Official Title: **A PHASE IB, OPEN LABEL, DOSE-ESCALATION STUDY EVALUATING THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF VEMURAFENIB IN COMBINATION WITH GDC-0973 WHEN ADMINISTERED IN BRAF$_{V600E}$ MUTATION–POSITIVE PATIENTS PREVIOUSLY TREATED (BUT WITHOUT PRIOR EXPOSURE TO BRAF OR MEK INHIBITOR THERAPY) OR PREVIOUSLY UNTREATED FOR LOCALLY ADVANCED/UNRESECTABLE OR METASTIC MELANOMA OR THOSE WHO HAVE PROGRESSED AFTER TREATMENT WITH VEMURAFENIB**

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PROTOCOL AMENDMENT, VERSION L: RATIONALE

Protocol NO25395 has been amended primarily to update the safety information for the identified risks of rhabdomyolysis and CPK elevations and hemorrhage associated with cobimetinib.

Specific changes to the protocol are as follows:

- The Medical Monitor has been changed (global).
- It has been clarified that changes as of Protocol Amendment K also apply to future amendments (global).
- Information has been added to reflect rhabdomyolysis and CPK elevations (Section 1.3.7.4) and hemorrhage (Section 1.3.7.1), and gastrointestinal toxicity (Section 1.3.7.8) associated with cobimetinib.
- Risks associated with vemurafenib have been updated (Section 3.10.1)
- Section 3.10.2 has been updated to reflect standard cobimetinib safety language, including identified risks associated with cobimetinib (Section 3.10.2.1), potential risks associated with cobimetinib (Section 3.10.2.2), and other risks associated with cobimetinib (Section 3.10.2.3).
- Language regarding impaired female fertility and developmental toxicity was clarified (Section 3.10.2.2).
- Survival will be followed every 12 weeks until death (Sections 3.11, 5, and 5.7).
- A minor correction was made to Table 10 in Section 5.1.1.
- The dose modification table has been updated to add hemorrhage and update recommendations for rhabdomyolysis and CPK elevations (Table 12 in Section 6.1.1).
- Language around treatment and follow-up of adverse events was clarified (Section 7.1.2).
- The outdated pregnant partner data release form number has been removed (Section 7.2.2).

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION L:
SUMMARY OF CHANGES

Global Changes

The Medical Monitor has changed.

It has been clarified that changes as of Protocol Amendment K also apply to future amendments.

Protocol Synopsis

The synopsis has been updated to reflect the changes to the protocol.

Section 1.3.7.1: Hemmorhage

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, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III study GO28141, Grade 1–4 hemorrhagic events were reported in 13.0% of patients treated with cobimetinib plus vemurafenib and in 7.3% of patients treated with placebo plus vemurafenib. The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3–4 hemorrhage events were reported in 1.2% of patients who received cobimetinib plus vemurafenib and 0.8% of patients who received placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients who use concomitant medications that increase the risk of bleeding (including anti-platelet or anticoagulant therapy).

Instructions and dose modifications for hemorrhage events are included in Table 12, in Section 6.1.1.

Section 1.3.7.4: Rhabdomyoloysis and Increased CPK

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in post-marketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for dose modifications for elevated CPK and rhabdomyolysis are included in Table 12, in Section 6.1.1.

~~Section 1.3.7.5: Diarrhea~~

~~Diarrhea has been reported in all cobimetinib clinical studies in cancer patients. In the Phase I single agent study (MEK4592g), diarrhea of any grade was reported in 67.0% of patients, 6.1% of patients experienced Grade 3 diarrhea, and no Grade 4 or 5 events were reported as of the data cutoff date. Serious events of diarrhea were reported in 1.7% of patients. In the Phase III study (GO28141), diarrhea was the most common adverse event reported. Diarrhea events of all grades were reported in 56.7% of patients, and Grade 3 or 4 events were reported in 6.3% of patients treated with vemurafenib+cobimetinib. No Grade 5 events of diarrhea were reported as of the data cutoff date. Serious events of diarrhea were reported in 1.2% of patients treated with vemurafenib+cobimetinib.~~

~~In the majority of cases, diarrhea was effectively managed with antidiarrheal agents and supportive care. Any modification of study treatment for diarrhea should follow the guidelines in the protocol (Section 6.1).~~

~~Section 1.3.7.8: Creatine Phosphokinase Elevation~~

~~Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as in combination with other agents. In the Phase III study (GO28141), elevated CPK was reported as an adverse event more frequently in patients treated with vemurafenib+cobimetinib (29.9% all grades, 10.2% Grade≥3 events) than vemurafenib+placebo (3.3% all grades, 0.4% Grade≥3 events). No patients experienced Grade 5 events. Serious events were reported in 2 patients (0.8%) treated with vemurafenib+cobimetinib; in both cases the cobimetinib dose was reduced and the events resolved.~~

~~The vast majority of CPK elevations reported were asymptomatic, non serious, and resolved with or without study drug interruption. These events were not associated with rhabdomyolysis or myocardial injury.~~

~~Refer to Section **Error! Reference source not found.** for management of CPK elevation.~~

Section 1.3.7.8: Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult cancer patients.

In the Phase III study GO28141, diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in 59.9% of patients and Grade 3 or 4 events were reported in 6.5% of patients treated with cobimetinib plus vemurafenib versus 30.9% and 0.8%, respectively, in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported in 1.2% of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III Study GO28141, nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm (nausea 39.0% vs. 23.8%; vomiting 21.3% vs. 12.1%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea 0.8%, vomiting 1.2%).

In the Phase I single-agent study (MEK4592g), all grades of nausea and vomiting were both reported as 33.9% with 0.9% reported for Grade ≥3 nausea and none reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine antiemetic prophylaxis is not recommended.

Section 3.10.1: Risks Associated with Vemurafenib

Other safety events for vemurafenib used in monotherapy include new primary malignancies such as cutaneous malignancies, non-cutaneous squamous cell carcinoma, and other malignancies; tumor promotion in BRAF wild-type malignancies; hypersensitivity reactions; hepatotoxicity; ophthalmologic reactions; embryo-fetal toxicity; radiation sensitization and radiation recall; and renal failure.

Section 3.10.2.1: Identified Risks Associated with Cobimetinib

Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with Cotellic. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III study GO28141, Grade 1-4 hemorrhagic events were reported in 13.0% of patients treated with cobimetinib plus vemurafenib, and in 7.3% of patients treated with placebo plus vemurafenib. The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3-4 hemorrhage events were reported in 1.2% of patients receiving cobimetinib plus vemurafenib and 0.8% of patients receiving placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Instructions for Dose Modification for hemorrhage events are included in Table 12 in Section 6.1.1.

Rhabdomyolysis and CPK Elevations

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥ 3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥ 3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for Dose Modification for elevated CPK and rhabdomyolysis are included in Table 12 in Section 6.1.1.

Section 3.10.2.2: Potential Risks Associated with Cobimetinib

~~Increased CPK or Rhabdomyolysis~~

~~Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when combined with other agents. In the Phase III Study GO28141, CPK was evaluated at baseline and at regular intervals. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. While almost all elevations in CPK were asymptomatic laboratory findings, a clinical diagnosis of rhabdomyolysis was reported for 1 patient in each treatment arm in Study GO28141. In the patient who received cobimetinib and vemurafenib, CPK levels were>10×ULN (Grade 4). Thus, Grade 4 elevations in CPK levels may be associated with rhabdomyolysis, which has also been observed with other MEK inhibitors.~~

~~In the Phase III study, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (29.9% all grades, 12% Grade≥3 events) than with placebo plus vemurafenib (3.3% all grades, 0.4% Grade≥3 events). No patients experienced Grade 5 events. Serious adverse events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib; in both cases the cobimetinib dose was reduced and the events resolved. In the Phase I single-agent study (MEK4592g), 1 patient experienced a Grade 3 increase in CPK.~~

Impaired Female Fertility ~~and Developmental Toxicity~~

Heading change only.

Teratogenicity and Developmental Toxicitiy

Heading change only.

Section 3.10.2.3: Other Risks Associated with Cobimetinib

~~Hemorrhage~~

~~Hemorrhage events, including cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported in clinical studies of cobimetinib.~~

~~In the Phase III Study GO28141, hemorrhagic events were reported in 9.8% of patients treated with cobimetinib plus vemurafenib, and in 5.9% of patients treated with placebo plus vemurafenib. Events that were reported at frequencies>1% higher in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib were hematuria (2.0% vs. 0.8%, respectively) and cerebral hemorrhage (1.2% vs. 0%, respectively). The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3–4 hemorrhage events were reported in 1.2% of patients who received cobimetinib plus vemurafenib and 0.8% of patients who received placebo plus vemurafenib.~~

Section 3.11: End of Study

Upon study treatment discontinuation or withdrawal from study treatment, patients are required to continue the following assessments as indicated in the Schedule of Assessments:

- *A study completion visit will be performed 28 days after the last dose of study treatment for all patients.*
- *Survival will be collected via telephone calls and/or clinic visits every 12 weeks until death, weithdrawal of consent of loss to follow-up.*
-

All patients will be followed for survival information unless a patient requests to be withdrawn from follow up; this request must be documented in the patient's medical record and signed by the investigator. If the patient withdraws from study follow up, the study staff may use a public information source (such as county records) to obtain information about survival status only. Survival follow-up can be conducted via telephone.

~~A study completion visit will be performed 28 days after the last dose of study treatment for all patients. Patients will continue to be followed every 12 weeks until 6 months after last study treatment for survival. Survival follow up can be conducted via telephone.~~

Section 5: Schedule of Assessments

The schedule of assessments has been updated to reflect the changes to the text.

Table 10: Schedule of PK Sampling for Patients Previously Treated with Vemurafenib

Footnotes have been added to the table (correction).

Section 5.7: Patients who have Discontinued Study Drug

All patients who discontinue vemurafenib and cobimetinib or cobimetinib monotherapy treatments will be followed for survival. Survival status will be assessed every 12 weeks until ~~6 months after last study treatment,~~ withdrawal of consent, death, or loss to follow-up, whichever occurs first.

Section 6.1.1: Vemurafenib and Cobimetinib Dose Modification

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines

The table has been updated for hemorrhage and rhabdomyolysis/CPK elevaations.

Section 7.1.2: Treatment and Follow-up of Adverse Events

Unrelated severe or life-threatening adverse events: Follow until one of the following occurs:

- Resolved or improved to baseline

- Intensity (severity) improved to Grade 2 *or lower*

Section 7.2.2: Pregnancy

NOTE: The investigator should fill out a Pregnancy Reporting Form, [SRD-0115311], only if the pregnant partner has signed a Pregnant Partner Data Release Form, ~~[gcp_for000186]~~.

Sample Informed Consent Form

The sample informed consent form has been updated to reflect current safety information for cobimetinib.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IB, OPEN LABEL, DOSE-ESCALATION STUDY EVALUATING THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF VEMURAFENIB IN COMBINATION WITH GDC-0973 WHEN ADMINISTERED IN BRAF^{V600E} MUTATION-POSITIVE PATIENTS PREVIOUSLY TREATED (BUT WITHOUT PRIOR EXPOSURE TO BRAF OR MEK INHIBITOR THERAPY) OR PREVIOUSLY UNTREATED FOR LOCALLY ADVANCED/UNRESECTABLE OR METASTIC MELANOMA OR THOSE WHO HAVE PROGRESSED AFTER TREATMENT WITH VEMURAFENIB**
PROTOCOL NUMBER:	NO25395
VERSION NUMBER:	L
EUDRACT NUMBER:	Not applicable
IND NUMBER:	109307
TEST PRODUCT:	Vemurafenib (RO5185426) and cobimetinib (GDC-0973; RO5514041)
MEDICAL MONITOR:	[redacted] *M.D., Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB, OPEN-LABEL, DOSE-ESCALATION STUDY EVALUATING THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF VEMURAFENIB IN COMBINATION WITH GDC-0973 WHEN ADMINISTERED IN BRAF^{V600E} MUTATION–POSITIVE PATIENTS PREVIOUSLY TREATED (BUT WITHOUT PRIOR EXPOSURE TO BRAF OR MEK INHIBITOR THERAPY) OR PREVIOUSLY UNTREATED FOR LOCALLY-ADVANCED/UNRESECTABLE OR METASTATIC MELANOMA OR THOSE WHO HAVE PROGRESSED AFTER TREATMENT WITH VEMURAFENIB**
PROTOCOL NUMBER:	NO25395
VERSION NUMBER:	*L*
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IND NUMBER:	109307
TEST PRODUCT:	Vemurafenib (RO5185426) and cobimetinib (GDC-0973; RO5514041)
PHASE:	Ib
INDICATION:	BRAF^{V600E}-Positive Metastatic Melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES

PRIMARY OBJECTIVES

To evaluate the safety and tolerability of the vemurafenib and cobimetinib (GDC-0973/XL518) combination, and in doing so,

- To identify the dose-limiting toxicities (DLTs) that determine the maximum-tolerated dose of the vemurafenib and cobimetinib combination
- To identify a potential Phase II/III dose and schedule for the vemurafenib and cobimetinib combination
- To characterize Day 1 and steady-state pharmacokinetics of cobimetinib when administered in combination with vemurafenib and to characterize the steady-state pharmacokinetics of vemurafenib administered alone and in combination with cobimetinib

Secondary Objectives

- To assess the anti-tumor activity of the vemurafenib and cobimetinib combination
- To assess the mechanisms of response and resistance to vemurafenib and cobimetinib combination therapy (including genetic alterations of RAS, RAF, and MEK)
- To assess the BRAF^{V600E} mutation status of patients who progressed on vemurafenib monotherapy
- To identify factors that may pre-dispose patients to squamous cell carcinoma (SCC) development

- To assess the pharmacodynamic (PD) effects of vemurafenib and cobimetinib when administered in combination, as measured by changes in fluorodeoxyglucose–positron emission tomography (FDG-PET)
- To assess the PD effects of vemurafenib and cobimetinib when administered in combination, as measured by changes in molecular biomarkers in sequential paired biopsies
- To assess the PD utility of FDG-PET and changes in molecular biomarkers in sequential paired biopsies in a subset of patients (up to n=20) treated with single-agent cobimetinib

STUDY DESIGN

This is an open-label, multicenter, Phase Ib, dose-escalation study designed to assess the safety, tolerability, and pharmacokinetics of continuous daily oral dosing of vemurafenib administered in combination with orally dosed cobimetinib administered daily for 14 consecutive days followed by 14 days off (14/14), for 21 consecutive days followed by 7 days off (21/7), or as a continuous daily dose. Patients with previously untreated, $BRAF^{V600E}$ mutation-positive, locally advanced/unresectable or metastatic melanoma OR those who have progressed on vemurafenib monotherapy immediately prior to enrolling in this trial are eligible. Patients in the former category who were previously treated must have had no prior exposure to any BRAF or MEK inhibitor therapy. Treatment will continue until disease progression, unacceptable toxicity, or any other discontinuation criterion is met (Section 4.5). Vemurafenib will be dosed daily, and cobimetinib will be dosed on a 14/14, 21/7, or a continuous schedule in a 28-day cycle. Alternate dosing regimens and schedules may be interrogated depending on the nature and timing of the toxicities encountered.

There are 2 stages to this study: a dose-escalation stage and a cohort-expansion stage. During the dose-escalation stage, 10 dose-escalation cohorts of 3–6 patients each will be enrolled in order to identify a safe and tolerable dose of each agent to be administered during the cohort-expansion stage, i.e., the potential recommended Phase II/III dose combination. Approximately 20 additional patients will be enrolled into each of (minimally) two expansion cohorts during the cohort-expansion stage. One cohort will consist of patients who have progressed on vemurafenib monotherapy immediately prior to enrolling in this trial, and the other will consist of previously untreated or treated patients without prior exposure to any BRAF or MEK inhibitor therapy. Therefore, approximately 130 patients (not including patients treated with cobimetinib monotherapy) will be enrolled in the trial at approximately 7–10 sites in total in the United States and Australia.

