and cobimetinib.

8.2.2.6 Investigations:

- **Prior to initiation of treatment (i.e., after registration but prior to C1D1), for QTc > 500 msec,** treatment not recommended. Consult with study chair prior to initiating treatment with vemurafenib and cobimetinib.
- For **grade 3 QTc interval prolonged,** delay vemurafenib until grade ≤ 2 then restart at 1 dose level decreased. Electrolytes (K, Mg, and Ca) should be monitored and any electrolyte abnormalities should be corrected prior to reinstitution of therapy.
- For **third occurrence of grade 3 QTc interval prolonged**, discontinue vemurafenib and cobimetinib.
- For **grade 4 QTc interval prolonged**, discontinue vemurafenib and cobimetinib.

8.2.2.7 Eye toxicity

- For **grade 2 uveitis**, delay vemurafenib until grade ≤ 1, then resume at 1 dose level decreased.

- For **grade 3 or 4 uveitis**, discontinue vemurafenib and cobimetinib.
- For **grade 2 eye retinopathy,** delay cobimetinib until grade ≤ 1, then resume at 1 dose level decreased.
- For **grade 3 or 4 retinopathy**, discontinue cobimetinib.
- For **retinal vascular disorder- retinal vein occlusion grade ≥ 2,** discontinue cobimetinib.

8.2.2.8 Hematologic toxicity

For **grade 4 anemia**, delay cobimetinib until grade ≤ 3, then resume at 1 dose level decreased.

8.2.2.9 Hypersensitivity:

- For **grade 2 or 3 allergic reaction**, delay cobimetinib and vemurafenib until grade ≤ 1.
- For **grade ≥ 4 allergic reaction**, discontinue cobimetinib and vemurafenib.

8.2.2.10 Pulmonary toxicity

- For **grade 2 pneumonitis**, delay cobimetinib until grade ≤ 1, then resume at 1 dose level decreased.
- For **grade 3 or 4 pneumonitis**, discontinue cobimetinib.

8.2.2.11 Vascular toxicity:

- For **grade 2 or 3 hypertension,** delay cobimetinib until grade ≤ 1, then resume at 1 dose level decreased.
- For **grade 4 hypertension**, discontinue cobimetinib.

8.2.2.12 Hemorrhage:

- For **grade 3 hemorrhage,** delay cobimetinib until grade ≤ 1 (or grade ≤ 2 if no grade 1 exists), then resume at 1 dose level decreased.
- For **grade 4 hemorrhage,** discontinue cobimetinib.

8.2.2.13 New primary malignancies (cutaneous and non cutaneous)

No dose modification for cobimetinib required.

8.2.2.14 Rhabdomyolysis and CPK elevations

For **grade 4 CPK** elevation or CPK elevation and myalgia, withhold cobimetinib for up to 4 weeks. If improved to Grade 3 or lower, resume at the next lower dose level

8.2.2.15 Other toxicities

- For **all other grade 3 toxicities considered at least possibly related to treatment**, omit the responsible drug(s) until toxicity improves to ≤ grade 1, then resume the responsible drug(s) at the next lower dose level.
- For **all other grade 4 toxicities considered at least possibly related to treatment**, discontinue the responsible drug(s). If the responsible drug is vemurafenib, discontinue both cobimetinib and vemurafenib. The exception is hyperglycemia (see Section 8.2.4) or electrolyte abnormalities that can be managed with medical therapy, where the responsible drugs do not need to be discontinued if the adverse event is adequately managed.

8.2.3 Dose modifications for obese patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

8.2.4 Hyperglycemia and metabolic effects

Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision. Use of oral anti-hyperglycemic agents, such as metformin, for patients experiencing Grade ≥ 2 hyperglycemia may be implemented. For Grade 3 or greater hyperglycemia, consider increasing dose of anti-hyperglycemic agents, such as metformin, and initiating insulin. Anti-hyperglycemic agents should be used to control severe hyperglycemia per institutional standard of care. Reommended management of hyperglycemia:

- For Grade 2 or greater hyperglycemia, consider initiating oral glucose lowering medication such as metformin
- For Grade 3 or greater hyperglycemia, hydration status should be clinically assessed. If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate. If patient is asymptomatic, consider increasing oral glucose lowering medication. If patient is symptomatic, rapid/short acting insulin should be initiated according to institution sliding scale coverage as per institutional guidelines, and consider increasing oral glucose lowering medication. For persistent Grade 3 or greater hyperglycemia, please consult with endocrinologist. Grade 4 hyperglycemia should lead to agent discontinuation only if it does not respond to initial medical treatment with appropriate glucose lowering medication.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 for dose modifications and adverse event reporting through Rave. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the form "Adverse Events: Solicited" is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Blurred vision	Eye Disorders
Diarrhea	Gastrointestinal disorders
Fatigue	General disorders and administration site conditions
Alanine aminotransferase increased	Investigations
Aspartate aminotransferase increased	Investigations
CPK increased	Investigations
Photosensitivity	Skin and subcutaneous tissue disorders
Rash maculo-papular	Skin and subcutaneous tissue disorders

9.2 CTCAE routine reporting requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a

Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.
b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 AEs of special interest

9.3.1 AEs of special interest related to radiotherapy

In addition to routine reporting requirements as outlined in Sections 9.1 and 9.2, the following adverse events of special interest must be reported via routine event reporting for any grade regardless of attribution, and may necessitate reporting via CTEP-AERS (see Section 9.4). These adverse events must be reported for patients on Cohort A who receive radiation therapy after treatment with vemurafenib and cobimetinib.

Adverse Events: Late CRF, as part of Clinical Follow-up, should be used to report AEs during radiotherapy occurring greater than 30 days after the patient's last treatment date.

CTCAE v4.0 Term	**CTCAE v4.0 System Organ Class (SOC)**
Hearing impaired	Ear and labyrinth disorders
External ear inflammation	Ear and labyrinth disorders
Endocrine disorders- Other, specify	Endocrine disorders
Retinopathy	Eye disorders
Optic nerve disorder	Eye disorders
Nausea	Gastrointestinal Disorders
Vomiting	Gastrointestinal Disorders
Dermatitis radiation	Injury, poisoning and procedural complications
Wound dehiscence	Injury, poisoning and procedural complications
Radiation recall reaction (dermatologic)	Injury, poisoning and procedural complications
Cognitive disturbance	Nervous system disorders
Edema cerebral	Nervous system disorders
Central nervous system necrosis	Nervous system disorders
Ischemia cerebrovascular	Nervous system disorders
Alopecia	Skin and subcutaneous tissue orders

9.3.2 AEs of special interest related to vemurafenib + cobimetinib

In addition to routine reporting requirements as outlined in Sections 9.1 and 9.2, the following adverse events of special interest must be reported via routine event reporting regardless of attribution, and may necessitate reporting via CTEP-AERS (see Section 9.4). If a grade is not specified in the table below, then reporting is required for any grade of that AE. These events must be reported in Rave in same time frame as serious adverse events (see table in Section 9.4).

Adverse Events: Other CRF should be used to report AEs occurring between registration and within 30 days of the patient's last treatment date.

Adverse Events: Late CRF should be used to report AEs occurring greater than 30 days after the patient's last treatment date.