For a small subset of patients who have progressed on vemurafenib monotherapy immediately prior to enrollment in this trial (up to 20), there is also an option for treatment with single-agent cobimetinib at 60 mg on a 21/7 schedule (see Section 3.1.2). The PD data obtained from this patient group will be reviewed with the vemurafenib plus cobimetinib combination PD data to enhance understanding of the combination PD data.

Participation in this cohort is limited to patients meeting one of the following criteria. Patients previously treated with vemurafenib at a dose of:

1. 480 mg twice daily (bid) due to tolerability issues at higher doses and who progressed at this dose prior to enrolling in this study
2. 720 mg or 960 mg bid vemurafenib for whom a treatment slot does not exist in the currently enrolling dose escalation cohort(s), and who are not able to wait for the next available cohort to open

Note: The total number of cobimetinib monotherapy patients who satisfy either criterion 1 or 2 above is limited to 20.

See Section 3.1.1 for details on dose escalation for all cohorts.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

- Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0
- Incidence and nature of DLTs
- Changes in vital signs, ECGs, and clinical laboratory results during the course of study (See Section 5.3).

PHARMACOKINETIC OUTCOME MEASURES

The goal of pharmacokinetic (PK) sampling is to describe vemurafenib and cobimetinib pharmacokinetics when given in combination and in comparison with historic controls when the agents were given as monotherapy. The relationship between vemurafenib and cobimetinib concentrations and anti-tumor activity will also be described.

Vemurafenib and cobimetinib PK parameters will be determined in all patients who receive study treatment using non-compartmental analysis and/or population methods.

For both vemurafenib and cobimetinib, the following PK parameters will be estimated:

- Total exposure ($AUC_{0\text{-last}}$)
- Maximal plasma concentration (C_{max})
- Minimal plasma concentration (C_{min})
- Other PK parameters may be determined after visual inspection of observed concentration–time data.

Pharmacodynamic Outcome Measures

- FDG-PET response rates based on modified definitions proposed by the European Organization for Research of Cancer and as assessed by an independent, blinded FDG-PET Image Reading Facility (As of Protocol Version K *and future amendments*, central collection of scans is no longer required.)
- Changes in effector molecules of the MAPK pathway that are directly or indirectly affected by BRAF and MEK inhibition (including but not limited to ERK and phosphorylated ERK and MEK) by immunohistochemistry using biopsies at baseline, between Days 10–14 of Cycle 1, and at disease progression (when available).

Efficacy Outcome Measures

- Objective response (OR)
- Progression-free survival
- Duration of response (DOR)
- Overall survival

SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial, in particular, the use of stringent inclusion and exclusion criteria (Sections 4.2 and 4.3) and close monitoring of patients as indicated below and in Section 3.10.4.

Because this is the first time vemurafenib and cobimetinib will be administered to humans in combination, all patients will be monitored closely for toxicity. All adverse events will be recorded during the trial and for up to 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever comes first. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in Section 3.10.

Safety monitoring by an independent Data Safety Monitoring Board has ceased following the results of the primary efficacy analysis of the Phase III study, GO28141. As with other vemurafenib studies, the risk for SCC will be mitigated by utilization of the Risk Management Plan (RMP) that is described in Section 5.3.4.6 of this protocol.

STUDY TREATMENT

Patients enrolled in a given cohort will receive vemurafenib and cobimetinib at a specified dose combination as described in Section 3. Vemurafenib will be dosed orally bid and cobimetinib will be dosed orally once daily. Study drug will be shipped in bulk to the study sites in bottles.

Patients in screening (written informed consent) for this study who were previously receiving 960 mg bid vemurafenib will be dose-reduced to 720 mg bid for 7–14 days prior to Cyle, 1 Day 1 in Cohorts 1, 1A, 2, 2A, or 1C. Patients receiving 960 mg bid vemurafenib prior to screening initiation (written informed consent) and assigned to Cohorts 1B, 1D, 3, 4, or 5 will continue receiving 960 mg bid vemurafenib, assuming this dose has been adequately tolerated prior to starting the study. Patients in screening (written

informed consent) for this study who are treatment naïve to vemurafenib at the time of consent will only start vemurafenib on Cycle 1, Day 1 once they are deemed eligible for enrollment.

Vemurafenib will be dosed daily, and cobimetinib will be dosed on a 14/14, a 21/7, or a continuous daily schedule in a 28-day cycle.

On study visit days, the daily doses of cobimetinib will be taken in the clinic after pre-dose assessments have been performed. After establishing patient eligibility for continued administration of study drugs, patients will be given a sufficient number of tablets and/or capsules to last until the next visit. In some cases, extra tablets and/or capsules may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., due to inclement weather or distance of patient's home from study center).

Cobimetinib should be taken at approximately the same time each day, preferably in the morning, and no later than 4 hours after the scheduled time. Each dose of cobimetinib should be taken with a glass of water.

For vemurafenib, patients will receive study medication bottles, each containing tablets that are 240 mg each. The number of tablets for the morning and evening dose will depend on the cohort assignment, with at least 8 hours between doses. Each dose of vemurafenib should be taken with a glass of water. As soon as feasible after signing informed consent, patients previously treated with vemurafenib should continue vemurafenib treatment with study drug provided expressly for this particular study and discontinue their supply of study drug from the antecedent vemurafenib study.

Both cobimetinib and vemurafenib will be taken at the same time in the morning.

On PK sample collection days, patients will be required to come into the clinic and have vemurafenib and cobimetinib administered as part of the scheduled study visit after pre-dose assessments have been performed. Vemurafenib and cobimetinib may be taken with or without food, including on PK sampling days.

Patients will be instructed as to the number and strength of the tablets and capsules to take according to their assigned dose cohort. The cobimetinib tablets and capsules should never be opened or chewed or opened; the vemurafenib tablets should never be chewed.

If a dose is missed (not taken within 4 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Patients will be asked to record the time and date they take each dose in a medication diary. Missed doses should be recorded in a patient diary. Patients will be instructed to bring all unused study medication and their medication diaries to each study visit for assessments of compliance.

The protocol requires a study evaluation to occur on Day 1 of every cycle but allows a period of ± 3 days. Patients on the 14/14 and 21/7 dosing schedule of cobimetinib are required to have the minimum number of days per cycle without cobimetinib dosing 14 and 7 days, respectively. Patients are still expected to return for PK blood draws according to the schedule outlined in Tables 10 and 11. For example, if a patient on a 21/7 cobimetinib dosing schedule has a study evaluation 2 days earlier than the nominal study day, the patient cannot restart cobimetinib until he/she has had at least 7 days without cobimetinib dosing.

Dose modifications, interruptions, and delays of vemurafenib and/or cobimetinib study treatment during and after the DLT assessment window should be made on the basis of the guidelines provided in Table 12 of the protocol. Recognizing that new knowledge will be acquired and unforeseen safety issues may arise in the course of the study, the guidelines are not exhaustive and do not represent the full spectrum of care or treatment options described. The dose modification guidelines are not intended to replace clinical judgment or dictate care of individual patients.

CONCOMITANT THERAPY AND CLINICAL PRACTICE

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient within 7 days before screening through the study completion visit. Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria (see Sections 4.2 and 4.3). Patients who experience toxicities may be treated symptomatically as clinically indicated. All concomitant medications should be recorded on the appropriate electronic Case Report Form.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and

anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drug.

Hematopoietic growth factors (e.g., erythropoietin and granulocyte colony-stimulating factors) and pain medications administered as dictated by standard practice are acceptable while the patient is enrolled in the study. However, growth factors should not be administered prophylactically before initial treatment with study drug; nor should they be used during the DLT observation period.

STATISTICAL METHODS

No statistical model will be used in the efficacy analysis and no formal hypothesis testing is planned. Descriptive statistics will be used to summarize the clinical activity, pharmacokinetics, and PD effect of vemurafenib and cobimetinib as described in the section on study objectives.

DLTs that occur in the first 28 days after initial dose of vemurafenib and cobimetinib will be used to determine the recommended dose. Subsequent DLTs will be reported and summarized as well.

The safety and efficacy (e.g., OR rate, DOR) will be presented by dose cohort in the dose-escalation stage and treatment group (patients previously treated with vemurafenib; patients previously untreated or treated [but without prior exposure to any BRAF or MEK inhibitor therapy] for locally advanced/unresectable or metastatic disease) in the dose-expansion stage. The final analysis will be performed on all patient data collected through the 28 days after last patient's last dose of study drug or at least 12 months after last patient in, whichever occurs later. Once all applicable patients complete 6 months SCC follow-up after end of treatment, an additional analysis will be performed to summarize any SCC findings per the RMP. From protocol amendment j forward, following cessation of study drug, surveillance of SCC should be performed in accordance with the local standard of care.

SAFETY DATA ANALYSES

The treated population is defined as all patients who receive any amount of study medication. All safety analyses will use the treated population. Patients who enroll in the dose-escalation stage who complete the DLT assessment window (Day 28) or experience a DLT in the assessment window and are withdrawn from study will be evaluable for determination of the recommended dose.

Safety will be assessed through summaries of DLTs, adverse events, changes in laboratory test results, changes in vital signs, and vemurafenib and cobimetinib exposures. Descriptive statistics will be used to summarize all safety data. Summary tables and listings will be presented by assigned dose cohort.

Adverse event data will be reported in listings and presented in frequency tables by MedDRA terms. All adverse events occurring on or after treatment on Cycle 1, Day 1 will be summarized. Summaries of adverse event by grade, seriousness, and relationship to study treatment will be presented, as well as summaries of adverse events leading to death or to premature withdrawal from study treatment. Serious adverse events, including deaths, will be listed separately and summarized.

Relevant laboratory and vital signs (temperature, heart rate and blood pressure) data will be presented using summary statistics.

Laboratory data will be presented as summary tables for worst toxicity grade compared with baseline using Standard Internationale units. Descriptive statistics will be used to summarize Eastern Cooperative Oncology Group performance status. Vital signs, ECGs, and ophthalmologic and dermatologic test results will be reported in the listings.

Exposure to study medication will be summarized by total duration of study medication, number of cycles started, and cumulative dose using descriptive statistics. Dose interruptions/modifications and their reasons will be presented.

PHARMACOKINETIC ANALYSES

Several PK parameters derived from the blood PK samples will be analyzed using descriptive statistics (means, standard deviations, coefficients of variation, median). They will include C_{max}, C_{min}, and AUC. Additional parameters such as apparent CL, volume of distribution, and $t_{1/2}$ will be estimated if the concentration data are sufficient.

Estimation of the PK parameters will be performed using standard non-compartmental methods. Actual sampling times will be used to calculate PK parameters.

Steady-state pharmacokinetics of vemurafenib and cobimetinib will be summarized descriptively. Relevant PK parameters will be correlated with dose, safety, or efficacy variables.

DETERMINATION OF SAMPLE SIZE

Design considerations were not made with regard to explicit power and type I errors but to obtain preliminary safety, PK, and PD information in this patient population. The number of patients expected to be treated with combination therapy in this two-stage study is approximately 130, assuming approximately 30–60 patients enroll in the dose-escalation stage, and at least 40 patients enroll in at least two expansion cohorts.

The sample size for this trial is based upon the dose-escalation rules described in Table 13, which describe the properties of the dose-escalation rules with different underlying rates of DLT.

Patients who withdraw from the study prior to completing the DLT assessment window for reasons other than DLTs will be replaced.

An expansion cohort of approximately 20 patients treated at the recommend dose will provide a reasonable chance (87.8%) of observing at least one or more adverse events when the true frequency of the adverse event is 10% at a given dose level. Table 14 provides probabilities of seeing at least one adverse event among 20 patients for probabilities ranging from 0.001 to 0.20 (i.e., adverse event frequencies of 0.1% to 20%). For example, if the true probability of an adverse event is 0.20 or greater, there is a more than a 98.8% chance of seeing at least one such event in an expansion cohort of 20 patients.

Preliminary evaluation of activity in the RAS/RAF-mutant population is an important study objective. With an expansion cohort of 20 patients RAS/RAF-mutant patients, if the true response rate is at least 20%, the chance of seeing at least one response is >98.8%.

GLOSSARY OF ABBREVIATIONS

14/14	14 days on/14 days off
21/7	21 days on/7 days off
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
AUC	area under the plasma concentration–time curve
BCC	basal cell carcinoma
bid	twice daily
BORR	best overall response rate
CL	clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentrations
CPK	creatine phosphokinase
CRC	colorectal cancer
CT	computed tomography
cuSCC	cutaneous squamous cell carcinoma
DDI	drug–drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data Safety Monitoring Board
EAP	expanded access protocol
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for Research of Cancer
ERK	extracellular signal-regulated kinase
FDG-PET	fluorodeoxyglucose–positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FNA	fine needle aspiration

GLOSSARY OF ABBREVIATIONS

IB	Investigator Brochure
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRF	Image Reading Facility
KA	keratoacanthoma
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MBP	micro-precipitated bulk powder
MedDRA	Medical Dictionary for Regulatory Affairs
MEKi	MEK inhibitor
MTD	maximal tolerated dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
OR	objective response
OS	overall survival
PD	pharmacodynamics
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic
pMEK	phosphorylation of MEK
PPI	proton-pump inhibitor
qd	once daily
RCR	Roche Clinical Repository

GLOSSARY OF ABBREVIATIONS

RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
RVO	retinal vein occlusion
SCC	squamous cell carcinoma
SD	stable disease
SNP	single nucleotide polymorphism
$t_{1/2}$	terminal half-life
TEN	toxic epidermal necrolysis
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Melanoma

Approximately 160,000 new cases of melanoma are diagnosed globally each year [1]. According to a World Health Organization (WHO) report, about 48,000 melanoma related deaths occur worldwide every year [2]. The highest incidence rates of melanoma occur in Australia and New Zealand where the annual incidence is more than double the highest rates recorded in Europe. In Australia, melanoma represents the fourth most common cancer among males and the third most common cancer among females. Currently, the lifetime risk for development of melanoma in Australia is now 1 in 14 for men and 1 in 24 for women [3, 4]. In the United States, it is estimated that over 68,000 new melanoma cases will be diagnosed and over 8,000 patients will die from the disease during 2009. Further, incidence rates for melanoma have increased sharply by approximately 6% per year in the United States since the 1970s.

There are a limited number of treatments available for metastatic melanoma, and the response to available treatments to date has been extremely poor.

1.2 Role of BRAF Kinase in Melanoma

Recent advances in the understanding of the biology of melanoma have resulted in identifying the role of BRAF kinase in melanoma. Mutated BRAF dimers constitutively activate the RAS-RAF pathway leading to the generation of transcriptional signalling that promotes tumor growth. BRAF mutations in melanoma have been identified in 50%–68% of metastatic melanomas, specifically melanomas that arise from intermittent sun-exposed skin (e.g., in superficial spreading and nodular melanomas) [5, 6, 7, 8]. BRAF mutations are uncommon in acral, mucosal, and uveal melanomas. At the same time, BRAF mutations are common in benign nevi, suggesting that BRAF mutations are an early event in melanoma oncogenesis. About 90% of the BRAF mutations seen in metastatic melanoma occur in codon V600 and over 90% of the V600 mutations are V600E (1799 T>A) [9]. Other uncommon variants, such as V600K, V600R, and V600D (in order of decreasing frequency), have also been identified, primarily in melanoma. Nonclinical data indicate that these variant mutations, like V600E, result in constitutive activation of the BRAF kinase. Most of the transforming activity of the $BRAF^{V600E}$ is thought to result through the constitutive activation of the mitogen-activated protein kinase (MAPK) pathway [10]. The therapeutic relevance of BRAF is supported by the demonstration that depletion of mRNA for oncogenic BRAF by siRNA leads to growth inhibition of melanoma cell lines in vitro [11, 12]. This has led to the development of agents that can inhibit BRAF kinase and tests to identify mutations [13, 14, 15].

The **cobas**® BRAF V600 mutation assay and Sanger Sequencing techniques have been utilized to identify $BRAF^{V600}$ mutation status in clinical trials.

1.2.1 Study Drug Vemurafenib (BRAF Inhibitor)

Vemurafenib (also known as RO5185426 and PLX4032) is a low molecular weight, orally available inhibitor of the oncogenic form of the BRAF serine-threonine kinase

commonly found in metastatic melanoma. It is a potent and highly selective inhibitor of V600E-mutant BRAF.

Vemurafenib is currently approved as a treatment for adult patients with unresectable or metastatic $BRAF^{V600}$ mutation–positive melanoma who have been diagnosed with the cobas® 4800 BRAF V600 Mutation Test in a number of countries worldwide, including the United States, Canada, members of the European Union, and numerous other countries worldwide.

1.2.2 Clinical Pharmacokinetics of Vemurafenib

Pharmacokinetic (PK) information is available for patients treated with 160 to 1120 mg twice daily (bid) of the optimized clinical formulation (also referred to as the micro-precipitated bulk powder [MBP] formulation). The MBP formulation has been provided as 40-mg capsules (dry granulation method), 80 mg capsules (wet granulation method), and 120-mg capsules (roller compaction method) in the PLX06-02 Phase I trial, a dose-escalation study in patients with metastatic melanoma.

The vemurafenib MBP formulations were developed to increase bioavailability. Dose-proportional increases were seen in exposure with the 40-, 80-, and 120-mg capsules, particularly from 240 to 960 mg bid. There were some patients who were high and low exposure outliers. The reason for this variability is currently unknown.

Steady-state exposure is expected to be reached by 15 days and mean steady-state levels of vemurafenib (area under the concentration–time curve [$AUC_{0–24h}$]) ranged from 428 µM·h to 1800 µM·h in the PLX06-02 Phase I trial. The 960 mg bid dose of vemurafenib achieved mean steady-state exposures of 90 µM and 1800 µM·h for maximum plasma concentration (C_{max}) and $AUC_{0\text{-}24h,}$ respectively. The mean effective half-life of vemurafenib across all dose cohorts was ~50 hours (range of 30–80 hours).

Mean steady-state vemurafenib exposures (C_{max} and $AUC_{0\text{-}8h}$) achieved with the to-be-marketed 240-mg tablet formulation in the Phase II study, NP22657 (n=60), were found to be 11% higher compared with the 120-mg capsule formulation (PLX06-02, n=30) in metastatic melanoma patients dosed with 960 mg bid.

Additional information can be obtained from the vemurafenib IB.

1.2.3 Clinical Safety of Vemurafenib

Vemurafenib clinical safety for the treatment of patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma has been derived mainly from the following studies:

- PLX06-02, Phase I: clinical cutoff: 3 June 2010.
    - Dose Escalation Phase: (patients with solid tumors); original formulation, n = 26, MBP formulation, n = 30.
    - Treatment Extension Phase: Metastatic melanoma patients, n = 32,
    - Treatment Extension Phase: Metastatic colorectal cancer (CRC) patients, n = 21.
- NP22657 (BRIM2), Phase II: clinical cutoff: 31 January, 2011; n = 132, Update: 1 February 2012

- NO25026 (BRIM3), Phase III: clinical cutoff: 1 March 2011; vemurafenib n = 337; dacarbazine (DTIC) n = 338. Update: 1 February 2012
- NP25163 Phase I clinical pharmacology study: clinical cutoff: 1 March 2011; updated clinical cutoff: 30 May 2013; n = 52.
- MO25515, post-approval safety study: interim analysis: February 2012, n = 2398.

In addition, the pharmacokinetics of the to-be-marketed (MBP) formulation have been evaluated in Phase I clinical pharmacology studies, including a CYP450 metabolism study (NP22676; n = 25), a study to evaluate the pharmacokinetics of the 240-mg MBP film-coated tablets (NP25163; n = 50), a mass balance study (NP25158; n = 7), and a food-effect study (NP25396; n = 40). Please refer to the vemurafenib IB for more detailed information.

1.2.3.1 *Adverse Events and Dose-Limiting Toxicities of Vemurafenib*

The Phase I Study PLX06-02 showed that vemurafenib was generally well tolerated in patients in the dose-escalation and melanoma-extension cohort at doses up to 960 mg bid. At the highest dose level tested, 1120 mg bid, 4 of 6 patients developed protocol-defined, non–life threatening, dose-limiting toxicities (DLTs; including Grade 3 rash with pruritus, fatigue, and arthralgia) that resolved with temporary drug interruption. All 4 patients were rechallenged at a lower dose and continued on treatment.

Table 1 provides a summary of adverse events reported in ≥ 10% of patients with metastatic melanoma (n = 62) who received the MBP formulation of vemurafenib in the dose-escalation and treatment-extension cohorts of Study PLX06-02.

Table 1 Study PLX06-02: Adverse Events Reported in Patients (≥10%) with Metastatic Melanoma[a]

System Organ Class Preferred Term	Overall AEs n (%)	Related [b] Any Grade n (%)	Any Relationship and Grade ≥ 3 n (%)	Related [b] and Grade ≥ 3 n (%)
Number of patients reporting AEs (n=62)[c]	**62 (100)**	**58 (93.5)**	**37 (59.7)**	**25 (40.3)**
Skin and subcutaneous tissue disorders	**52 (83.9)**	**52 (83.9)**	**6 (9.7)**	**6 (9.7)**
Rash	32 (51.6)	30 (48.4)	2 (3.2)	2 (3.2)
Photosensitivity	19 (30.6)	19 (30.6)	1 (1.6)	1 (1.6)
Pruritus	19 (30.6)	19 (30.6)	1 (1.6)	1 (1.6)
Alopecia	19 (30.6)	19 (30.6)	0	0
Palmar-plantar erythrodysaesthesia syndrome	9 (14.5)	9 (14.5)	2 (3.2)	2 (3.2)
Dry skin	10 (16.1)	10 (16.1)	0	0
Skin exfoliation	9 (14.5)	9 (14.5)	1 (1.6)	1 (1.6)
General disorders and administration site	**48 (77.4)**	**31 (50.0)**	**8 (12.9)**	**5 (8.1)**
Fatigue	31 (50.0)	20 (32.3)	4 (6.5)	4 (6.5)
Pyrexia	13 (21.0)	5 (8.1)	0	0
Edema peripheral	11 (17.7)	4 (6.5)	0	0
Musculoskeletal and connective tissue disorders	**41 (66.1)**	**33 (53.2)**	**6 (9.7)**	**4 (6.5)**
Arthralgia	28 (45.2)	26 (41.9)	2 (3.2)	2 (3.2)
Myalgia	11(17.7)	9 (14.5)	0	0
Pain in extremity	10 (16.1)	7 (11.3)	0	0
Gastrointestinal disorders	**35 (56.5)**	**24 (38.7)**	**3 (4.8)**	**1 (1.6)**
Nausea	23 (37.1)	16 (25.8)	1 (1.6)	1 (1.6)
Vomiting	14 (22.6)	7 (11.3)	0	0
Diarrhea	10 (16.1)	8 (12.9)	0	0
Constipation	12 (19.4)	3 (4.8)	0	0
Abdominal pain	8 (12.9)	2 (3.2)	1 (1.6)	0
Investigations	**32 (51.6)**	**20 (32.3)**	**6 (9.7)**	**5 (8.1)**
Alanine aminotransferase increased	8 (12.9)	8 (12.9)	2 (3.2)	2 (3.2)
Blood alkaline phosphatase increased	7 (11.3)	5 (8.1)	2 (3.2)	2 (3.2)
Aspartate amino transferase increased	7 (11.3)	6 (9.7)	1 (1.6)	1 (1.6)
Weight decreased	8(12.9)	3(4.8)	0	0
Metabolism and nutrition disorders	**34 (54.8)**	**18 (29.0)**	**6 (9.7)**	**3 (4.8)**
Anorexia	14 (22.6)	8 (12.9)	0	0
Hyperglycemia	13 (21.0)	4 (6.5)	1 (1.6)	1 (1.6)

[a] Includes 5 patients with solid tumors: thyroid cancer (n=3), rectal carcinoma (n=1), ovarian cancer (n=1).
[b] Considered possibly or probably related to study therapy.
[c] One patient initiated treatment with crystalline formulation and subsequently transitioned to the MBP formulation after completing six cycles.

Table 1 Study PLX06-02: Adverse Events Reported in Patients (≥10%) with Metastatic Melanoma[a] (cont.)

System Organ Class Preferred Term	Overall AEs n (%)	Related [b] Any Grade n (%)	Any Relationship and Grade ≥ 3 n (%)	Related [b] and Grade ≥ 3 n (%)
Nervous system disorders	**29 (46.8)**	**20 (32.3)**	**3 (4.8)**	**1 (1.6)**
Headache	13 (21.0)	8 (12.9)	1 (1.6)	0
Dysgeusia	7 (11.3)	7 (11.3)	0	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**25 (40.3)**	**17 (27.4)**	**16 (25.8)**	**15 (24.2)**
Squamous cell carcinoma	17 (27.4)	17 (27.4)	17 (27.4)	17 (27.4)
Injury, poisoning, and procedural complications	**17 (27.4)**	**10 (16.1)**	**1 (1.6)**	**1 (1.6)**
Sunburn	12 (19.4)	10 (16.1)	1 (1.6)	1 (1.6)
Respiratory, thoracic, and mediastinal disorders	**20 (32.3)**	**6 (9.7)**	**2 (3.2)**	**1 (1.6)**
Cough	7 (11.3)	3 (4.8)	0	0
Blood and lymphatic system disorders	**16 (25.8)**	**7 (11.3)**	**3 (4.8)**	**1 (1.6)**
Anemia	12 (19.4)	5 (8.1)	2 (3.2)	1 (1.6)

[a] Includes 5 patients with solid tumors: thyroid cancer (n=3), rectal carcinoma (n=1), ovarian cancer (n=1).
[b] Considered possibly or probably related to study therapy.
[c] One patient initiated treatment with crystalline formulation and subsequently transitioned to the MBP formulation after completing six cycles.

Forty-four percent of the 62 patients who received the MBP formulation in the dose-escalation and the melanoma-extension cohort had their vemurafenib dose interrupted and/or dose reduced as a result of adverse events that included a broad range of adverse events and laboratory abnormalities (i.e., ALT, AST, alkaline phosphatase [ALP], and γ-glutamyl transpeptidase [GGT]), the majority of which were Grade 3 in intensity and resolved with no sequelae.

Three of 62 (4.8%) patients discontinued treatment as a result of adverse events (pancreatitis, hyperbilirubinemia with edema of the lower extremities, nausea, seizures related to brain metastasis and hemorrhagic cerebellar brain metastasis). The last two adverse events were described by the investigator as unlikely to be related to treatment.

1.2.3.2 *Clinical Safety in Phase II Trial: NP22657 (BRIM-2)*

Study NP22657 (BRIM-2), an open-label, multicenter, Phase II trial of 132 previously treated patients who received vemurafenib for metastatic melanoma. All 132 (100%) patients had at least one adverse event (AE). Treatment-related AEs occurred in 130 (98%) patients. The majority of AEs were of mild or moderate intensity. The most commonly reported AEs (occurred in ≥ 30% of patients) were arthralgia (68%), fatigue (57%), rash (54%), photosensitivity reaction (52%), nausea (42%), alopecia (38%), pruritus (32%), diarrhea (32%), skin papilloma (31%), and hyperkeratosis (30%).

The percentage of patients in NP22657 (BRIM2) with at least one Grade ≥ 3 adverse event was 73%. The percentage of patients with at least one ≥ Grade 3 treatment-related AE was 61%. The most commonly reported treatment-related Grade ≥ 3 AEs (incidence ≥ 5%) were: squamous cell carcinoma (SCC) of skin (23%), serum GGT increase (9%), basal cell carcinoma (7%), rash (7%), maculopapular rash (6%), and arthralgia (6%).

1.2.3.3 *Clinical Safety in Phase III Trial: NO25026 (BRIM-3)*

The percentages of patients with at least one AE in the vemurafenib and DTIC treatment groups were 99% and 91%, respectively. The majority of AEs were of mild or moderate intensity. The most commonly reported AEs (occurred in ≥ 30% of patients) in the vemurafenib group were in the system organ class of skin and subcutaneous tissue disorders (vemurafenib 93% vs. DTIC 23%), the most common of which were alopecia, rash, and photosensitivity.

Other AEs that occurred in ≥10% of vemurafenib-treated patients and at an incidence more than twice that observed in the DTIC group included SCC of skin, skin papilloma, arthralgia, headache, dysgeusia, pyrexia, peripheral edema, pain in extremity, myalgia, decreased appetite, diarrhea, hyperkeratosis, seborrheic keratosis, and dry skin.

Among the 37 patients who switched from DTIC to vemurafenib, 32 patients (86%) had at least one AE, and 26 patients (70%) reported at least one treatment-related AE. The majority of AEs were of mild or moderate intensity.

Grade ≥ 3 Adverse Events

Fifty-nine percent of patients in the vemurafenib arm and 33% of patients in the DTIC arm experienced one or more adverse event ≥ Grade 3 in intensity. The percentage of vemurafenib-treated patients with cutaneous SCC and keratoacanthoma (KA) were 16% and 9%, respectively, compared with <1% and 0% for DTIC-treated patients (all cases of cutaneous squamous cell carcinoma [cuSCC] and KA were considered to be treatment related, Grade 3 intensity, and serious).

Other common Grade ≥ 3 AEs in the vemurafenib group included photosensitivity reaction (9%), rash (8%), maculopapular rash (8%), and arthralgia (4%); the corresponding frequency of these AEs in the DTIC group were 0%, 0%, 0%, and <1%.

Grade 4 Adverse Events

The overall incidence of Grade 4 AEs was lower in the vemurafenib group (13 patients [4%] with 14 AEs) than the dacarbazine group (22 patients [8%] with 27 AEs). Grade 4 AEs in the vemurafenib group included: pulmonary embolism (3 patients), increased GGT (2 patients), increased blood CPK, increased blood bilirubin, increased lipase, ageusia, intraventricular hemorrhage, pneumonia, pneumothorax, respiratory distress, neutropenia (all in one patient each). Five vemurafenib patients had a total of six Grade 4 AEs that were considered by the investigator to be related to treatment (increased blood bilirubin, GGT increased [two patients], ageusia, increased CPK, and neutropenia). One of the 37 crossover patients experienced a Grade 4 AE of

decreased neutrophil count after the date of crossover. It was judged by the investigator to be unrelated to treatment and non-serious.

Grade 5 Adverse Events

Grade 5 AEs were reported in 6 patients (2%) in the vemurafenib group at the time of the clinical cutoff (1 March 2011). Only one AE (intracranial tumor hemorrhage) was considered by the investigator to be treatment-related. Each of the other patients experienced the following Grade 5 AEs (all unrelated to study treatment): general physical health deterioration, cerebrovascular accident, pneumonia, aortic aneurysm rupture, and cardiac failure.

1.2.3.4 *Profile in Global Safety Study MO25515*

In the MO25515 post-approval safety study (February 2012), out of the 2207 patients who received at least 1 dose of vemurafenib, 1913 (87%) have reported AEs, 78% of which were related to vemurafenib, with 32% of these Grade 3 adverse events and 2% Grade 4 adverse events.