CTCAE v4.0 Term	**CTCAE v4.0 System Organ Class (SOC)**
Grade ≥ 2 Heart failure	Cardiac disorders
Grade ≥ 2 Left ventricular systolic dysfunction	Cardiac disorders
Optic nerve disorder	Eye disorders
Retinal detachment (including neurosensory retinal detachment)	Eye disorders
Retinal vascular disorder (including retinal vein occlusion)	Eye disorders
Retinopathy (including serous retinopathy and central serous chorioretinopathy)	Eye disorders
Eye disorders (other) – (including retinal pigment epithelium detachment, or any other eye disorders)	Eye disorders
Events suggestive of Drug Induced Liver Injury (report as Hepatobiliary disorders – Other, specify)	Hepatobiliary disorders
Grade ≥ 2 Ejection fraction decreased	Investigations
Grade ≥ 3 Electrocardiogram QT corrected interval prolonged	
Grade ≥3 Hemorrhage event (report per specific CTCAE hemorrhage location)	Eye disorders Gastrointestinal disorders Hepatobiliary disorders Injury, poisoning and procedural complications Renal and urinary disorders Reproductive system and breast disorders Respiratory, thoracic and mediastinal disorders
Intracranial hemorrhage	Nervous system disorders

Treatment related secondary malignancy	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Neoplasms benign, malignant and unspecified (incl cysts and polypos) – Other, including: • New or worsening malignancies • Non-cutaneous squamous cell carcinoma • Skin cancers • Gastrointestinal polyps	Neoplasms benign, malignant and unspecified (incl cysts and polyps)

9.4 Expedited adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for expedited AE reporting. CTCAE version 5.0 will be utilized for AE reporting via CTEP-AERS beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 and CTCAE version 4.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [redacted]

All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP Web site.[redacted]

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.4.1 Expedited reporting requirements for adverse events that occur on studies under an Alliance-IND/IDE within 30 days of the last administration of the investigational agent/intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject

and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3 – 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are outlined in Section 9.4.2.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.4.2 Additional instructions or exclusions to CTEP-AERS expedited reporting requirements for phase 2 and 3 trials utilizing an agent under a non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Grade 1-3 fatigue does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 alopecia and hospitalization resulting from such do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.

- Grade 1-3 alopecia does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 nausea, abdominal pain, vomiting, constipation or diarrhea does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 1-2 dysguesia, mucositis oral, anorexia, or weight loss do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade Grade 1-2 headache or dizzines does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 1-2 fever or chills does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 arthralgia, back pain, myalgia, pain in extremety, or palmar-plantar erythrodysesthesia syndrome does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 peripheral motor neuropathy or peripheral sensory neuropathy does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 gerneralized edema or edema limbs does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 accute kidney injury does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 electrocardiogram QT corrected interval prolonged does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 photosensitivity or eye disorders-other does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 serum amylase increased or hyperglycemia do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 pruritis, skin papilloma, hyperkeratiosis, dry skin, rash acneiform, or rash maculoppapular do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 skin and subcutaneous tissue disorders-Other (including actinic keratosis, keratosis pliaris) does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 alanine amino transferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, CPK increased, or GGT increased do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 1-2 anemia, neutrophil count decreased, hyponatremia, or hypophosphatemia do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE v4.0, secondary malignancies may be reported as one of the

following three options: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol. Second malignancies, which are unrelated to the treatment of a prior malignancy (and are **NOT** a metastasis from the initial malignancy), require **ONLY** routine reporting unless otherwise specified. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history of prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- CTEP-AERS reports should be submitted electronically.
- All pregnancies and suspected pregnancies occurring in female patients or in the partner of a male patient during therapy or within 28 days after completion of treatment on A071102 must be reporting via CTEP-AERS. In CTCAE version 5.0, use the event term, *"pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade 4)"*.
    a. CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, congenital abnormalities).
    b. Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.
    c. The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP AERS. A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

9.5 CAEPRS

9.5.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Vemurafenib (Zelboraf, RO5185426, NSC 761431)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

[redacted]

for further clarification. *Frequency is provided based on 5019 patients.* Below is the CAEPR for Vemurafenib (Zelboraf, RO5185426).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, April 2, 2019[1]

Adverse Events with Possible Relationship to Vemurafenib (Zelboraf, RO5185426) (CTCAE 5.0 Term) [n= 5019]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
EYE DISORDERS		
		Uveitis
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Constipation	
	Diarrhea	
Nausea		
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Edema limbs	
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
IMMUNE SYSTEM DISORDERS		
	Allergic reaction*	
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
	Folliculitis	
	Infections and infestations - Other (nasopharyngitis)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Injury, poisoning and procedural complications - Other (radiation injury)[2]
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	Creatinine increased	
	Electrocardiogram QT corrected interval prolonged	
	GGT increased	

Adverse Events with Possible Relationship to Vemurafenib (Zelboraf, RO5185426) (CTCAE 5.0 Term) [n= 5019]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Neutrophil count decreased*	
	Serum amylase increased*	
	Weight loss	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia		
	Back pain	
	Musculoskeletal and connective tissue disorder - Other (Dupuytren's contracture and plantar fibromatosis)*	
	Myalgia	
	Pain in extremity	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Skin papilloma	
	Treatment related secondary malignancy - Cutaneous squamous cell carcinoma (SCC), including keratocanthoma or mixed keratocanthoma subtype	
		Treatment related secondary malignancy - including non-cutaneous squamous cell carcinoma, melanoma and others
		Treatment related secondary malignancy - progression of RAS mutant tumors
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Dysgeusia	
		Facial nerve disorder
	Headache	
	Peripheral motor neuropathy*	
	Peripheral sensory neuropathy*	
RENAL AND URINARY DISORDERS		
	Acute kidney injury*	
		Renal and urinary disorders - Other (renal failure)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia		
	Dry skin	

Adverse Events with Possible Relationship to Vemurafenib (Zelboraf, RO5185426) (CTCAE 5.0 Term) [n= 5019]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Hyperkeratosis		
	Palmar-plantar erythrodysesthesia syndrome	
Photosensitivity		
	Pruritus	
Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (DRESS; drug reaction with eosinophilia and systemic symptoms)
	Skin and subcutaneous tissue disorders - Other (including actinic keratosis, keratosis pilaris)	
	Skin and subcutaneous tissue disorders - Other (panniculitis)*	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria*	

*Denotes adverse events that are <3%

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted]

Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Radiation injury includes recall phenomenon and radiation sensitization. Observed events include radiation dermatitis and skin necrosis; radiation pneumonitis, hepatitis, and esophagitis; and radiation proctitis and cystitis.

Adverse events reported on vemurafenib (Zelboraf, RO5185426) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that vemurafenib (Zelboraf, RO5185426) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia

CARDIAC DISORDERS - Heart failure; Pericardial effusion; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Ear pain; Vertigo

EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (chorioretinopathy); Eye disorders - Other (ocular hyperemia); Eye disorders - Other (retinal vein occlusion); Eye disorders - Other (visual disturbance); Eye disorders - Other (vitritis); Eye pain; Floaters; Photophobia; Scleral disorder; Watering eyes

GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Mucositis oral

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis)

INFECTIONS AND INFESTATIONS - Conjunctivitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Lipase increased; Lymphocyte count decreased; Platelet count decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (blood phosphorus level increased)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness; Joint range of motion decreased; Muscle cramp; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (adenomatous colon polyp)

NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Lethargy; Seizure; Somnolence; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Irritability

RENAL AND URINARY DISORDERS - Hemoglobinuria; Proteinuria; Urinary frequency; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Premature menopause

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Dyspnea; Epistaxis; Nasal congestion; Pharyngolaryngeal pain; Postnasal drip; Respiratory failure; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Hyperhidrosis; Nail changes; Nail discoloration; Skin and subcutaneous tissue disorders - Other (acrochordon); Skin and subcutaneous tissue disorders - Other (demal cyst); Skin and subcutaneous tissue disorders - Other (madarosis)

VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Vasculitis

Note: Vemurafenib (Zelboraf, RO5185426) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.5.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cobimetinib (RO5514041, GDC0973, NSC 781257)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. *Frequency is provided based on 274 patients*. Below is the CAEPR for Cobimetinib (RO5514041, GDC0973).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple

investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, March 25, 2020[1]

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
		Cardiac disorders - Other (cardiomyopathy)
		Cardiac disorders - Other (left ventricular dysfunction)
		Heart failure
EYE DISORDERS		
	Eye disorders - Other (chorioretinopathy)[2]	
	Eye disorders - Other (eye disorders)[3]	
		Eye disorders - Other (retinal vein occlusion)[2]
	Retinal detachment	
GASTROINTESTINAL DISORDERS		
Diarrhea		
	Mucositis oral	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
Fatigue		
	Fever[2]	
Generalized edema[4]		
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Alkaline phosphatase increased[2]	
	Aspartate aminotransferase increased[2]	
CPK increased		
	Ejection fraction decreased	
	GGT increased[2]	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hypokalemia	
	Hyponatremia	

Adverse Events with Possible Relationship to Cobimetinib (RO5514041, GDC0973) (CTCAE 5.0 Term) [n= 274]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
		Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (new primary malignancies, cutaneous and non-cutaneous)[2]
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
	Photosensitivity[2]	
	Pruritus	
	Rash acneiform	
Rash maculo-papular[5]		
VASCULAR DISORDERS		
	Vascular disorders - Other (hemorrhage)[6]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Observed in combination with Vemurafenib.

[3]Includes photopsia, blurred vision, vitreous floaters.

[4]Includes peripheral edema, periorbital edema, edema, and facial edema.

[5]Includes rash, dermatitis acneiform, rash pruritic, rash generalized dermatitis, exfoliative rash, rash erythematous, and rash maculo-papular.

[6]Hemorrhage includes cerebral hemorrhage, contusion, ecchymosis, epistaxis, gastrointestinal hemorrhage, hematuria, rectal hemorrhage, retinal hemorrhage, and vaginal hemorrhage.

Adverse events reported on cobimetinib (RO5514041, GDC0973) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that cobimetinib (RO5514041, GDC0973) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (cardiac ventricular thrombosis); Pericardial effusion
EAR AND LABYRINTH DISORDERS - Ear pain
EYE DISORDERS - Eye disorders - Other (retinal disorder); Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Dysphagia; Ileus; Lower gastrointestinal hemorrhage; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (autoimmune hepatitis); Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (cholangitis)
INFECTIONS AND INFESTATIONS - Catheter related infection; Gallbladder infection; Infections and infestations - Other (diverticulitis); Lung infection; Paronychia; Sepsis; Skin infection; Thrush; Urinary tract infection
INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Electrocardiogram QT corrected interval prolonged; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression); Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Encephalopathy; Facial muscle weakness; Nervous system disorders - Other (immune-mediated encephalitis); Nervous system disorders - Other (intracranial pressure increased); Nervous system disorders - Other (7th nerve palsy); Somnolence; Syncope
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Nasal congestion; Oropharyngeal pain; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Hyperkeratosis
SURGICAL AND MEDICAL PROCEDURES - Surgical and medical procedures - Other (medical device change)
VASCULAR DISORDERS - Hypertension; Thromboembolic event

Note: Cobimetinib (RO5514041, GDC0973) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

Product complaints: A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial. Please email any complaints related to the study agents to [redacted]

10.1 Vemurafenib (Zelboraf®) (RO5185426, PLX4032) (NSC#761431, IND EXEMPT)

Investigator Brochure Availability

The investigator brochure for Vemurafenib (Zelboraf®) (RO5185426, PLX4032) may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

Procurement

Vemurafenib will be provided by F. Hoffmann-LA Roche LTD and distributed by RxCrossroads by McKesson. Use the vemurafenib order form on the A071601 study page.

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation

Vemurafenib is available as 240 mg film coated tablets. Each vemurafenib tablet contains 240 mg vemurafenib and inactive ingredients include: Tablet core: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and hydroxypropyl cellulose. Coating: pinkish white: poly (vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red. Vemurafenib is available as bottles of 112 tablets.

Storage and stability

Store at room temperature 20ºC to 25 ºC (68 ºF to 77 ºF); excursions permitted between 15ºC and 30ºC (59ºF and 86ºF).

Administration

Vemurafenib is taken orally twice daily with or without food. Doses should be administered in the morning and evening, approximately 12 hours apart. If a dose of vemurafenib is missed, it can be taken up to 4 hours prior to the next scheduled dose. If vomiting occurs after a dose is taken, do not take an additional dose; continue with the next scheduled dose. Swallow tablets whole with a glass of water, do not crush or chew.

Drug Accountability

The NCI Investigational Agent Accountability Record Form for Oral Agents should be utilized.

Drug interactions

Vemurafenib is a substrate of CYP3A4 based on in vitro data; therefore, co-administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Avoid the co-administration of vemurafenib with strong CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or strong inducers (i.e. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) and replace these drugs with alternatives when possible.

Vemurafenib may increase concentrations of CYP1A2 substrates. Co-administration of tizanidine, a sensitive CYP1A2 substrate, increased tizanidine systemic exposure by 4.7-fold. Avoid the concomitant use of vemurafenib and CYP1A substrates with a narrow therapeutic window. If coadminstration cannot be avoided, monitor closely for toxicities and consider a dose reduction of CYP1A2 substrates.

Co-administration of vemurafenib with digoxin, a sensitive P-glycoprotein substrate, increased digoxin systemic exposure by 1.8-fold. Avoid the concurrent use of P-glycoprotein substrates

known to have narrow therapeutic indices. If use of these medications is unavoidable, consider a dose reduction of the P-glycoprotein substrate with narrow therapeutic indices.

Pharmacokinetics

Absorption: Bioavailability not determined.
Distribution: Vd ~ 106L. Plasma protein binding is > 99% to albumin and α1-acid glycoprotein.
Metabolism: Following oral administration of 960 mg of vemurafenib, mean data showed that vemurafenib and its metabolites represented 95% and 5% of the components in plasma over 48 hours respectively.
Half-life, elimination: 57 hours (range: 30 to 120 hours)
Time to peak: ~ 3 hours
Excretion: Feces ~94%, urine ~1%

Adverse events

See CAEPR in Section 9.5.1.