The most common adverse events (>10%) of any grade were arthralgia (31.2%), rash (26.2%), fatigue (20.7%), alopecia (16.9%), nausea (15.8%), photosensitivity reaction (11.3%), dry skin (11%), pruritus (10.6%), hyperkeratosis (10.5%), and headache (10%); adverse events were similar irrespective of presence or absence of brain metastases and Eastern Cooperative Oncology Group (ECOG) performance status. The most common grade 3/4 adverse events (≥1%) were rash (2.6%), arthralgia (2.5%), fatigue (1.5%), anaemia (1.0%), and cuSCC/KA (4.7%/3.3%). Of 1282 patients (58%) who discontinued treatment, most withdrew due to progressive disease (42.8%) or death (6.7%) but 5.1% withdrew due to adverse events (most commonly general physical deterioration). Adverse events resulted in treatment interruption in 512 patients (23.2%).

In a setting representative of routine clinical practice, vemurafenib is well tolerated for the treatment of BRAF V600–mutated metastatic melanoma, with a safety profile that resembles the safety profiles in the Phase I to III data.

1.2.3.5 *Deaths and Serious Adverse Events Associated with Vemurafenib*

Across all studies, the majority of reported deaths were attributed to progressive disease. In the pivotal, Phase III Study NO25026 (BRIM3), the percentage of patients who died was 19% in the vemurafenib group and 34% in the DTIC group. No patient died after crossing over from the DTIC group to the vemurafenib group as of the clinical cutoff date (1 March 2011). In Studies NP22657 (BRIM2) and NP25163, the percentages of patients who died were 39% and 25%, respectively.

Across the NO25026 (BRIM3), NP22657 (BRIM2), and NP25163 studies, the most commonly reported vemurafenib-related SAE was cuSCC.

In Study NO25026 (BRIM3), the percentage of patients who experienced one or more SAEs was 42% in the vemurafenib group and 18% in the DTIC group as of the clinical cutoff date. The percentage of patients who experienced one or more treatment-related SAEs was 31% and 5%, respectively. The most common treatment-related SAEs in the

vemurafenib group were cutaneous SCC (17%) and KA (9%). No other treatment-related SAE occurred in >1% of patients in either treatment group.

One notable treatment-related SAE occurred in a vemurafenib-treated patient after the 1 March, 2011 clinical cutoff date. This patient developed toxic epidermal necrolysis (TEN). The event improved slightly after the patient was given treatment but was not resolved at last report. The patient was discharged from the hospital and permanently discontinued treatment with vemurafenib.

In Study NP22657 (BRIM2), the percentage of patients who experienced one or more SAEs was 53%. The most common treatment-related SAEs included SCC of the skin (23%), basal cell carcinoma (7%), KA (3%), elevated LFTs (2%), rash (2%), pyrexia (2%), and arthralgia (2%).

In Study NP25163, the percentage of patients who experienced one or more SAEs was 33%. The most common treatment-related SAE was cutaneous SCC (19%). A single case of irreversible retinal vein occlusion (RVO) was reported [redacted] in a patient who received vemurafenib 960 mg bid.

1.2.4 Adverse Events of Special Interest for Vemurafenib

1.2.4.1 *Cutaneous Squamous Cell Carcinoma*

In Studies NO25026, NP22657, and NP25163, 79 (23.5%), 34 (25.8%), and 10 (19.2%) patients developed cuSCC/KA), respectively, and most cuSCC/KA cases were keratoacanthomas, 58/79 (73.4%), 30/34 (88.2%), and 19/19 (100%), respectively.

Although all events of cuSCC were to be reported per protocol as serious cuSCC events were generally treated with local excision and were not vemurafenib dose limiting. A risk management plan, including regular dermatological examinations, head and neck examinations, and chest computed tomography (CT) scans, has been established to monitor and treat SCC in patients who receive vemurafenib and during prolonged follow-up (see Section 5.3.4.6).

1.2.4.2 *Other Neoplasms*

1.2.4.2.1 *Non-Cutaneous Squamous Cell Carcinoma*

Rare cases of SCC of the head and neck have been reported in clinical trials where patients were treated with vemurafenib. One case in study NO25026 involved a patient who had a confirmed tonsilar SCC after receiving vemurafenib for >200 days. The patient had a 30 pack-year history of tobacco use. The patient's biopsy tested strongly positive for p16 by immunohistochemistry (IHC), but no evidence of a RAS mutation or epidermal growth factor receptor amplification or mutation was present.

A second case occurred in study NP25163 (PK/pharmacodynamics [PD] study). This patient had an invasive SCC of the tongue. He was previously treated for metastatic melanoma with ipilimumab, therapeutic vaccine (type not specified), and high–dose interleukin-2, prior to enrollment on NP25163. The patient had no known risk factors for head-and-neck SCC, and preliminary testing of the tumor was negative for the presence of human papilloma virus genome.

Patients in clinical trials will undergo monitoring including head and neck examination (which will consist of at least a visual inspection of oral mucosa and lymph node palpation), chest CT, and in relevant cases anal examinations and pelvic examinations (for women).

1.2.4.2.2 *Colonic Polyps*

Rare cases of adenomatous colonic polyps have been reported in patients treated with vemurafenib for 2 or more years while enrolled in a clinical trial. The clinical significance of colonic polyps is uncertain but physicians should be aware that they may occur in patients treated with vemurafenib.

1.2.4.2.3 *Progression of Cancers Associated with RAS Mutations*

Based on its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Reports of progression of NRAS-mutated chronic myelomonocytic leukemia [16] and KRAS-mutated pancreatic adenocarcinoma [17] have been published in peer-reviewed scientific journals. Vemurafenib should be used with caution in patients with a prior or concurrent cancer associated with RAS mutation. Full details are provided in the vemurafenib IB.

1.2.4.3 *QT Interval Prolongation*

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

Vemurafenib at 960 mg bid did not appear to have a clinically meaningful effect on heart rate and did not cause a meaningful change from the time-matched baseline in either the QRS or the PR (PQ) interval.

Two patients (1.5%) developed treatment-emergent absolute QTcP values >500 msec (CTC Grade 3), while 49 (37.1%) and 6 (4.5%) of patients exhibited QTcP values > 450 msec and > 480 msec, respectively. No patients had treatment-emergent QT (uncorrected) values > 500 msec. Maximal treatment-emergent individual QTcP changes from baseline of > 30 msec were observed in 58 (43.9%) patients, but only 1 patient (0.8%) exhibited a QTcP change from baseline of > 60 msec. Vemurafenib is associated with concentration-dependent QTc interval prolongation. In the first month of treatment, the largest mean change from baseline of 12.8 ms (upper boundary of the 2-sided 90% confidence interval of 14.9 ms) was observed at 2 hours post-dose on Day 15. In the first 6 months of treatment, the largest observed mean change from baseline of 15.1ms (upper boundary of the 2-sided 90% confidence interval of 17.7 ms) was detected at a pre-dose time point.

For a detailed summary of QTc interval prolongation among recipients of vemurafenib, see the vemurafenib IB.

1.2.4.4 *Liver Injury*

An analysis of liver–related adverse events reported with vemurafenib use showed that 63 cases (out of estimated exposure of approximately 20,000 patients) of medically confirmed serious adverse events were consistent with drug–induced liver injury based on clinical chemistry criteria from the Drug–Induced Liver Injury Expert Working Group

[20]. Of the 63 cases, 2 were assessed as severe, both reported as hepatic failure. There were no reported deaths among the 63 cases of liver injury; the outcomes of the 2 cases of severe liver injury were reported as completely resolved with vemurafenib discontinuation. 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, which suggested a trend towards cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

1.2.5 Other Adverse Events of Clinical Significance

1.2.5.1 *Drug Reaction with Eosinophilia and Systemic Symptoms*

As of 31 March 2013, 12 cases of drug reaction with eosinophilia and systemic symptoms syndrome have been observed with vemurafenib treatment, and no case was reported to result in death. The time to onset was 7 to 25 days. In the majority of patients (seven), vemurafenib was discontinued. Some patients (five) were treated with systemic steroids with corresponding improvement or resolution of symptoms. In addition, two patients with Grade 3 rash, who were treated with vemurafenib after ipilimumab, had biopsies that showed pathology consistent with drug hypersensitivity reaction [17]. Full details are provided in the vemurafenib IB.

1.2.5.2 *Neutropenia*

A review of the Roche safety database found neutropenia to be an uncommon (6 cases per 1000 person-years, 0.6%) adverse drug reaction associated with the use of vemurafenib, typically occurring during the first 6–12 weeks of treatment. It appeared to be reversible, usually within 2 weeks, with either temporary interruption, dose reduction, or discontinuation of vemurafenib, and in some cases was managed with granulocyte-colony stimulating factor.

1.2.5.3 *Pancreatitis*

Pancreatitis has been identified in patients being treated with vemurafenib. Seventeen cases of pancreatitis with no strong risk factors or alternative explanations have been reported. Eight of the 17 cases were assessed as likely associated with vemurafenib use based on event onset latency and re-challenge/de-challenge information. The clinical presentation including mild to moderate severity was consistent with the clinical picture of drug-induced pancreatitis [18].

1.2.5.4 *Panniculitis*

Twenty-six cases of medically confirmed panniculitis cases, out of an estimated 14,926 patients treated with vemurafenib, have been reported; 85% of the cases were assessed as causally associated with vemurafenib treatment. The majority of the cases are in females (n =21), and in most cases the latency was 10 to 20 days after the initial dose.

1.2.5.5 *Potentiation of Radiation Toxicity*

As of Q4 2014, an adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. This is based on 20 cases of radiation injuries, adjudicated as radiation recall (n=8) and radiation sensitization (n=12). The nature and severity of the events in all 20 cases were evaluated as worse than expected for the normal tissue

tolerance to therapeutic radiation with fatal outcome in 3 cases. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Full details are provided in the vemurafenib IB.

1.2.5.6 *Ipilimumab and Vemurafenib*

In a Phase I trial (CA 184161, sponsored by Bristol-Myers Squibb), asymptomatic Grade 3 increases in transaminases and bilirubin occurred with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID) [21]. All liver laboratory abnormalities were asymptomatic and reversible with permanent discontinuation of the study drugs or, in some cases, administration of corticosteroids. Based on these data, concurrent administration of ipilimumab and vemurafenib is not recommended outside of a clinical trial. Full details are provided in the vemurafenib IB.

1.2.6 Clinical Efficacy of Vemurafenib

Clinical efficacy data to support the use of vemurafenib for the treatment of patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma is primarily based on results from the following studies:

- PLX06-02, Phase I: clinical cutoff: 3 June 2010.
  - Dose escalation phase: (patients with solid tumors); original formulation, n=26, MBP formulation, n=30.
  - Treatment-extension phase: Metastatic melanoma patients, n=32,
  - Treatment-extension phase: Metastatic colorectal cancer patients, n=21.
- NP22657 (BRIM2), Phase II: clinical cutoff: 31 January 2011; n=132,
- NO25026 (BRIM3), Phase III: clinical cutoff: 31 March 2011; vemurafenib n=337; dacarbazine (DTIC) n=338.

In the Phase III Study NO25026 (BRIM3), after a median 6.21 months of follow-up in the vemurafenib arm, the Kaplan-Meier estimate of median survival among patients randomized to vemurafenib was not reached (95% CI: 9.59 months, not reached). Among patients randomized to dacarbazine, after a median 4.46 months of follow-up, the KM estimate of median survival was 7.89 months (95% CI: 7.26, 9.63 months). The Kaplan-Meier estimate of the 6-month survival rate among patients randomized to vemurafenib was 83% (95% CI: 79%, 87%) and among patients randomized to dacarbazine was 63% (95% CI: 57%, 69%). The hazard ratio for death was 0.44 (95% CI: 0.33, 0.59) in favor of vemurafenib. Treatment with vemurafenib demonstrated a clinically meaningful and statistically significant improvement in PFS compared with dacarbazine treatment ($p<0.0001$). There was a statistically significant improvement in BORR (confirmed) as assessed by the investigator with vemurafenib (48.4%; 95% CI: 41.6%, 55.2%) compared with dacarbazine (5.5%; 95% CI: 2.8%, 9.3%, $p <0.0001$).

In the Phase II Study, NP22657 (BRIM2), after a median duration of follow-up of 10.4 months, the primary endpoint of confirmed BORR was 53% (95% CI: 44.2%, 61.8%). Secondary endpoints of median response duration was

6.7 months (95% CI: 5.6, 9.8), median OS had not been reached (95% CI: 11.2, not reached). Median PFS was 6.8 months (95% CI: 5.6, 8.1).

In the Phase I Study, PLX06-02, patients in the melanoma extension cohort had a KM estimate of median survival of 384 days, median duration of response of 227 days (7.6 months), median PFS of 233 days (7.8 months), and a 1-year OS survival rate of 55%.

Table 2 summarizes the efficacy data across the 3 studies (NO25026, NP22657 and PLX06-02).

Table 2 Summary of Overall Survival by Study

	NO25026 [a]		NP22657 [b]	PLX06-02 [c]
	DTIC n = 338 (%)	Vemurafenib n = 337 (%)	Vemurafenib n = 132 (%)	Melanoma Ext n = 32 (%)
Patients included in analysis	338 (100)	337 (100)	132 (100)	32 (100)
Patients with event	121 (35.8)	78 (23.1)	52 (39.4)	22 (68.8)
Patients without event	217 (64.2)	259 (76.9)	80 (60.8)	10 (31.3)
Hazard ratio (unstratified)	0.44			
(95% CI)	(0.33, 0.59)		—	—
Time to event (months)		Not reached	Not reached	
Median (KM)	7.89	(9.59, not	(11.2, not	384 days
(95% CI)	(7.26, 9.63)	reached)	reached)	(318, 795 days)
6-month survival rate (KM)	63%	83%	77%	87%
(95% CI)	(57%, 69%)	(79%, 87%)	(70%, 85%)	(NA)
1-year survival rate (KM)				55%
(95% CI)	—	—	—	(NA)
Duration of follow-up Median				
(mos)	4.46	6.21	10.4	NA
Min–max	0.0–11.7	0.4–13.9	0.6 to 14.7	NA

DTIC = dacarbazine; KM = Kaplan-Meier estimate; NA=not available.

[a] Clinical cutoff: 31 March 2011.

[b] Clinical cutoff: 31 January 2011.

[c] Clinical cutoff: 3 June 2010.

For further details please refer to the Investigator's Brochure.

1.3 Role of MEK Kinase in Melanoma

The best characterized substrate of BRAF is MEK kinase. Phosphorylation of MEK (pMEK) by BRAF results in increased MEK catalytic activity. Cancer cells transformed by $BRAF^{V600E}$ are exceptionally sensitive to MEK inhibition in vitro. It has been reported that allosteric MEK inhibitors can result in G1 phase growth arrest in melanoma cells [24, 25, 26]. In vitro, MEK inhibitors reduce cell proliferation, soft agar colony formation, and matrigel invasion of $BRAF^{V600E}$-mutant melanoma cells and are also effective against $BRAF^{V600E}$ melanoma xenografts, suggesting a potentially important role for MEK inhibitors in melanoma and other tumors harboring the $BRAF^{V600E}$ mutation [25].

1.3.1 Study Drug Cobimetinib (MEK Inhibitor)

Cobimetinib (GDC-0973/XL518) is a potent and highly selective inhibitor of MEK1/2, a central component of the RAS/RAF pathway.

Cobimetinib in combination with vemurafenib is currently approved as a treatment for adult patients with unresectable or metastatic $BRAF^{V600}$ mutation–positive melanoma who have been diagnosed with the cobas® 4800 BRAF V600 Mutation Test in a number of countries worldwide, including the United States, Canada, members of the European Union, and several other countries worldwide.