Nursing guidelines

- Instruct patients to take doses by mouth, approximately 12 hours apart in am and pm. Can be taken regardless of food intake. If patient misses a dose by more than 4 hours, do not make up that dose. Swallow whole, do not crush or chew.
- Instruct patient to report any rash, which is common. Patients that have rash and/or blisters accompanied by fever and/or oral or anogenital lesions, should be seen emergently to rule out Steven's Johnson Syndrome.
- Diarrhea and nausea are common. Treat symptomatically and monitor for effectiveness.
- Photosensitivity is common and can be quite severe with blistering burns, with little sun exposure. Instruct patients to photo protect with sunscreen, protective clothing, and avoidance of intense sun exposure.
- Warn patients of possibility of secondary skin cancers. Instruct patients to report any new lesions to study team immediately.
- Warn patient of possible alopecia.
- Monitor LFT's, especially in combination therapy.
- Agent may cause arthralgias. Treat symptomatically and monitor for effectiveness.
- Hand-foot syndrome has been seen. Instruct patients to report any pain and/or redness, thickening of skin and/or skin peeling of hands or feet to the study team.
- Agent causes QTc prolongation. Instruct patients to discuss any new medications with the study team, prior to starting such agents.
- Agent can cause peripheral edema.
- Rarely ocular toxicity can occur including retinitis, uveitis, and retinal vein occlusion. Instruct patients to report any vision changes and/or eye pain to the study team.

10.2 Cobimetinib (Cotellic®) (RO5514041) (NSC#781257, IND EXEMPT)

Investigator Brochure Availability

The investigator brochure for Cobimetinib (Cotellic®) (RO5514041) may be obtained by contacting the Alliance Central Protocol Operations Program office at [redacted]

Procurement

Cobimetinib will be provided by F. Hoffmann-LA Roche LTD and distributed by RxCrossroads by McKesson. Use the cobimetinib order form on the A071601 study page.

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

At the end of the trial, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation

Cobimetinib is available as 20 mg film coated tablets. Each cobimetinib tablet contains 22 mg cobimetinib fumerate (which corresponds to 20 mg of the cobimetinib free base) and the following inactive ingredients: Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate. Coating: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc. Cobimetinib is available as bottles of 63 tablets.

Storage and stability

Store at room temperature at 59°F−77°F (15°C−25°C).

Administration

Cobimetinib is taken orally once daily Days 1 through 21 of a 28-day cycle with or without food. If a dose of cobimetinib is missed (i.e., 6 hours or more late for cobimetinib), do not make up that dose; resume dosing with the next scheduled dose.

Drug Accountability

The NCI Investigational Agent Accountability Record Form for Oral Agents should be utilized.

Drug interactions

Coadministration of cobimetinib with itraconazole (a strong CYP3A4 inhibitor) increased cobimetinib systemic exposure by 6.7-fold. Avoid concurrent use of cobimetinib and strong or moderate CYP3A inhibitors.

Coadministration of cobimetinib with a strong CYP3A inducer may decrease cobimetinib systemic exposure by more than 80% and reduce its efficacy. Avoid concurrent use of cobimetinib and strong or moderate CYP3A4 inducers including but not limited to carbamazepine, efavirenz, phenytoin, rifampin, and St. John's wort.

Pharmacokinetics

Absorption: Bioavailability was 46% (90 CI 40-53%) in healthy subjects. A high-fat meal had no effect on cobimetinib AUC and Cmax after a single 20 mg cobimetinib dose in healthy subjects.
Distribution: 95% bound to human plasma proteins. Vd 806 L.
Metabolism: CYP3A oxidation and UGT2B7 glucuronidation.
Half-life, elimination: 44 hours (range 23-70).
Time to peak: Median time to Tmax 2.4 (range 1-24) hours.
Excretion: Feces (76%; ~7 as unchanged drug); Urine (~18%; ~2% as unchanged drug)

Adverse events

See CAEPR in Section 9.5.2.

Nursing guidelines

- Agent can cause decreased LVEF function. Instruct patients to report any lower extremity swelling, shortness of breath, and/or chest pain to study team.
- Diarrhea and other gastrointestinal side effects are common. Treat symptomatically and monitor for effectiveness of intervention.
- Rash is common and is usually acneiform in nature. Instruct patient to report any rash immediately.
- Cytopenias can be seen. Monitor CBC w/diff closely. Instruct patient to report any signs or symptoms of infection and/or unusual bruising or bleeding to the study team.
- Bleeding including serious and/or fatal hemorrhage can be seen. Instruct patient to report any bleeding to study team.
- Monitor LFT's.
- Rarely interstitial lung disease can be seen. Instruct patient to report any cough, dyspnea to the study team.
- Rhabdomyolysis is a rare but serious side effect of this agent. Instruct patients to report any weakness, muscle pain, or just feelings or unwellness to the study team immediately.
- Instruct patient that it is important to only take agent on days 1-21 of the cycle. If any days in the 21 days are missed, they should not be made up and patients should cease taking agent on day 21.
- Rarely ocular complications can occur, including chorioretinopathy, retinal detachment and other visual disturbances. Instruct patients to report any visual disturbances and/or eye pain to the study team immediately.
- In combination with vemurafenib, patients may experience pyrexia. Instruct patients to report any fever or chills to the study team.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the criteria specified below. Volumetric criteria by central radiology review will be used for assessment of the primary endpoint. Bidimensional area will be used locally for making about whether to proceed with treatment as per modified RANO guidelines[23].

Imaging consistency monitoring rule: After 10 enrollments to the study, central imaging review will be performed to evaluate for discordance between local imaging review and central imaging review. See Section 13.5.3 for details.

11.1 Schedule of evaluations:

For the purposes of this study, patients should be reevaluated with MRI every 2 cycles. See Section 5.0 for further details. Supporting documentation should be submitted as per Section 6.1.1 and images submitted as per Section 6.3.

11.2 Definitions of measurable and non-measurable disease

11.2.1 Measurable disease

Bidimensionally measurable lesions with clearly defined margins by MRI scans, with a minimum diameter of 10mm in both dimensions. Necrosis or cystic changes (nonenhancing disease) should be measured separately from and summed with contrast enhancing disease for measurements of tumor area.

11.2.2 Non-measurable disease

Unidimensionally measurable lesions, masses with margins not clearly defined.

11.3 Guidelines for evaluation of measurable disease

11.3.1 Measurement methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.

11.3.2 Acceptable modalities for measurable disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. CT slice thickness of > 5 mm is not allowed. CT should ONLY be used for patients unable to undergo MR imaging because of non-compatible device or life-threatening gadolium allergy.

  MRI should be acquired as outlined in Appendix II. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

11.3.3 Measurement at follow-up evaluation:

- A subsequent scan must be obtained 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR) for confirmation of response.
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.4.5).

11.4 Measurement of treatment/intervention effect

11.4.1 Measurable lesions

Bidimensionally enhancing measurable lesions with clearly defined margins by MRI or CT scan. Necrosis or cystic changes (nonenhancing disease) should be measured separately from and summed with contrast enhancing disease for measurements of tumor area (unlike with glial tumors under RANO, given a different significance in craniopharyngioma).

A maximum of 1 target lesion should be followed.

11.4.2 Non-measurable lesions

Non-measurable sites of disease (Section 11.2.2) should also be recorded at baseline. These lesions should be followed in accord with Section 11.4.5.1.

11.4.3 Target Lesions

Measurable lesions should be identified as target lesions and recorded and measured (sum of the products of the perpendicular diameters) at baseline. As compared to traditional RANO, target lesions will encompass both enhancing and cystic components of the tumor as the area of these lesions will be combined to summate the entire tumor area. Target lesion components should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repeated measurements by imaging techniques.

11.4.4 Non-Target Lesions

For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered non-target lesions and should also be recorded. Rarely, unequivocal progression of a non-target lesion requiring discontinuation of therapy, or development of a new contrast-enhancing lesion may occur even in the setting of stable disease (SD) or partial response (PR) in the target lesions. These changes would qualify as progression. Non-target lesions also include measurable lesions that exceed the maximum number of 5. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

11.4.5 Response criteria

11.4.5.1 All measurable lesions followed by CT/MRI must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring measurable lesions.

Note: Non-measurable lesions should be evaluated at each assessment, especially in the case of first response or confirmation of response.

11.4.5.2 Evaluation of measurable lesions for local radiology review

- **Complete response (CR):** All of the following must be true:

  Disappearance of all measureable lesions on consecutive MRI or CT 4 weeks apart. No new lesions. No evidence of non-measurable disease. Lesions must be assessed using the same techniques at baseline. If Appendix II is not followed, imaging should continue per baseline acquisition parameters. Neurologically/clinically stable or improved. No corticosteroids for vasogenic edema.

- **Partial response (PR):**

  ≥ 50% decrease under baseline in the sum of products of perpendicular diameters all enhancing, necrotic and cystic measurable components. No progression of nonmeasurable disease. No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. If Appendix II is not followed, imaging should continue per baseline acquisition parameters. Neurologically/clinically stable or improved. Stable or reduced corticosteroid dose for vasogenic edema.

- **Progression (PD):** At least one of the following must be true:

  > 25% increase in the sum of products of all measurable lesion components (including enhancing, necrotic and cystic components) over smallest sum observed (over baseline if no decrease) using the same techniques as baseline. OR clear worsening of any nonmeasurable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer)

  >25% increase in the sum of products of all measurable lesion components (including enhancing, necrotic and cystic components) but < 50% increase in the sum of products of all measurable lesion components (including enhancing, necrotic and cystic components) AND no new lesions/sites in scans obtained AND no clear clinical deterioration: When all of these conditions are met, the patient may continue on drug for 4 weeks. Imaging must be repeated 4 weeks later

(+/- 7 days). If imaging at 4 weeks shows continued growth of greater than 25%, then patient has definitive progression and date of progression should be back dated to the first MRI where there was a >25% increase.

- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD. Stable clinically

11.4.5.3 Evaluation of non-measurable lesions for local review

- **Complete response (CR):** Disappearance of all non-measurable lesions.
- **Stable disease (SD):** Persistence of one or more non-measurable lesions.
- **Progression (PD):** Unequivocal progression of existing non-measurable lesions (NOTE: Unequivocal progression should not normally trump measurable lesion. It must be representative of overall disease status change.)

11.4.5.4 Evaluation of measurable lesions for central radiology review

Criteria for central radiology review is based on volumetric criteria that has been used in other brain tumors, including benign brain tumors[24-26].

- **Complete response (CR):** All of the following must be true:

  Disappearance of all measurable lesions on consecutive magnetic resonance imaging (MRI) or CT 4 weeks apart. No new lesions. No evidence of non-measurable disease. Lesions must be assessed using the same techniques at baseline. Neurologically/clinically stable or improved

- **Partial response (PR):**

  ≥20% decrease under baseline in the volume of all measurable lesions. No progression of nonmeasurable disease. No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline. Neurologically/clinically stable or improved

- **Progression (PD):** At least one of the following must be true:

  > 20% increase in the volume of all measurable lesions using the same techniques as baseline, OR clear worsening of any nonmeasurable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer)

- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD. Stable clinically

11.4.5.5 Evaluation of non-measurable lesions for central radiology review

- **Complete response (CR):** Disappearance of all non-measurable lesions.
- **Non-CR/Non-PD:** Persistence of one or more non-measurable lesions.
- **Progression (PD):** Unequivocal progression of existing non-measurable lesions (NOTE: Unequivocal progression should not normally trump measurable lesion. It must be representative of overall disease status change.)

11.4.5.6 Evaluation of volumetric vs. two-dimensional tumor measurements

A correlation between volumetric and two-dimensional tumor measurements and their relative changes with relevant patient outcomes will be made through central radiology review, in order to determine whether there exist any advantages in volumetric tumor measurements over two-dimensional tumor measurements.

11.4.6 Overall objective status

The overall objective status for an evaluation is determined by combining the patient's status on measurable and nonmeasurable disease, and new disease as defined in the following tables:

For Patients with Measurable Disease

Summary of the Modified RANO Response Criteria Table

	CR	PR	SD	PD[1]
Target Lesion (Sum of Products of Enhancing, Necrotic, and Cystic Measureable Components)	None	≥ 50% decrease	< 50% decrease to < 25% increase	≥ 25% increase*
Non-target Lesion Sites	Stable or decrease	Stable or decrease	Stable or decrease	Increase*[1]
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worsened*
Requirement for Response	All	All	All	Any*

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
* Progression occurs when any of the criteria with * are present
1 This is considered PD if the increase in a nontarget lesion is felt likely to represent tumor progression.
NA – Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

11.4.7 Symptomatic neurologic deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Worsening of neurologic examination.
- Worsening of tumor-related and/or neurologic symptoms.
- Decline in performance status of >1 level on ECOG scale.
- Increase in seizure frequency or severity lasting > 14 days

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD will continue on therapy as outlined below:

- Cohort A: Patients can continue on therapy for a total of 4 cycles in cohort A, and then go on to receive radiation, surgery or both as outlined in Section 7.1.1. In special circumstances, continuation of therapy with vemurafenib and cobimetinib may be granted, but only with approval from the radiation oncology chair (see Section 7.1.1 for additional details). If continuation is approved, then therapy with cobimetinib and vemurafenib can continue until documented progression, unacceptable adverse events, or drug hold >28 days.
- Cohort B: Patients can continue therapy with cobimetinib and vemurafenib until documented progression, unacceptable adverse events, or drug hold >28 days (see Section 7.1.2). After treatment is completed or discontinued, patients will be followed per the study calendar in **Section 5.0**.

12.1.2 Disease progression: Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.1.3 Discontinuation of study agent: If the patient discontinues protocol therapy due to reasons other than PD (i.e. for unacceptable adverse events, drug hold >28 days), prior to the completion of planned therapy as per Section 7.0, patients should go on to clinical and survival follow up per the study calendar (Section 5.0). This includes:

- Patients who discontinue treatment before the end of 4 cycles of treatment to begin alternative therapy.
- Patients who discontinue continued treatment with vemurafenib and cobimetinib to begin alternative therapy (i.e. patients on Cohorts A or B who choose to continue therapy with vemurafenib and cobimetinib post the initial 4 cycles).

12.1.4 Discontinuation of study agent in patients with expected AEs: See Section 8.2.4 for more information.

12.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

12.3 Extraordinary medical circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study design

This is a prospective, single-arm phase 2 study evaluating the efficacy of BRAF and MEK inhibitor combination in patients with papillary craniopharyngiomas. The primary endpoint of response rate (RR) while being treated with BRAF and MEK inhibitors will be evaluated in two cohorts, separately, i.e., newly diagnosed patients (untreated cohort) and patients who have progressed after prior radiation treatment with or without surgical resection (recurrent cohort). The statistical design is the same for each cohort. Simon's two-stage design with one interim analysis for futility will be applied to evaluate RR within each cohort. The accrual will not be halted at the interim analysis unless the accrual is too rapid.