1.3.2 Nonclinical Studies with Cobimetinib

Cobimetinib inhibits proliferation of a variety of human tumor cell lines by inhibiting MEK1 and MEK2. In addition, Cinhibits extracellular signal-regulated kinase (ERK) phosphorylation in xenograft tumor models (breast, lung, colon, and melanoma) and stimulates apoptosis. cobimetinib accumulates in tumor xenografts and remains at high concentrations in the tumor after plasma concentrations have declined. The activity of cobimetinib to inhibit ERK1 phosphorylation is more closely correlated with its concentrations in tumor tissue than in plasma; in general, there is a good correlation between reduced ERK1 phosphorylation and efficacy in tumor xenograft models. Tumor regression has been observed in several human tumor xenograft models. This tumor regression was dose dependent with up to 100% regression at the highest doses tested. The models studied included CRC, malignant melanoma, breast carcinoma, and anaplastic lung carcinoma.

1.3.3 Nonclinical Metabolism and Pharmacokinetics of Cobimetinib

The pharmacokinetics of cobimetinib were characterized in multiple species including mice, rats, dogs, and monkeys; clearance (CL) of drug from plasma was moderate and volume of distribution was moderate to high. Plasma protein binding of cobimetinib across nonclinical species ranged from 93% to 99%. Plasma protein binding in humans was 94.8% at 1 μM. The current understanding of cobimetinib with respect to pathways of elimination is limited, and metabolite identification studies are ongoing. Cobimetinib inhibits CYP2D6 and CYP3A4, with approximate IC50 values of 1.8 μM and 5.9 μM, respectively. Preliminary data suggest that cobimetinib is a substrate of CYP3A4; therefore, caution is recommended when administering cobimetinib with potent inhibitors or inducers of CYP3A4 or with drugs that are substrates of CYP2D6 or CYP3A4. Preliminary in silico assessment (SimCYP, Sheffied, United Kingdom) suggests that cobimetinib poses a low risk of causing a drug-drug interaction (DDI) or being subject to a DDI at doses up to 80 mg cobimetinib. Cobimetinib appears to be a substrate of P-glycoprotein (Pgp).

1.3.4 Nonclinical Safety of Cobimetinib

The nonclinical toxicity of cobimetinib was characterized in single- and repeat-dose general toxicity studies in rats and dogs, in vitro genotoxicity studies, and in cardiovascular, neurobehavioral, and respiratory safety pharmacology studies.

Key findings from the 7- or 28-day GLP toxicity studies in rats and dogs, as well as the 13-week study in rats and dogs, are summarized below and a more detailed description can be found in the cobimetinib (GDC-0973) IB.

Treatment-related findings in rats dosed daily at 3 mg/kg for 28 days were present only in the adrenal cortex, thymus, and bone marrow. All cobimetinib–associated microscopic changes appeared fully reversible (except in the mandibular lymph node). The mean

exposures in rats at STD10 of 3 mg/kg (Day 1) were 1.29 μM·hr and 0.735 μM·hr in female and male rats, respectively; on Day 28, the mean exposures at 3 mg/kg were 1.72 μM·hr and 0.940 μM·hr in female and male rats, respectively. In dogs, repeat-dose toxicity associated with cobimetinib treatment was observed only in the 7-day, repeat–dose range finding study at doses of ≥ 3 mg/kg administered daily for up to 7 days and included findings suggestive of liver toxicity (increased ALT, AST, and alkaline phosphatase [ALP] values), gastrointestinal tract toxicity (macroscopic tissue discoloration), lymphoid tissue toxicity (decreased lymphocyte counts), and dehydration (increased RBC, hemoglobin, HCT, and BUN values).

No significant toxicities were observed in a 28-day, repeat-dose toxicity study in dogs at doses up to 1 mg/kg. In the definitive 28-day, repeat-dose toxicity studies of cobimetinib in rats and dogs, the no observed adverse effect level (NOAEL) in each species was determined to be 1 mg/kg once daily (qd). The mean exposures in dogs at 1 mg/kg (Day 1) were 4.02 μM·hr and 5.89 μM·hr in female and male dogs, respectively, and on Day 28, the mean exposures at 1 mg/kg were 6.89 μM·hr and 11.6 μM·hr in female and male dogs, respectively.

No new cobimetinib–related adverse events were observed in either rats or dogs in the 13-week studies that were not already apparent in the shorter-term studies. Dogs appeared to be more sensitive to the adverse effects of cobimetinib, which could be explained by the higher exposures in dogs than in rats. The NOAEL was determined to be 3 mg/kg in rats (Day 90 AUC: 2.20 μM·hr and 1.31 μM·hr in females and males, respectively) and 0.3 mg/kg in dog qd x 13 weeks (Day 90 AUC: 0.94 μM·hr and 1.37 μM·hr in females and males respectively). Significant cobimetinib–related adverse findings upon repeated administration up to 13 weeks were noted in the gastrointestinal tract, bone marrow, lymphoid tissues, adrenal gland, liver, kidney, and skin. Cobimetinib caused a dose-related bone marrow and lymphoid depletion in dogs with correlative decrease in lymphocyte counts. Changes in erythrocytic parameters due to concurrent treatment-associated dehydration were associated with gastrointestinal and renal toxicities that were generally reversible upon discontinuation of cobimetinib administration.

Administration of cobimetinib to conscious telemerized dogs at doses up to 3 mg/kg resulted in no adverse effects on cardiovascular function (including QTc interval), although GDC-073 effectively inhibited hERGK plus channel activity in vitro (IC50 = 1 μM). Cobimetinib administration in rats resulted in no adverse effects on neurobehavioral or respiratory function.

For more details, please refer to the cobimetinib (GDC-0973) IB.

1.3.5 Clinical Pharmacokinetics of Cobimetinib

The key PK findings from the clinical studies conducted in patients and healthy subjects are summarized below.

- Cobimetinib exposure (AUC at steady state and C_{max} at steady state) was dose-proportional across the dose range of 0.05 mg/kg (3.5 mg for a 70-kg adult) to 100 mg (clinically relevant dose range) following oral administration.

- The absolute bioavailability was 46%, and the fraction absorbed was estimated to be 88%, which indicates significant first pass metabolism.
- Cobimetinib binds to plasma proteins (95%) in a concentration-independent manner.
- Cobimetinib was extensively metabolized by CYP3A and UGT2B7 and eliminated in feces with minimal renal elimination. Cobimetinib was the predominant moiety in plasma as no metabolites were circulating at > 10% of total radioactivity.
- Cobimetinib has a mean terminal elimination half-life ($t_{1/2}$) of 43.6 hours.
- Cobimetinib does not alter the pharmacokinetics of midazolam (sensitive CYP3A substrate) or dextromethorphan (sensitive CYP2D6 substrate) in patients with cancer. Substrates of CYP3A and CYP2D6 can be co-administered with cobimetinib without any dose adjustment.
- Co-administration with a high-fat meal or the proton-pump inhibitor (PPI) rabeprazole did not alter cobimetinib pharmacokinetics. Cobimetinib can therefore be administered without regard to food, PPIs, or other acid-reducing agents.
- Cobimetinib AUC increased by approximately 7-fold and C_{max} by approximately 3-fold when co-administered with a strong CYP3A inhibitor (itraconazole). Hence, concomitant administration of strong CYP3A inhibitors with cobimetinib is not recommended.
- Physiologically-based PK simulations indicate that weak inhibitors of CYP3A will not alter cobimetinib PK, while moderate inhibitors will increase cobimetinib AUC approximately 3- to 4-fold in the presence of moderate and strong inducers.

For more information, please refer to the cobimetinib (GDC-0973) IB.

1.3.6 Clinical Experience of Cobimetinib Monotherapy: Study MEK4592g

Study MEK4592g is a multicenter, Phase I, non-randomized, open-label, dose-escalation study.

The study consisted of five treatment stages:

- Stage I: Dose-escalation cohorts; patients were treated on a 21 days on, 7 days off (21/7) schedule to determine the maximal tolerated dose (MTD). The MTD for the 21/7 schedule was found to be 60 mg.
- Stage IA: Dose-escalation cohorts; patients were treated on a 14 days on, 14 days off (14/14) schedule to determine the MTD on an alternate dosing regimen. The MTD for the 14/14 schedule was found to be 100 mg.
- Stage II: Expansion cohort with the MTD determined in Stage I (60 mg qd 21/7) in approximately 20 patients using fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scans of avid tumors that harbored a BRAF, NRAS, or KRAS mutation and with FDG-PET–avid disease.
- Stage IIA: Expansion cohort with the MTD determined in Stage IA (100 mg qd 14/14) in approximately 20 patients with FDG-PET–avid tumors that harbored a BRAF, NRAS, or KRAS mutation.
- Stage III: A dedicated DDI study at the MTD determined in Stage I (60 mg qd 21/7) in approximately 20 patients with solid tumors.

The primary objectives of Stages I, IA, II, and IIA of this study were to evaluate the safety and tolerability of cobimetinib administered orally as repeated doses in patients with solid tumors and to determine the MTD of daily oral administration of cobimetinib in patients with solid tumors. The primary objective of Stage III of this study was to evaluate the possible effect of cobimetinib on the pharmacokinetics of dextromethorphan and midazolam. Study MEK4592g has been completed; a total of 115 subjects were treated.

1.3.6.1 *Dose-Limiting Toxicities*

Four DLTs were observed in Stage I (21/7 dosing schedule) of Study MEK4592g. At the 40-mg dose level, a DLT of Grade 4 hepatic encephalopathy was reported, which resolved following lactulose therapy, routine supportive care, and discontinuation of cobimetinib. At the 60-mg dose level, a DLT of Grade 3 rash was reported that improved with skin toxicity management and drug holiday. At the 80-mg dose level, two DLTs were reported: Grade 3 diarrhea despite treatment with anti-diarrheal medications and Grade 3 rash.

Two DLTs were observed in Stage IA (14/14 dosing schedule) of Study MEK4592g. At the 125-mg dose level, 1 patient had Grade 3 rash and another had Grade 3 blurred vision associated with neurosensory detachment of the retina.

1.3.6.2 *Adverse Events*

An overview of treatment-emergent adverse events, regardless of relationship to study drug, with frequency ≥ 10% in all patients in Study MEK4592g is presented in Table 3.

All patients in Study MEK4592g experienced an adverse event. The most frequent adverse events were diarrhea (67.0%), fatigue (50.4%), rash (49.6%), nausea and vomiting (33.9% each), and edema peripheral (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.

Among the patients who received cobimetinib 60 mg qd 21/7, the most frequent treatment-emergent adverse events were diarrhea (64.4%), rash (53.3%), fatigue (48.9%), nausea and edema peripheral (31.1% each), and vomiting (28.9%).

Table 3 Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug That Occurred in 10% or More of Patients in Study MEK4592g

MedDRA System Organ Class and Preferred Term	60 mg qd 21/7 n = 45	All Patients n = 115
Patients with at least one AE, n (%)	45 (100)	115 (100)
Blood and lymphatic system disorders	9	26
Anemia	8 (17.8)	21 (18.3)
Gastrointestinal disorders	43	109
Diarrhea	29 (64.4)	77 (67.0)
Nausea	14 (31.1)	39 (33.9)
Vomiting	13 (28.9)	39 (33.9)
Abdominal pain	6 (13.3)	28 (24.3)
Constipation	10 (22.2)	24 (20.9)
Stomatitis	4 (8.9)	14 (12.2)
General disorders and administration site conditions	29	82
Fatigue	22 (48.9)	58 (50.4)
Edema peripheral	14 (31.1)	33 (28.7)
Infections and infestations	10	35
Urinary tract infection	5 (11.1)	14 (12.2)
Investigations	19	36
Aspartate aminotransferase increased	5 (11.1)	12 (10.4)
Metabolism and nutrition disorders	25	65
Decreased appetite	11 (24.4)	27 (23.5)
Dehydration	10 (22.2)	27 (23.5)
Hypokalaemia	5 (11.1)	14 (12.2)
Hyponatraemia	4 (8.9)	12 (10.4)
Musculoskeletal and connective tissue disorders	13	36
Back pain	5 (11.1)	13 (11.3)
Nervous system disorders	17	42
Dizziness	7 (15.6)	21 (18.3)
Headache	3 (6.7)	14 (12.2)
Skin and subcutaneous tissue disorders	35	84
Rash	24 (53.3)	57 (49.6)
Dry skin	4 (8.9)	16 (13.9)
Dermatitis acneiform	8 (17.8)	13 (11.3)
Pruritus	4 (8.9)	13 (11.3)

Table 3 Treatment-Emergent Adverse Events Regardless of Relationship to Study Drug That Occurred in 10% or More of Patients in Study MEK4592g (cont.)

60 mg qd 21/7: Patients who received the proposed cobimetinib commercial dosing regimen (60 mg qd 21/7) (pool from Stages I, IA, II, IIA and III).

All Patients: Patients who received cobimetinib on all schedules and doses (pooled from Stage I, IA, II, IIA, and III).

Note: Event coding is from the MedDRA, v16.0. At each level of patient summarization, a patient is counted once if the patient experienced one or more events. Treatment emergent refers to adverse events with onset on or after the date of first dose of study drug.

Source: Modified from Study MEK4592g Summary of Clinical Safety

Data cutoff: 11 June 2013.

1.3.6.3 *Grade ≥ 3 Adverse Events*

Table 4 summarizes the Grade ≥ 3 treatment-emergent adverse events that affected 2 patients of all patients in Study MEK4592g (n = 115) and of those who received cobimetinib 60 mg 21/7 (n = 45).

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

Table 4 Grade ≥ 3 Treatment-Emergent Adverse Events in Study MEK4592g

MedDRA System Organ Class and Preferred Term	60 mg qd 21/7 n=45	All Patients n=115
Patients with at least one Grade ≥ 3 AE, n (%)	26 (57.8)	75 (65.2)
Blood and lymphatic system disorders	2	11
Anaemia	2 (4.4)	9 (7.8)
Leukopenia	1 (2.2)	2 (1.7)
Lymphopenia	1 (2.2)	2 (1.7)
Cardiac disorders	1	4
Cardio-respiratory arrest	0	2 (1.7)
Gastrointestinal disorders	9	26
Diarrhea	0	7 (6.1)
Abdominal pain	3 (6.7)	5 (4.3)
Gastrointestinal hemorrhage	0	2 (1.7)
Ileus	1 (2.2)	2 (1.7)
Intestinal obstruction	1 (2.2)	2 (1.7)
General disorders and administration site conditions	6	13
Fatigue	6 (13.3)	10 (8.7)
Chest pain	0	2 (1.7)
Hepatobiliary disorders	1	4
Bile duct obstruction	0	3 (2.6)
Infections and infestations	2	6
Urinary tract infection	2 (4.4)	3 (2.6)
Pneumonia	0	2 (1.7)
Investigations	7	14
Aspartate aminotransferase increased	1 (2.2)	3 (2.6)
Blood creatine phosphokinase increased	2 (4.4)	3 (2.6)
Electrocardiogram QT prolonged	2 (4.4)	3 (2.6)
Gamma-glutamyltransferase increased	1 (2.2)	3 (2.6)
Alanine aminotransferase increased	0	2 (1.7)
Blood bilirubin increased	1 (2.2)	2 (1.7)
Blood lactate dehydrogenase increased	1 (2.2)	2 (1.7)
Metabolism and nutrition disorders	7	21
Hyponatremia	4 (8.9)	11 (9.6)
Hypokalemia	2 (4.4)	7 (6.1)
Dehydration	2 (4.4)	5 (4.3)
Hypophosphatemia	0	3 (2.6)

Table 4 Grade ≥ 3 Treatment-Emergent Adverse Events in Study MEK4592g (cont.)