13.2 Statistical design and analysis for the primary endpoint

13.2.1 Primary endpoints

The primary end point is response rate (RR), defined as the number of responses achieved during treatment with BRAF and MEK inhibitors divided by the total number of evaluable patients. For the recurrent cohort, only responses achieved during the first four cycles of treatment with BRAF and MEK inhibitors will count toward the primary endpoint. A patient will be deemed to have a response if CR or PR measured by central radiologic review (see Section 11.4.5.4 and 11.4.5.5) is achieved. Contrast-enhanced magnetic resonance imaging (MRI) or CT will be performed every 2 cycles with volumetric assessment.

13.2.2 Statistical design

Simon's two-stage design with one interim analysis for futility will be applied to evaluate RR within each cohort. The decision rules are included in Section 13.2.3. Each cohort will require 16 evaluable patients. For the entire study, a total of 32 evaluable patients are required. Within each cohort, a total of 16 evaluable patients provides 89% power to detect a true response rate of at least 30%, with a one-sided significance level of 0.041 against the null hypothesis of 5% response rate. The overall family-wised type I error rate is 0.08. The following table shows the study characteristics of the design within each cohort:

If the true success proportion is ...	**0.05**	**0.10**	**0.15**	**0.20**	**0.25**	**0.30**
then the probability of declaring that the regimen warrants further studies is ...	0.041	0.201	0.422	0.628	0.785	0.886
and the probability of stopping at stage 1 is ...	0.630	0.387	0.232	0.134	0.075	0.040

13.2.3 Analysis plan

Within each cohort, the interim and final efficacy analyses will be conducted after the 9th and 16th enrolled evaluable patient, respectively, is off treatment:

- Interim analysis decision rules: If there is at least one response observed, then the accrual will be continued to full accrual. Otherwise, the accrual will be terminated and conclude that the regimen does not warrant for further investigation.
- Final analysis decision rule: At the end of this trial, it will be concluded that the regimen warrants further investigation if at least 3 responses are observed.

In addition, point estimates will be generated for response rates within each cohort with corresponding 95% binomial confidence intervals (Duffy and Santner). There will be no formal comparison of rates among two cohorts

13.3 Sample size, accrual time and study duration

13.3.1 Sample size

The study design to be utilized is fully described in Section 13.1. There will be 16 evaluable patients assigned to each cohort (total of 32 evaluable patients). We anticipate accruing an additional 2 patients in each cohort to account for ineligible patients or cancellations. Thus the maximum target accrual is 36 in total. In the event that the additional accrual does not produce the required number of evaluable patients, we retain the option of continuing accrual until that goal is met.

13.3.2 Accrual rate and duration

This phase II study is designed to accrue 16 evaluable patients in each cohort, over approximately 2-4 years. There is little information available for what the precise accrual rate will be. However our goal is to accrue the 32 evaluable patients (with an anticipated maximum of 36 patients to get 32 evaluable) within 2-4 years.

13.3.3 Primary endpoint completion date for clinicaltrials.gov reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least six months after being taken off the study treatment.

13.4 Supplementary analysis plans

13.4.1 Secondary Endpoints

- **Progression free survival**: progression free survival (PFS) will be estimated using the C Kaplan-Meier method within each cohort. Median PFSs and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made among the cohorts.
- **Toxicity:** As per NCI CTCAE v 4.0, the term toxicity is defined as adverse events that are classified as possibly, probably, or definitely related to study treatment. Toxicities will be evaluated via the ordinal CTCAE standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by patient and treatment cohort will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of the analysis. No formal comparison will be made among the cohorts.
- **Response as defined by Enhancing Volume:** Response by Enhancing Volume will be estimated using Response Rate (RR) - where response rate is defined as the number of responses achieved during treatment with BRAF and MEK inhibitors divided by the total number of evaluable patients. For this endpoint, only decreasing volume in enhancing disease will count toward the criteria for response. The same thresholds for CR and PR as seen in Section 11.0 will be used. Point estimates will be generated for response rates within each cohort with corresponding 95% binomial confidence intervals (Duffy and Santner).
- **Response as defined by Non-Enhancing Volume:** Response by Non-Enhancing Volume will be estimated using Response Rate (RR) - where response rate is defined as the number of responses achieved during treatment with BRAF and MEK inhibitors divided by the total number of evaluable patients. For this endpoint, only decreasing volume in non-enhancing disease will count toward the criteria for response. The same thresholds for CR and PR as seen in Section 11.0 will be used.

Point estimates will be generated for response rates within each cohort with corresponding 95% binomial confidence intervals (Duffy and Santner).

- **Overall Survival:** overall survival (OS) will be estimated using the Kaplan-Meier method within each cohort. Median overall survivals and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made among the cohorts.
- **Duration of Response:** Duration of response is defined from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that progressive disease or death is documented. Only patients who have achieved a CR or PR will be included in this analysis. Patients who fail to return for evaluation or patients who are still alive and have not progressed at the time of analysis will be censored for progression at the time of the last tumor assessment. Duration of response will be estimated using the Kaplan-Meier method within each cohort. Median overall survivals and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made among the cohorts.

13.4.2 Exploratory Endpoints

All analyses listed below are for exploratory aims. No formal comparison will be made among the cohorts. All analyses will be purely descriptive. Detailed statistical analysis plan will be developed before any analyses.

- **Visual Field Analysis:** Standard reporting from visual field tests will be collected for analysis per Study calendar (Section 5.0) and Data submission requirements (Section 6.0). Key visual field parameters will be summarized at each evaluation time point. The changes in these key visual field parameters at different time points will be explored.
- **Pituitary Hormone Replacement Therapy:** Descriptive analyses will be used assess changes in pituitary hormone replacement over time in patients with papillary craniopharyngiomas who have received BRAF/MEK inhibitors
- **Time to Response:** Time to response will be estimated using the Kaplan-Meier method within each cohort. Median overall survivals and survival rates will be estimated with their 95% confidence intervals. No formal comparison will be made among the cohorts.
- **Toxicity Associated with Radiation:** As per NCI CTCAE v 4.0, the term toxicity is defined as adverse events that are classified as possibly, probably, or definitely related to study treatment. Toxicities will be evaluated via the ordinal CTCAE standard toxicity grading. Overall toxicity associated with radiation incidence as well as radiation toxicity profiles by patient and treatment cohort will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of the analysis. No formal comparison will be made among the cohorts.

13.5 Monitoring the study

13.5.1 Adverse event stopping rule

The stopping rule specified below is based on the current knowledge available. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under

investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

The AE stopping boundaries are defined as follows: at any time, if we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") within each cohort that satisfy the following criteria:

- if 2 or more patients in the first 10 treated patients (or 20% of all patients after 10 are accrued) experience a grade 4 or higher adverse event that excludes the following:
    - Hematologic Events
    - Any Asymptomatic Metabolic/Laboratory Abnormalities (excluding high CPK)

In the event that the boundary for the Adverse Event Stopping rule is crossed, the study team will consult with CTEP to evaluate the safety risk for participants of the trial and determine if a temporary suspension of accrual is needed.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.5.2 Accrual monitoring stopping rule

The study design assumes that 1-2 patients will accrue per month to each cohort, leading to a 1 to 2 year total accrual period (including leading time for sites to open the studies). At 12 months, if the total accrual is below 25% of the expected (fewer than 8 patients) the study team will evaluate with the scientific question will be of interest at the completion of the accrual period. If it is deemed that the scientific question is likely not to have relevance at the end of the projected accrual period, the study may close. Otherwise, the study team will continue to boost the accrual rates. The accrual rate will be checked every subsequent 6 months and the likelihood that the study questions will still be of interest at the end of the trial will be evaluated and based on this, a decision will be made whether or not to continue accrual to the study.