MedDRA System Organ Class and Preferred Term	60 mg qd 21/7 n=45	All Patients n=115
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4	7
Malignant neoplasm progression	1 (2.2)	2 (1.7%)
Nervous system disorders	1	7
Syncope	0	5 (4.3%)
Respiratory, thoracic and mediastinal disorders	7	10
Respiratory arrest	3 (6.7)	3 (2.6%)
Skin and subcutaneous tissue disorders	2	8
Rash	0	5 (4.3%)
Vascular disorders	3	10
Hypertension	2 (4.4)	4 (3.5%)
Deep vein thrombosis	1 (2.2)	3 (2.6%)

60 mg QD 21/7: Patients who received the proposed cobimetinib commercial dosing regimen (60 mg QD 21/7) (pool from Stages I, IA, II, IIA and III).

All Patients: Patients who received cobimetinib on all schedules and doses (pooled from stage I, IA, II, IIA and III).

Note: Event coding is from the MedDRA, Version 16.0. At each level of patient summarization, a patient is counted once if the patient experienced one or more events. Treatment emergent refers to adverse events with onset on or after the date of first dose of study drug.

Source: Modified from Study MEK4592g Summary of Clinical Safety

Data cutoff: 11 June 2013.

1.3.6.4 *Serious Adverse Events*

A total of 49 patients (42.6%) experienced a serious adverse event. The most common types of serious adverse events were gastrointestinal disorders (n = 17), but there were no trends in specific preferred terms. The gastrointestinal serious adverse events, such as intestinal obstructions and gastrointestinal hemorrhages, occurred in patients with gastrointestinal malignancies. Serious adverse events reported for ≥ 2 patients among all patients in the study were anemia, bile duct obstruction, dehydration, syncope, and respiratory arrest (3 patients each [2.6%]).

1.3.6.5 *Deaths*

Study MEK4592g accrued a patient population with metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. In addition, in Study MEK4592g disease progression was reported as an adverse event (Grade 5) instead of an outcome measure.

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 progressive disease, all deaths in Stage I occurred because of progressive disease, 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 of the deaths were assessed by the investigator as treatment related. Other etiologic factors that contributed to the deaths included the patients' underlying diseases and malignant tumor progression.

1.3.6.6 *Clinical Efficacy*

Assessment of responses was an exploratory endpoint in Study MEK4592g. Best overall response was assessed for 74 of 97 patients in Stages I, IA, II and IIA of the study who had measurable lesions and at least 1 post-baseline tumor assessment. Overall, 6 patients (all of whom had melanoma; 6.2%) had a confirmed partial response, 28 patients (28.9%) had stable disease, and 40 patients (41.2%) had progressive disease. Twenty-three patients had non-measurable lesions or measurable lesions with no post-baseline tumor assessments.

In Stage III of Study MEK4592g, 18 patients were accrued. Best overall response was assessed for 14 of 18 patients in Stage III with measurable lesions and at least 1 post-baseline tumor assessment. Overall, 4 patients (22.2%) had stable disease as their best overall response, 8 patients (44.4%) had disease progression, and 2 patients (11.1%) had unconfirmed tumor response.

1.3.7 Adverse Events Associated with Cobimetinib (GDC-0973)

Information related to cobimetinib-associated risks is presented below based mainly on review of data from the pivotal Phase III study, GO28141, following the primary efficacy analysis (data cutoff 9 May 2014) and study MEK4592g. Please refer to the cobimetinib IB for full details.

1.3.7.1 *Hemorrhage*

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, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III study GO28141, Grade 1–4 hemorrhagic events were reported in 13.0% of patients treated with cobimetinib plus vemurafenib and in 7.3% of patients treated with placebo plus vemurafenib. The majority of hemorrhagic events were Grade 1 or 2 and non-serious. Grade 3–4 hemorrhage events were reported in 1.2% of patients who received cobimetinib plus vemurafenib and 0.8% of patients who received placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients who use concomitant medications that increase the risk of bleeding (including anti-platelet or anticoagulant therapy).

Instructions and dose modifications for hemorrhage events are included in Table 12, in Section 6.1.1.

1.3.7.2 *Serous Retinopathy*

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed with MEKi, including cobimetinib. The majority of events in cobimetinib-treated patients were reported as chorioretinopathy or retinal detachment. In the Phase I single-agent study (MEK4592g), also with ocular examinations prescribed for patients reporting visual disturbance, 2.6% of patients (including 1 patient with a Grade 2 event that was not coded at the time of the data cutoff date) experienced serous retinopathy events, all of which were Grade 1 or 2.

In the Phase III study (GO28141), with prospective serial ocular examinations, serous retinopathy events were reported more frequently in patients treated with vemurafenib + cobimetinib than vemurafenib + placebo (24% vs. 2.1%), and approximately 50% were asymptomatic Grade 1 events. Few patients treated with vemurafenib + cobimetinib experienced Grade ≥ 3 ocular events (2.8%); the majority of these were managed with dose modification of both cobimetinib and vemurafenib, and all were resolved or resolving as of the data cutoff date.

1.3.7.3 *Left Ventricular Dysfunction*

Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in left ventricular ejection fraction (LVEF) may be asymptomatic. Without active surveillance for reduction in LVEF, there were no events in this risk category reported in the Phase I single agent study (MEK4592g).

In the Phase III study (GO28141), with active surveillance, reductions in LVEF were reported more frequently in patients treated with vemurafenib + cobimetinib than vemurafenib + placebo (6.7% vs. 2.9%). Of the patients treated with vemurafenib + cobimetinib, 2 patients (0.8%) had symptomatic reduction in LVEF and the remaining patients were asymptomatic. One patient in each arm (0.4% each) experienced serious events; these were symptomatic. Most events in patients treated with vemurafenib + cobimetinib (88%) improved or resolved with management according to the dose modification guidelines. No Grade 4 or 5 events of reduction in LVEF have been reported in cobimetinib clinical studies as of the data cutoff dates. Reduction in LVEF has also been observed in patients treated with MEKi other than cobimetinib.

Investigators should monitor patients for clinical signs and symptoms of cardiac dysfunction.

1.3.7.4 *Rhabdomyolysis and Increased CPK*

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in

the Phase III study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in post-marketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥ 3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥ 3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for dose modifications for elevated CPK and rhabdomyolysis are included in Table 12, in Section 6.1.1.

1.3.7.5 *Liver Laboratory Abnormalities*

Liver laboratory test abnormalities, including elevations in AST and/or ALT, have been reported as adverse events and serious adverse events in patients treated with vemurafenib + cobimetinib. In the Phase III study (GO28141), liver laboratory test abnormalities reported as Grade ≥ 3 adverse events occurred more frequently in patients treated with vemurafenib + cobimetinib than vemurafenib + placebo (20.5% vs. 15.1%). Liver laboratory test abnormalities reported as Grade ≥ 3 adverse events at frequencies ≥ 2% higher in patients treated with vemurafenib + cobimetinib than vemurafenib + placebo included increased ALT (11.4% vs. 6.3%), increased AST (8.3% vs. 2.1%), and increased ALP (4.3% vs. 1.7%).

In Study MEK4592g, there were no reported adverse events or serious adverse events for clinically significant Grade 4 elevations in liver laboratory tests, and no patient experienced findings suggestive of drug-induced liver injury or liver failure.

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms of GO28141, the majority of Grade ≥ 3 liver laboratory test abnormalities resolved.

Refer to Section 6.1 for management of liver laboratory abnormalities.

1.3.7.6 *Rash*

Skin toxicities of rash have been reported in patients treated with cobimetinib as a single agent or in combination with other therapies.

In the Phase III study (GO28141), combined rash events of all types and grades were reported more frequently in patients treated with vemurafenib + cobimetinib than vemurafenib + placebo (71.7% vs. 65.7%), although Grade ≥ 3 events (approximately 16%) and types of rash reported were similar between study arms. Specific events in patients treated with vemurafenib + cobimetinib included rash (39% all grades, 5.9% Grade ≥ 3, 1.6% serious events) and rash maculo-papular (14.6% all grades, 6.3% Grade ≥ 3, 1.2% serious events).

In the Phase I single-agent study (MEK4592g), reported rash events included rash (49.6% all grades, 4.3% Grade ≥ 3 events) and rash maculo-papular (1.7% all grades, 0.9% Grade ≥ 3 events).

Refer to Section 6.1 for management of rash.

1.3.7.7 *Photosensitivity*

Although no evidence of phototoxicity was observed with cobimetinib as a single agent, photosensitivity events, including photosensitivity reaction, solar dermatitis, and sunburn, have been reported in cobimetinib clinical studies in combination with vemurafenib.

In the Phase III study (GO28141), photosensitivity events were reported more frequently in patients treated with vemurafenib + cobimetinib (41.3% all grades, 3.1% Grade ≥ 3) than vemurafenib + placebo (31.4% all grades, 1.6% Grade ≥ 3). No serious photosensitivity events were reported in either study arm.

Refer to Section 6.1 for management of photosensitivity.

1.3.7.8 *Gastrointestinal Toxicity*

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult cancer patients.

In the Phase III study GO28141, diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in 59.9% of patients and Grade 3 or 4 events were reported in 6.5% of patients treated with cobimetinib plus vemurafenib versus 30.9% and 0.8%, respectively, in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported in 1.2% of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III Study GO28141, nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm (nausea 39.0% vs. 23.8%; vomiting 21.3% vs. 12.1%). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea 0.8%, vomiting 1.2%).

In the Phase I single-agent study (MEK4592g), all grades of nausea and vomiting were both reported as 33.9% with 0.9% reported for Grade ≥ 3 nausea and none reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine antiemetic prophylaxis is not recommended.

1.4 Rationale for the Study

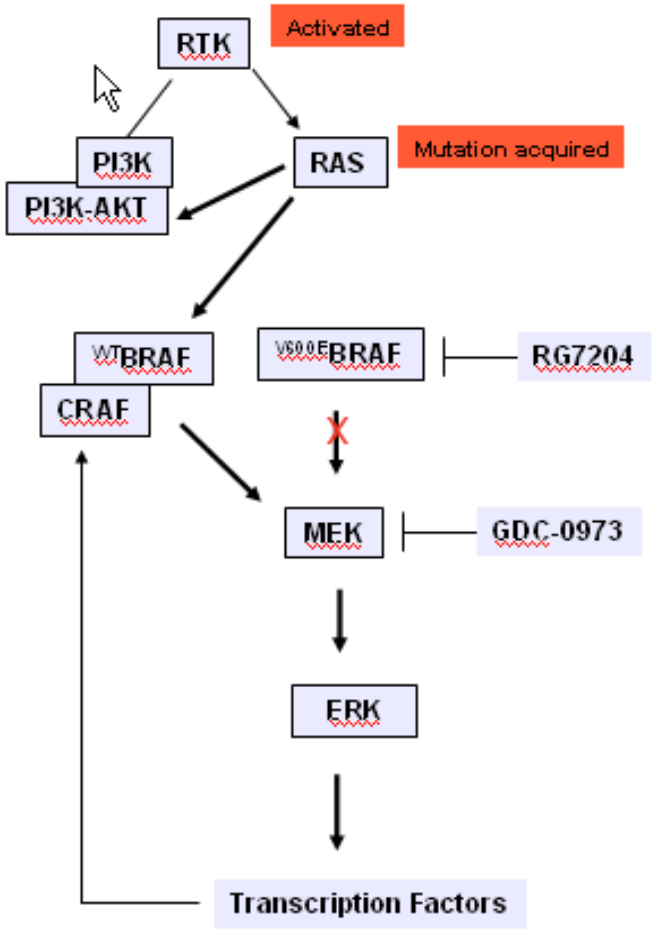
The rationale for the clinical investigation of the vemurafenib/cobimetinib drug combination is to simultaneously target BRAF and MEK in patients with previously untreated $BRAF^{V600E}$ mutation-positive, locally advanced/unresectable or metastatic melanoma, those previously treated but without prior exposure to any BRAF or MEK inhibitor (MEKi) therapy, OR those who have progressed after treatment with vemurafenib monotherapy, based on the following:

- The overall clinical activity of vemurafenib in patients with $BRAF^{V600E}$-positive metastatic melanoma
- The ability of the MEK inhibitor cobimetinib to suppress pERK signaling when given as monotherapy and the potential to act additively or synergistically when given in combination with vemurafenib
- An expectation of a tolerable safety profile for the vemurafenib and cobimetinib combination based upon xenograft BRAF inhibitor and MEKi combinations.
- Potential safety benefit by decreasing the risk of developing SCC with vemurafenib monotherapy

A proportion of $BRAF^{V600E}$-positive melanoma patients who responded to vemurafenib in the Phase I extension cohort, Phase II and III studies have subsequently progressed. The pattern of progression has been mixed or asynchronous, occurring in a subset of lesions (typically less than 30% of those targeted). The majority of progressing patients, approximately 70%, exhibited this pattern of asynchronous progression, suggesting that there may be some benefit to continuing treatment with vemurafenib.

The reason(s) for this pattern of mixed progression in $BRAF^{V600E}$-positive patients treated with vemurafenib is unclear. No gatekeeper or activating BRAF mutations have been noted. Biopsies of progressing lesions demonstrate increased pERK, suggesting the possibility of reactivation of the RAS/RAFMEK/ERK pathway, in the presence of vemurafenib. This may be attributed to one of the following factors illustrated in Figure 1.

Figure 1: Potential Mechanisms of Resistance to BRAF Inhibitors in Melanoma Cells



RG7204 = vemurafenib.

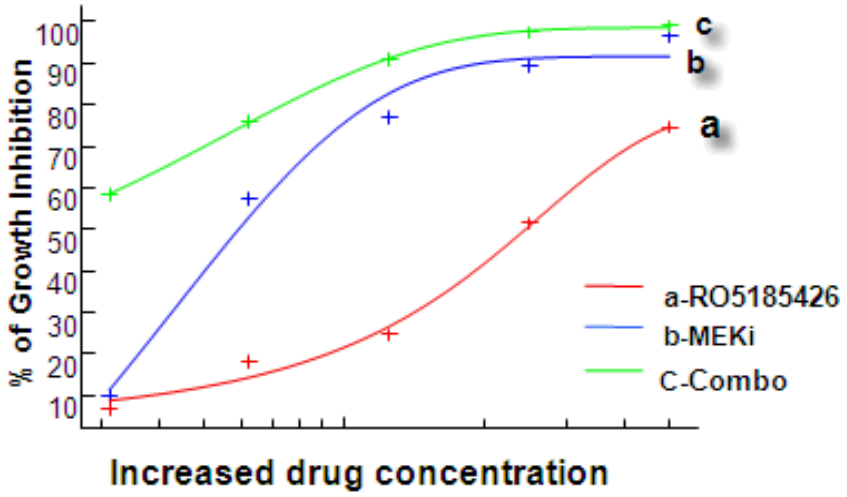
Although the escape mechanism of RAS-RAF pathway suppression is unknown, the formation of BRAF-CRAF or CRAF-CRAF dimers and the reactivation of MEK-mediated signaling are likely to be integral components of this process [27, 28, 29].

Combining the MEK inhibitor cobimetinib with vemurafenib in patients with $BRAF^{V600E}$-positive melanoma who experience discordant/mixed progression on vemurafenib monotherapy may re-establish suppression of the RAS-RAF pathway in progressing lesions while maintaining pathway suppression in non-progressing lesions.

To date, assessments of the combination of vemurafenib with cobimetinib have not been conducted. However, nonclinical data from two studies provide proof-of-concept support for combining a BRAF inhibitor with a MEK inhibitor to suppress ERK signaling and restore sensitivity to BRAF inhibition.

In an in vitro resistance model, cells resistant to both BRAF and MEK inhibition were exposed to vemurafenib, to a combination of vemurafenib with RO5068760 (a MEK inhibitor), and to RO5068760. The combination of BRAF inhibition by vemurafenib and MEK inhibition by RO5068760 (Figure 2) [30] abrogated the constitutive upregulation of ERK phosphorylation, inhibited cell cycle progression, and induced apoptosis in the resistant cells to a greater extent than either agent alone.

Figure 2: Combination of Vemurafenib with a MEK Inhibitor (RO5068760) Demonstrates a Synergistic Anti-Proliferation Effect in the Acquired-Resistance Melanoma Cell Model



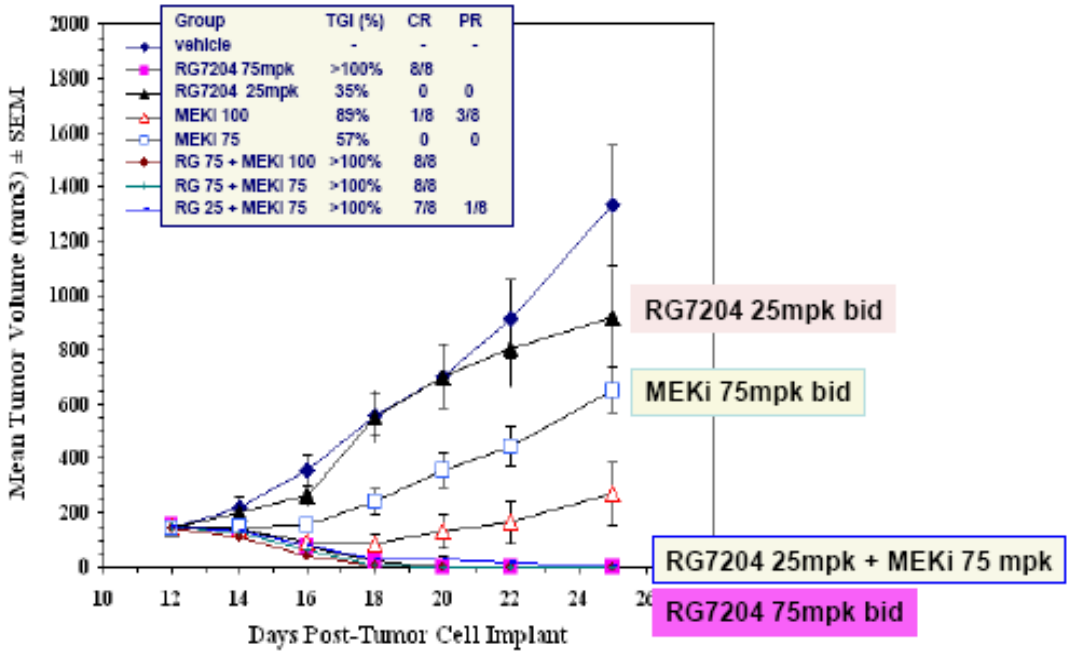
RO5185426 = vemurafenib.

An in vivo efficacy study in nude mice bearing $BRAF^{V600E}$-positive A375 melanoma xenograft tumors demonstrated synergistic anti-tumor activity when vemurafenib was combined with the MEK inhibitor RO5068760 (Figure 3). No toxicity was observed in the animal subjects treated during this xenograft study.

These in vivo and in vitro studies suggest that combined RAF/MEK pharmacologic inhibition of the BRAF pathway is more effective than either agent alone and may suppress the emergence of the pathway-specific resistance in tumors harboring the $BRAF^{V600E}$ mutation.

In light of the preclinical evidence suggesting additive or synergistic benefit from the combination of vemurafenib with cobimetinib, enrollment in the current study will also include patients with previously untreated, locally advanced/unresectable or metastatic melanoma, positive for the $BRAF^{V600E}$ mutation as well as those previously treated but without prior exposure to any BRAF or MEK inhibitor therapy.

Figure 3: Combination Study of Vemurafenib and the MEK Inhibitor RO5068760 in the BRAFV600E-Expressing A375 Melanoma Xenograft Model



RG7204 = vemurafenib.

Patients treated with vemurafenib have developed SCC, the majority of which are the KA subtype. The development of this adverse event of interest may be related to higher MAPK pathway signaling by the upregulation of pERK in the setting of mutant RAS (or upregulation of growth factor receptors). In addition to down regulating pERK signaling, thereby overcoming the tumor escape mechanism, the combination of vemurafenib and cobimetinib may have the potential to improve the safety profile of vemurafenib-treated patients by decreasing the incidence of SCC.

2. OBJECTIVES

2.1 Primary Objectives

Study NO25395 will be conducted in previously untreated or previously treated patients with $BRAF^{V600E}$ mutation-positive, locally-advanced and unresectable or metastatic melanoma OR those who have progressed on treatment with vemurafenib monotherapy immediately prior to enrollment in this trial. Patients in the former category who were previously treated must have had no prior exposure to any BRAF or MEK inhibitor therapy. See Section 4.2 for full inclusion criteria. The objectives of the trial are as follows.

Primary Objectives:

To evaluate the safety and tolerability of the vemurafenib and cobimetinib combination, and in doing so,

- To identify the DLTs that determine the MTD of the vemurafenib and cobimetinib combination
- To identify a potential Phase II/III dose and schedule for the vemurafenib and cobimetinib combination
- To characterize Day 1 and steady-state pharmacokinetics of cobimetinib when administered in combination with vemurafenib and to characterize the steady-state pharmacokinetics of vemurafenib administered alone and in combination with cobimetinib

Secondary Objectives:

- To assess the anti-tumor activity of the vemurafenib and cobimetinib combination
- To assess the mechanisms of response and resistance to vemurafenib and cobimetinib combination therapy (including genetic alterations of RAS, RAF, and MEK)
- To assess the $BRAF^{V600E}$ mutation status of patients who progressed on vemurafenib monotherapy
- To identify factors that may pre-dispose patients to SCC development
- To assess the PD effects of vemurafenib and cobimetinib when administered in combination, as measured by changes in FDG-PET
- To assess the PD effects of vemurafenib and cobimetinib when administered in combination, as measured by changes in molecular biomarkers in sequential paired biopsies
- To assess the PD utility of FDG-PET and changes in molecular biomarkers in sequential paired biopsies in a subset of patients (up to n=20) treated with single-agent cobimetinib

2.2 Exploratory Objectives

Roche is committed to the collection of biomarker samples in all clinical study protocols. The objective of biomarker profiling is to enable development of treatments specifically targeted for optimal patient benefit (personalized healthcare). Biomarker samples will be stored in the Roche Clinical Repository (RCR). RCR is a central facility for the long-term storage of human biological specimens including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA proteins/ peptides). Specimens stored in the RCR will be used for any of the following:

- Study the association of biomarkers with efficacy and/or adverse events associated with medicinal products
- Increase our knowledge and understanding of disease biology
- Develop biomarker or diagnostic assays; establish performance characteristics of these assays

- To evaluate the relationship between anti-tumor activity and changes in PD biomarkers when study drugs are administered in combination at the recommended MTD dose and schedule

3. STUDY DESIGN

3.1 Overview of Study Design

This is an open-label, multicenter, Phase Ib, dose-escalation study designed to assess the safety, tolerability, and pharmacokinetics of continuous daily oral dosing of vemurafenib administered in combination with orally dosed cobimetinib administered daily for 14 consecutive days followed by 14 days off (14/14), for 21 consecutive days followed by 7 days off (21/7), or as a continuous daily dose. Patients with previously untreated, or treated $BRAF^{V600E}$ mutation-positive, locally advanced/unresectable or metastatic melanoma OR those who have progressed on vemurafenib monotherapy immediately prior to enrolling in this trial are eligible. Patients in the former category who were previously treated must have had no prior exposure to any BRAF or MEK inhibitor therapy. Treatment will continue until disease progression, unacceptable toxicity, or any other discontinuation criterion is met (Section 4.5). For a small subset of patients who have progressed on vemurafenib monotherapy immediately prior to enrollment in this trial (up to 20), there is also an option for treatment with single-agent cobimetinib at 60 mg on a 21/7 schedule (see Section 3.1.2). The PD data obtained from this patient group will be reviewed with the vemurafenib plus cobimetinib combination PD data to enhance our understanding of the combination PD data.

Vemurafenib will be dosed daily and cobimetinib will be dosed on a 14/14, a 21/7, or a continuous schedule in a 28-day cycle. Alternate dosing regimens and schedules may be interrogated depending on the nature and timing of the toxicities encountered.

There are two stages to this study: a dose-escalation stage and a cohort-expansion stage. During the dose-escalation stage, 10 dose-escalation cohorts of 3–6 patients each will be enrolled in order to identify a safe and tolerable dose of each agent to be administered during the cohort-expansion stage, i.e., the potential recommended Phase II/III dose combination. Approximately 20 additional patients will be enrolled into each of (minimally) two expansion cohorts during the cohort-expansion stage. One cohort will consist of patients who have progressed on vemurafenib monotherapy immediately prior to enrolling in this trial, and the other will consist of previously untreated or treated patients without prior exposure to any BRAF or MEK inhibitor therapy. Therefore, approximately 130 patients (not including patients treated with cobimetinib monotherapy) will be enrolled in the trial at approximately 7-10 sites in total in the United States and Australia.

3.1.1 Stage 1: Dose-Escalation Cohort

The dose-escalation stage is designed to evaluate the safety, tolerability, MTD, pharmacokinetics, and any anti-tumor activity of vemurafenib when administered in combination with cobimetinib.

Stage 1 will be conducted in previously untreated or treated patients with $BRAF^{V600E}$-positive metastatic melanoma (unresectable Stage IIIc and Stage IV, according to the American Joint Committee on Cancer [AJCC] classification) OR those who have discordant/mixed progression on treatment with vemurafenib monotherapy in a previous clinical trial or postmarketing setting immediately preceding enrollment in this trial. Patients in the former category who were previously treated must have had no prior exposure to any BRAF or MEK inhibitor therapy. Please see Sections 4.2 and 4.3 for a detailed description of the eligibility criteria. Patients who have FDG-PET avid disease will undergo FDG-PET imaging as a PD biomarker and potential early readout of anti-tumor activity.

a) Starting Doses and Overall Study Design

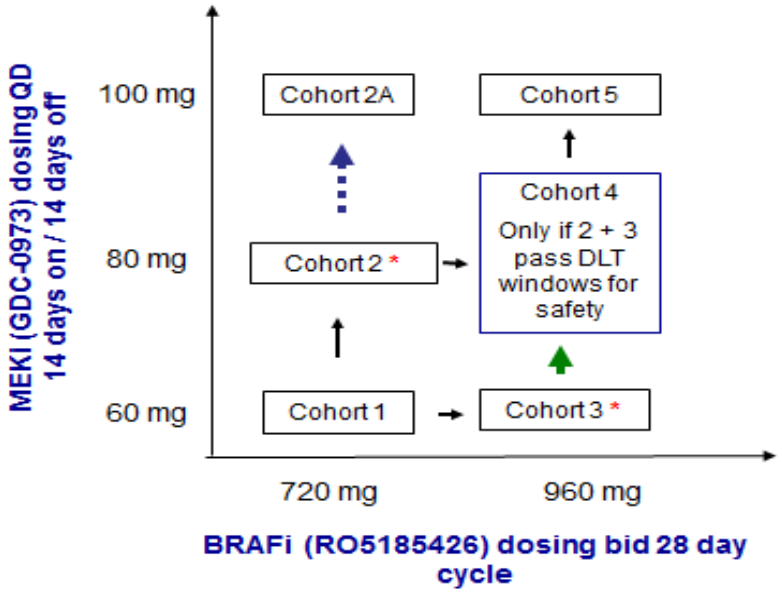
A 3+3 dose-escalation schema will be used. The starting dose of vemurafenib will be 720 mg bid for 28 consecutive days of each 28-day cycle of combination dosing, which is one dose level below the single-agent MTD of 960 mg bid established in the vemurafenib Phase Ia trial (PLX06-02) and which is utilized in the dose-modification scheme in the Phase II and Phase III trials of vemurafenib. This dose level was selected in an attempt to maintain RAS/RAF/ERK pathway suppression in non-progressing melanoma lesions. The effectiveness of this dose is supported by data from the Phase I through III clinical trials. In the Phase I trial, approximately 30% of patients have required dose reductions to 720 mg bid, while continuing to show a response to vemurafenib monotherapy.

The starting dose of cobimetinib will be 60 mg per day for 14 consecutive days of each 28-day cycle of combination dosing, which is two dose levels below the single-agent MTD of 100 mg per day administered on this schedule as established in the cobimetinib Phase Ia trial (Study MEK4592g). Dose escalation will proceed in increments, taking into account the safety and tolerability of the combination.

b) Dose Escalation

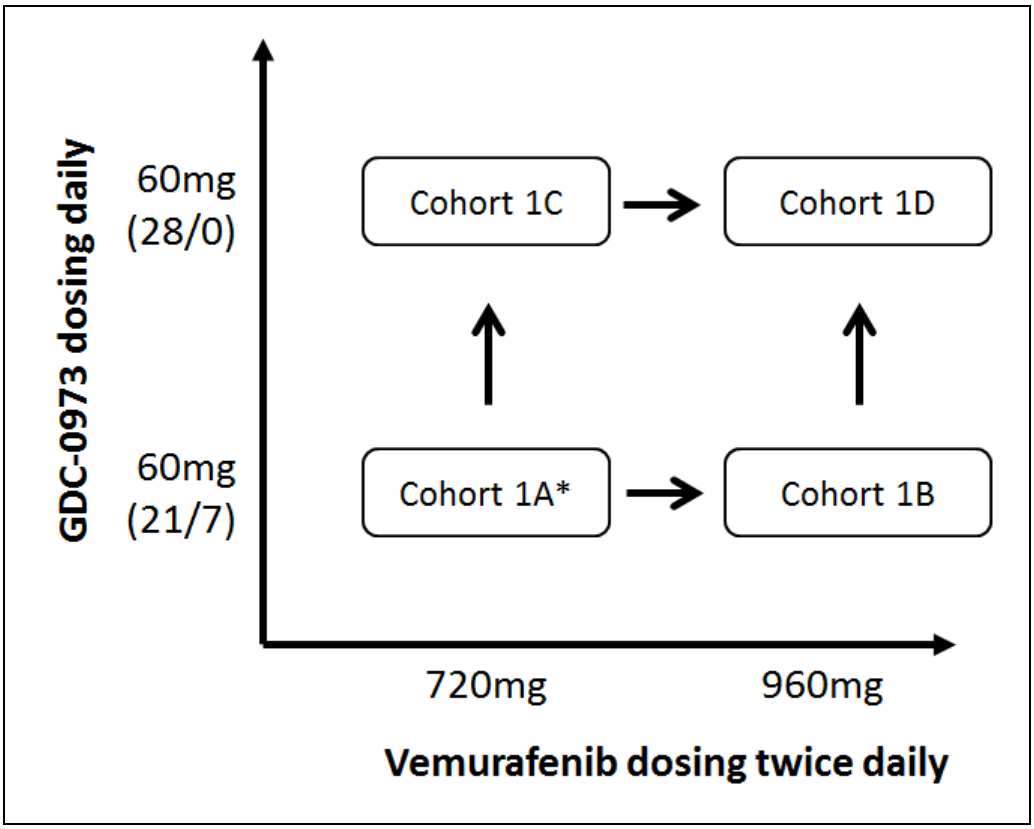
The dose-escalation schema and plan are detailed in Figure 4, Figure 5, and Table 5.

Figure 4: Dose-Escalation Plan for the Combination of Vemurafenib and Cobimetinib Administered on a 14/14 Schedule



* Simultaneous enrollment in Cohorts 1A (Figure 5), 2, and 3

Figure 5: Dose Escalation Scheme for the Combination of Vemurafenib and Cobimetinib Administered Either on a 21/7 Day or a Continuous Schedule



* Declaration of Cohort 1A safety and tolerability will trigger enrollment in several cohorts: Cohort 1B (under Amendment D), Cohort 1C (pending approval of Amendment E), and Cohort 1A expansion cohorts of patients who progressed on vemurafenib immediately prior to enrolling this trial (n = 20) and previously untreated with vemurafenib or other BRAF or MEK inhibitor (n = 20); see Section 3.1.