13.5.3 Imaging concordance: image consistency monitoring rule

After the first 10 patients are enrolled across two arms (i.e., regardless of arm) and who have received at least one dose of BRAF and MEK inhibitors and contrast enhanced MRI performed per protocol, if one out of the first 10 patients, or if at any time after the first 10 patients are enrolled, 10% or more patients are deemed having progressive disease per local bidimensional assessment but are not confirmed by central review assessment, then the study team will review with CTEP regarding implementation of real time central review of imaging in the remaining patients.

13.6 Study reporting

13.6.1 This study will be monitored by the study team on a monthly basis upon enrollment of the first patient. Reports containing a summary of adverse events by treatment arm will be reviewed. The study team will also monitor the accrual rate.

13.6.2 This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting

data using the CDUS can be found on the CTEP Web site [redacted]

Note: This study has been assigned to CDUS-Abbreviated reporting, no adverse events (routine or expedited) is required to be reported via CDUS.

13.6.3 This study will be monitored by the Food and Drug Administration due to the Investigational New Drug (IND) status of the agent. An IND report will be produced and submitted to the Regulatory Affairs Manager within 60 days of the anniversary date that the IND went into effect**.**

13.6.4 Results reporting on Clinicaltrials.gov: At study activation, this study will have been registered within the "ClinicialTrails.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Descriptive factors

Age: >= 70 vs. < 70

ECOG PS: 0-1 vs. 2

13.8 Inclusion of women and minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18 % minorities. Based on national statistics involving similar meningiomas, we expect about 15 % of patients will be classified as minorities by race and about 60 % of patients will be women. Expected sizes of racial by gender subsets for patients to this study are shown in the following table. Note that these values are for the maximum number of patients (36) that we expect to accrue.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					0
Asian	1				1
Native Hawaiian or Other Pacific Islander		1			1
Black or African American	1	1	1		3
White	17	10	2	2	31
More Than One Race					
Total	19	12	3	2	36

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." Not Hispanic or Latino
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 1 substudy and all patients are encouraged to participate.

14.1 Identification of blood and tissue-based molecular biomarkers (A071601-ST1)

14.1.1 Background

Our goal is to identify blood and tissue-based molecular biomarkers of therapeutic response in patients with papillary craniopharyngioma tumors that are simultaneously treated with inhibitors of BRAF and MEK. Our group recently published a whole-exome and targeted sequencing study in craniopharyngiomas, where we identified recurrent BRAF mutations in papillary craniopharyngiomas and recurrent beta-catenin mutations in adamantinomatous craniopharyngiomas[27]. The vast majority of papillary craniopharyngioma cases (~95%) harbored the oncogenic BRAF V600E mutation. In the correlative analyses for this clinical trial we propose to perform several genome wide analyses on craniopharyngioma samples. If normal patient DNA is available, we will perform whole exome sequencing on these samples. If normal patient DNA in unavailable we will perform targeted sequencing that is limited to roughly 500 cancer-associated genes. Transcriptome analysis will be performed on all samples where there is sufficient tissue. Common mechanisms of resistance have been reported in other cancers treated with BRAF/MEK inhibition[28]. This data will help us to identify genetic biomarkers of response and of resistance. These studies could provide suggestions as to other therapies that might aid tumors that do not respond to BRAF and MEK inhibition. We will also perform pharmacodynamics studies prior to and after treatment using immunohistochemical analysis, to assess evidence of MAPK pathway activation pre- and post-treatment with vemurafenib + cobimetinib combination.

Furthermore, using an assay which has been well-validated in melanoma patients,[29] we recently detected circulating BRAF V600E mutation in the blood of a patient with a papillary craniopharyngioma. We hope to validate the utility of this test through analysis of blood collected in this trial. We will assess whether the circulating BRAF V600E assay can be used to predict which patients have a papillary craniopharyngioma (i.e. 'liquid

biopsy'), and whether the levels of circulating BRAF V600E correlates with response to therapy.

We also propose to perform either whole exome, transcriptome sequencing or targeted sequencing of 500 cancer associated genes on post-treatment resection samples – on either residual tissue samples that are resected following a successful initial course of treatment or on recurrence samples that regrow following termination of treatment or while on treatment. We hope to identify mechanisms of resistance in those samples.

We may also perform immunofluorescence characterization of tissue pre- and post-treatment using a range of markers to characterize cell cycle status, relevant cell signaling pathways, immune infiltrates and other possibly relevant markers as outlined below.

14.1.2 Methods

Whole exome sequencing and analyses

Whole exome sequencing will be performed following DNA fragmentation and purification and then library preparation with DNA barcoding. Read pairs will be aligned to the hg19 reference sequence and somatic variant calling will be performed within the Firehose environment and will be annotated to genes and compared to events in the Catalogue of Somatic Mutations in Cancer (COSMIC). Whole exome sequencing will allow us to determine: 1. If there are genetic markers that are associated with response or resistance to therapy and 2. To determine if treatment results in the evolution of a population of cells with a recurrent molecular genetic aberration that drives resistance.

Transcriptome analyses

Transcriptome sequencing will be performed using Illumina Tru Seq™ RNA Sample Preparation at the Broad Institute from FFPE tissue samples (fresh frozen tissue when available). This method uses oligo dT beads to select mRNA from the total RNA sample. The selected RNA is heat fragmented and randomly primed before cDNA synthesis from the RNA template. The resultant cDNA then goes through Illumina library prep (end repair, base 'A' addition, adapter ligation, and enrichment) using Broad designed indexed adapters for multiplexing. After enrichment, the samples will be qPCR quantified and equimolar pooled before proceeding to Illumina sequencing. RNA-seq analysis will be carried out using PRADA (Pipeline for RNA-Sequencing Data Analysis)[30]. Somatic variant, small deletions and insertion calling will be performed within the Firehose environment with the published caller algorithms[31-35]. Transcriptome sequencing will allow us to determine if there is expression of genetic markers that are associated with response or resistance to therapy.

Targeted sequencing and analyses

Targeted sequencing of over 500 cancer associated genes will be performed on DNA that has been fragmented and used for library preparation with DNA barcoding. Read pairs will be aligned to the hg19 reference sequence and somatic variant calling will be performed within the Firehose environment and will be annotated to genes and compared to events in the Catalogue of Somatic Mutations in Cancer (COSMIC).

Circulating DNA

A highly-sensitive blood-based BRAF V600E mutation assay will be used to detect the mutation from the blood of patients with craniopharyngiomas[29]. We used this assay to detect BRAF V600E from the blood of a patient with a papillary craniopharyngioma treated at our institution. This protocol starts with an RT-PCR reaction followed by digestions with TspR1, a restriction enzyme which preferentially digests the wild-type product but not the V600E mutated PCR product. A second, nested PCR using the digested material is carried

out. After a second digestion with TspR1, the product is then subjected to a real time PCR specific for the V600E mutation and not wild type sequences.

Histopathologic and immunohistochemical analysis

All samples available from this cohort will be classified by WHO tumor classification criteria for tumor type. We can then analyze the data for histologic correlates of response to therapy. In the first treated patient we have observed marked activation of foamy macrophages with engorgement of the fibrovascular cores and infiltration into the neoplastic epithelium of the tumor. We also observed marked sclerosis of the cores. In addition, papillary craniopharyngiomas typically have numerous neutrophils scattered throughout the tumor epithelium, but these were noticeably absent from the treated tumor. We will assess post-resection tumors for these features. These H&E based assessments would then be corroborated by multiplexed immunofluorescence for T and B cells, macrophages and neutrophils (CD45/LCA, CD3, CD4, CD8, CD11b, CD20, CD68, IBA1, FOXP3, PD1, PD-L1, anti-neutrophil). We will also stain samples with an antibody that recognizes BRAF V600E mutant protein as well as characterizing the expression of cell cycle markers (Ki67, PCNA and phospho-histone H3) as well as signaling markers (pERK, pAKT and mTOR signaling markers). This work will be multiplexed and performed on one or two slides.

14.1.3 Statistical considerations

Due to small sample size, the primary objective of the analysis of all of the molecular correlatives is hypothesis generation and any significant findings would require additional research, testing and validation in an independent cohort.

As data permits, analyses of biomarkers will be summarized by descriptive statistics, including mean (standard deviation), median (range), and proportion (percentage) overall and per responders vs. non-responders.. Biomarkers will be compared between responders and non-responders with parametric or nonparametric techniques when it is appropriate. The association between biomarkers and time-to-event outcomes (e.g., OS, PFS) will be evaluated by Cox proportional hazards model. If the sample size permits, multivariable regression (Logistic regression for response endpoint and Cox model for OS/PFS) will be used to explore the relationship between these biomarkers measured at baseline and outcomes after adjusting for relevant covariates. Multiple comparison correction will be applied when it is necessary.

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APPENDIX I: REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II: REQUIRED MRI ACQUISITION PARAMETERS

Craniopharyngiomas, predominantly suprasellar in location, are usually best imaged with an MRI protocol tailored to the sella turcica, i.e. with a focused, smaller field of view similar to that used for pituitary gland imaging. If craniopharyngiomas become very large and spread from the suprasellar cistern, larger field of view imaging may be required to image all of the tumor, however.

For the majority of craniopharyngiomas, an MRI protocol including sagittal and coronal T1-weighted imaging of the sella, both before and otherwise identically after IV gadolinium administration, should be performed. Slice thickness should be 3 mm or less and with no interslice gap. 3-dimensional volumetric T1-weighted imaging of the sella turcica may be performed at 3T magnetic field strength, however, which achieves thinner partition. That is to say, either 1.5T or 3T scanners may be used for this study, though it is recommended to perform all MR studies through time on a given patient on the same imaging platform.

However, volumetric (3-dimensional), isotropic post-gadolinium imaging is also a specific requirement for this study to facilitate volumetric measurements of residual enhancing tumor and tumoral cysts. This requirement can be met by volumetric imaging of the sella, especially if at 3T. If 2D imaging of the sella is performed, this requirement for volumetric imaging can be met instead by adding post-gadolinium whole-head IR-GRE imaging such as MPRAGE, IR-SPGR, BRAVO, 3D turbo field echo (TFE), or 3D fast field echo (3D Fast FE), depending on vendor and availability.

A summary of imaging requirements:

<u>Sella (smaller FOV, e.g. 16 cm; no interslice gap):</u>

- T1-weighted, sagittal, 3 mm or less
- T1-weighted, coronal, 3 mm or less
- T2-weighted, coronal, 3 mm or less
- T1-weighted, sagittal, 3 mm or less, post-gadolinium
- T1-weighted, coronal, 3 mm or less, post-gadolinium

Alternatively, especially at 3T, pre- and post-gadolinium T1-weighted imaging of the sella can be acquired 3-dimensionally, e.g. with a volumetric, isotropic, FSE/TSE T1-weighted series such as SPACE or CUBE, with primary acquisition suggested in the coronal plane, 1 mm or less partition, and with 1.5 mm reconstructions in the coronal and sagittal planes.

Note: Post-gadolinium T1-weighted imaging should be performed at least 4 minutes following the administration of IV gadolinium. Inserting a T2-weighted pulse sequence between the pre- and post-gadolinium T1-weighted series is commonly done to help achieve this.

<u>Whole brain:</u>

- T2-weighted or T2-weighted FLAIR, 5 mm or less
- MPRAGE post-gad of whole head *if and only if* post-gadolinium 3D sella imaging is not performed.

Recommended parameters for post-gadolinium IR-GRE, adapted from the B. Ellingson et al. consensus recommendations for brain tumor imaging in clinical trials (*Neuro-Oncology* 2015;17(9): 1188-1198), would include:

- Sequence: IR-GRE
- Plane: any
- Mode: 3D
- TR (ms): 2100 (if Siemens and Hitachi scanners) and 5-15 (if GE, Philips and Toshiba scanners)
- TE (ms): minimum
- TI (ms): 1100 (if Siemens and Hitachi scanners) and 400-450 (if GE, Philips and Toshiba scanners)
- Flip angle: 10-15 degrees
- Frequency: 256
- Phase: 256
- NEX: 1 or more
- FOV: 256 mm
- Slice thickness: 1 mm
- Gap/spacing: 0
- Parallel imaging: up to 2x
- Scan time (approx.): 5-8 minutes

Please remember that isotropic voxels are desired for 3D imaging. Note that for patient tolerability and for image quality reasons, total MRI scan time should not exceed 60 minutes.

APPENDIX III: COBIMETINIB MEDICATION DIARY

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **cobimetinib.**
2. You will take your dose of **cobimetinib once** daily for 21 days, then DO NOT TAKE for 7 days.
3. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If a dose is missed (you are 6 hours late for your daily timed dose), do not make up that dose; resume dosing with the next scheduled dose.
5. Tablets should not be crushed.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22	**BREAK**			
23				
24				
25				
26				
27				
28				

Patient's Signature	Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of tablets taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

APPENDIX IV: VEMURAFENIB MEDICATION DIARY

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take vemurafenib.
2. You will take your dose of **vemurafenib** twice daily.
3. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If a dose of vemurafenib is missed, it can be taken up to 4 hours prior to the next scheduled dose. If vomiting occurs after the tablets are taken, do not take more tablets.
5. Swallow tablets whole with a glass of water, do not crush or chew.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of AM dose	# of tablets taken	Time of PM dose	# of tablets taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
Patient's Signature					Date	

	Physician's Office will complete this section: 1. Date patient started protocol treatment _____ 2. Date patient was removed from study _____ 3. Total number of tablets taken this month (each size) _____ 4. Physician/Nurse/Data Manager's Signature _____		

APPENDIX V: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drugs, cobimetinib and vemurafenib. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Cobimetinib and vemurafenib interacts with a certain specific enzyme in your liver.

- The enzyme(s) in question is CYP3A4 and cobimetinib and vemurafenib is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.
- The enzyme(s) in question is CYP1A2 and vemurafenib blocks this enzyme and may be affected by other drugs that are broken down by this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Cobimetinib and vemurafenib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Cobimetinib and vemurafenib must be used very carefully with other medicines that use certain liver enzymes. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4, or "substrates" of CYP1A2.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD You are enrolled on a clinical trial using the experimental study drugs cobimetinib and vemurafenib. This clinical trial is sponsored by the NCI. Cobimetinib and vemurafenib may interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Cobimetinib and vemurafenib** interacts with a specific liver enzyme called CYP3A4 and CYP1A2**,** and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4 or substrates of CYP1A2 ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.