If the Cohort 1 dose combination is safe and tolerable as per the rules for dose-limiting toxicity (Section 3.1.4), escalation will continue with simultaneous enrollment of Cohort 1A (Figure 5) when available, Cohort 2, and Cohort 3 (Figure 4). Cohort 2 will evaluate the combination of vemurafenib at a dose of 720 mg bid and cobimetinib at 80 mg/day on a 14/14 day schedule, and Cohort 3 will evaluate the combination of vemurafenib at a dose of 960 mg bid and cobimetinib at 60 mg/day on a 14/14 day schedule. Cohort 2A (Figure 4) may be enrolled only if the dose combination tested in Cohort 2 is declared safe and tolerable. Enrollment in Cohort 4 may occur only if the dose combinations tested in both Cohorts 2 and 3 are declared safe and tolerable. Cohort 4 will evaluate the combination of vemurafenib at 960 mg bid and cobimetinib at 80 mg/day on a 14/14 day schedule. If the Cohort 4 combination is safe and tolerable, further escalation will occur with enrollment in Cohort 5. Cohort 5 will evaluate the combination of both

vemurafenib and cobimetinib at their monotherapy MTDs (960 mg bid and 100 mg/day, respectively, 14/14 day schedule,).

Cohort 1A (Figure 5) will test the safety and tolerability of vemurafenib at a dose of 720 mg bid in combination with cobimetinib at 60 mg/day on a 21/7 day schedule. Cohorts 1B and 1C may enroll patients only after the Cohort 1A dose combination is declared safe and tolerable. Cohort 1B will test the safety and tolerability of vemurafenib at a dose of 960 mg bid in combination with cobimetinib at 60 mg/day on a 21/7 day schedule, and Cohort 1C will test the safety and tolerability of vemurafenib at a dose of 720 mg bid and cobimetinib at 60 mg/day on a continuous schedule. After both Cohorts 1B and 1C are deemed to be acceptably safe and tolerable, Cohort 1D will open to evaluate the combination of vemurafenib at a dose of 960 mg bid and cobimetinib at 60 mg/day on a continuous schedule.

There will be no intrapatient dose escalation during the DLT assessment window (Cycle 1, Days 1–28). After the DLT assessment window (Cycle 2 and beyond), patients without evidence of melanoma progression may receive cobimetinib at the highest cohort dose level for which there are at least 4 weeks of safety data demonstrating acceptable tolerability (i.e., no DLTs observed in a cohort of 3 evaluable patients or ≤1 DLT in a cohort of 6 evaluable patients). In some cases, this may allow the skipping of more than one dose level. For example, after Cohort 2A is determined to be safe and tolerable, patients in Cohort 2 may increase their daily dose of cobimetinib from 80 to 100 mg on a 14/14 schedule, and patients in Cohort 1 may increase their daily dose of cobimetinib from 60 to 100 mg on a 14/14 schedule. Patients that are beyond the Cycle 1 DLT assessment window are eligible for multiple, step-wise dose escalations (with agreement of the Sponsor's Medical Monitor) although dose escalations for an individual patient may not continue once that patient develops cobimetinib–related Grade ≥3 toxicity. Intrapatient dose modification will be allowed in patients within a given cobimetinib administration schedule once the next higher dose level(s) is deemed to be acceptably safe and tolerable. Patients treated on a 14/14 schedule cannot transition to a 21/7 or a continuous daily schedule.

In all such circumstances, the daily dose of vemurafenib may remain the same (at 720 or 960 mg bid) or increase from 720 to 960 mg bid, but only if the patient was tolerating 960 mg bid in a previous clinical study or postmarketing setting of vemurafenib monotherapy, immediately preceding enrollment in this trial.

All intrapatient dose escalations must begin on Day 1 of the next treatment cycle.

Table 5 outlines the vemurafenib and cobimetinib dose and schedule combinations planned for Cohorts 1, 1A, 1B, 1C, 1D, 2, 2A, 3, 4, 5, and the cobimetinib monotherapy cohort. All cohorts except the cobimetinib monotherapy cohort will be open to patients who either have progressed on vemurafenib monotherapy or are previously untreated or treated (but without prior exposure to BRAF or MEK inhibitor therapy) for locally advanced/unresectable or metastatic melanoma.

Table 5 Roadmap for Planned Dose Escalation

Cohort (Patient number)	VEMURAFENIB/ Cobimetinib dose, schedule	Eligible patients	Comments
1 (n=3-6)	720 mg bid/60 mg qd 14/14	Vemurafenib progressors, PTPs, and PUPs	After (if) cohort 1 dose combination is deemed safe, cohorts 1A, 2 and 3 will open to new patients simultaneously
1A (n=3-6)*	720 mg bid/60 mg qd 21/7	Vemurafenib progressors, PTPs, and PUPs	
1B (n=3-6)*	960 mg bid/60 mg qd 21/7	Vemurafenib progressors, PTPs, and PUPs	Cohort 1B may open to new patients only after Cohort 1A dose combination is deemed safe and tolerable
1C (n=3-6)†	720 mg bid/60 mg qd 28/0	Vemurafenib progressors, PTPs, and PUPs	Cohort 1C may open to new patients only after Cohort 1A dose combination is deemed safe and tolerable
1D (n=3-6))†	960 mg bid/60 mg qd 28/0	Vemurafenib progressors, PTPs, and PUPs	Cohort 1D may open to new patients only after Cohort 1B and 1C dose combinations are deemed safe and tolerable
2 (n=3-6)	720 mg bid/80 mg qd 14/14	Vemurafenib progressors, PTPs, and PUPs	
2A (n=3-6)	720 mg bid/100 mg qd 14/14	Vemurafenib progressors, PTPs, and PUPs	Cohort 2A may open to new patients only after Cohort 2 dose combination is deemed safe and tolerable
3 (n=3-6)	960 mg bid/60 mg qd 14/14	Vemurafenib progressors, PTPs, and PUPs	
4 (n=3-6)	960 mg bid/80 mg qd 14/14	Vemurafenib progressors, PTPs, and PUPs	Cohort 4 will open to new patients only after both Cohorts 2 and 3 dose combinations are deemed safe and tolerable
5 (n=3-6)	960 mg bid/100 mg qd 14/14	Vemurafenib progressors, PTPs, and PUPs	
Cobimetinib monotherapy (up to 20)	60 mg qd 21/7	Vemurafenib IB progressors only	

Abbreviations: PTPs= patients previously treated for locally advanced/unresectable or metastatic melanoma but without prior exposure to any BRAF or MEK inhibitor therapy; PUPs = previously untreated patients with $BRAF^{V600E}$ mutation-positive, locally advanced/unresectable or metastatic melanoma

*New cohorts not represented in Amendment C.

†New cohorts not represented in Amendment D.

Dose De-Escalation

The dose-escalation plan for vemurafenib and cobimetinib combination therapy may not be tolerable. In this case, a dose de-escalation plan may be adopted at the discretion of the study Sponsor.

If the Cohort 1 dose combination is not tolerated, dose de-escalation for either vemurafenib or cobimetinib will occur. Dose de-escalation will occur with simultaneous

enrollment into Cohort -1 (in which only vemurafenib is de-escalated to a lower dose level of 480 mg bid) and Cohort -2 (in which only cobimetinib is de-escalated to a lower dose level of 40 mg on a 14/14 schedule). If Cohort -1 or Cohort -2 dose combinations are not tolerated, there may be one further dose de-escalation to Cohort 3 (in which both vemurafenib and cobimetinib doses are decreased).

Table 6 Roadmap for Planned Dose–De-escalation Cohorts in the Setting of Cohort 1 Failure

Cohort	Vemurafenib	Cobimetinib (14/14 schedule)
–1	480 mg bid	60 mg qd
–2	720 mg bid	40 mg qd
–3	480 mg bid	40 mg qd

Table 6 outlines potential vemurafenib and cobimetinib dose combinations planned for Cohorts -1, -2, and -3 if needed. As described above, these potential cohorts would only be opened if dose de-escalation is needed because the Cohort 1 dose combination is not safe and tolerable.

If the Cohort 1A, 1B, 1C, or 1D dose combination is not tolerated, dose de-escalation for cobimetinib may occur at the Sponsor's discretion. Table 7 outlines the vemurafenib and cobimetinib dose combination planned for Cohorts -1A, -1B, -1C, and -1D, if needed. These cohorts would only be opened if the dose combination tested in Cohort 1A, 1C, and 1D are not deemed safe and tolerable.

Table 7 Roadmap for Planned Dose De-Escalation Cohort in the Setting of Cohorts 1A, 1C, or 1D Failure

Cohort	Vemurafenib	Cobimetinib (21/7 schedule)	Cobimetinib (28/0 schedule)
-1A	720 mg bid	40 mg qd	NA
-1B	960 mg bid	40 mg qd	NA
-1C	720 mg bid	NA	40 mg qd
-1D	960 mg bid	NA	40 mg qd

NA= not applicable.

Cohort Assignment

Patients eligible to participate in this protocol will have the ability to enroll in a single vemurafenib and cobimetinib combination cohort or in the cobimetinib monotherapy cohort. Enrollment in the cobimetinib monotherapy cohort will be limited to 20 patients in total.

See the guidance below.

Dose-Escalation Cohorts 1, 1A, 1B, 1C, 1D, 2, 2A, 3, 4, and 5

Patients who progressed on vemurafenib monotherapy immediately preceding enrollment in this trial:

Patients who have tolerated 720 mg or 960 mg vemurafenib bid may be enrolled in Cohorts ≥ 1. Patients who are initiating study therapy and for whom a slot does not exist in the currently enrolling dose cohort have the option of receiving a previously cleared vemurafenib/ cobimetinib dose combination or waiting until a slot in the current or next dose-escalation cohort is available. Expansion of previously cleared cohorts should increase the accuracy of the safety assessment. Enrollment in a previously cleared cohort requires consent of the Medical Monitor as the priority for enrollment in this study is into advancing cohorts. The size of a given cohort above the number required to assess safety may be limited by the Medical Monitor at any time during the study.

Patients whose vemurafenib dose was limited to 720 mg bid due to tolerability issues will not be allowed to receive dose combinations containing 960 mg bid of vemurafenib (Cohorts 1B, 1D, and 3−5).

Patients previously treated with 960 mg bid of vemurafenib may enroll in cohorts where vemurafenib dosing is limited to 720 mg bid (Cohorts 1, 1A, 1C, 2, 2A). In these cases, patients must have their vemurafenib dose reduced to 720 mg bid for at least 1 week prior to starting the vemurafenib plus cobimetinib combination.

Previously untreated patients with locally advanced/unresectable or metastatic melanoma or those previously treated but without prior exposure to any BRAF or MEK inhibitor therapy:

This category of patients can enroll in all cohorts except the cobimetinib monotherapy cohort. Patients who are initiating study therapy and for whom a slot does not exist in the currently enrolling dose cohort have the option of receiving a previously cleared vemurafenib/ cobimetinib dose combination or waiting until a slot in the current or next dose-escalation cohort is available. Expansion of previously cleared cohorts should increase the accuracy of the safety assessment. Enrollment in a previously cleared cohort requires consent of the Medical Monitor, as the priority for enrollment in this study is into advancing cohorts. The size of a given cohort above the number required to assess safety may be limited by the Medical Monitor at any time during the study.

De-Escalation Cohorts -1 to -3 and -1A, -1B, -1C, and -1D

Patients who previously tolerated 720 mg or 960 mg bid of vemurafenib must be dose reduced to the lower, cohort-specific vemurafenib dose for at least 1 week prior to starting the vemurafenib plus cobimetinib combination in Cohorts -1, -2, -3 and -1A, -1C, and -1D.

Cobimetinib Monotherapy Cohort

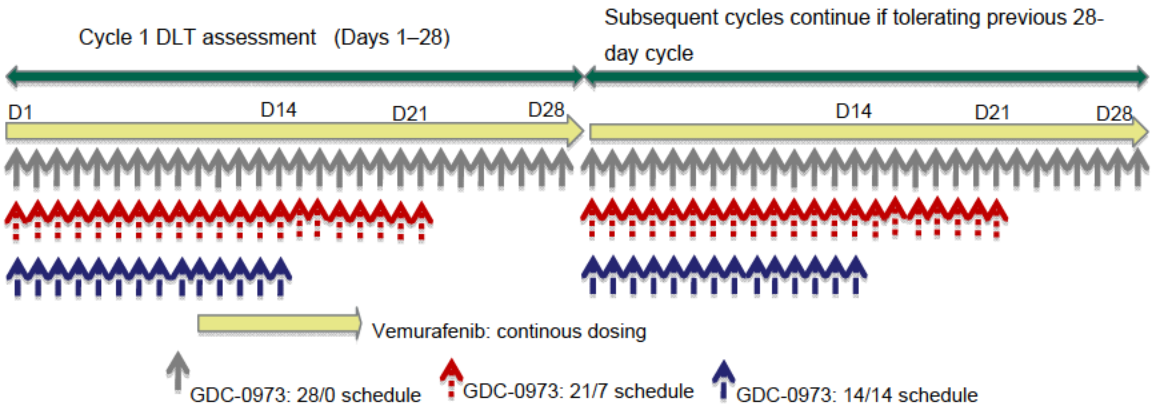
Participation in this cohort is limited to patients meeting one of the following criteria. Patients previously treated with vemurafenib at a dose of:

1. 480 mg bid due to tolerability issues at higher doses and who progressed at this dose prior to enrolling in this study
2. 720 mg or 960 mg bid vemurafenib for whom a treatment slot does not exist in the currently enrolling dose escalation cohort(s), and who are not able to wait for the next available cohort to open
3. Note: The total number of cobimetinib monotherapy patients who satisfy either criterion 1 or 2 above is limited to 20.

Dosing in the combination cohorts:

For patients in the vemurafenib and cobimetinib dose combination cohorts, all cycles will be 28 days. Vemurafenib will be dosed bid on Days 1–28; cobimetinib will be dosed qd on Days 1–14, followed by 14 days off on Days 15–28, qd on Days 1-21, followed by 7 days off on Days 22–28 or qd on Days 1–28 (Figure 6).

Figure 6: Dosing Schema for Patients Receiving Vemurafenib and Cobimetinib



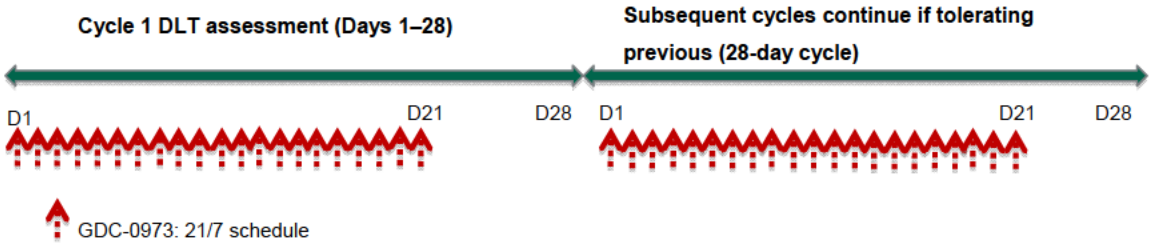
3.1.2 Option to Receive Single-Agent Cobimetinib

Enrollment in this cohort is limited to 20 patients and will require the approval of the Medical Monitor. See Section 3.1.1 for details on the eligible patient population.

Dosing for Single-Agent Cobimetinib

For patients receiving single-agent cobimetinib, all cycles will be 28 days. cobimetinib dose will be 60 mg qd on Days 1–21, followed by 7 days off on Days 22–28 (Figure 7).

Figure 7: Dosing Schema for Patients Receiving Single-Agent Cobimetinib



3.1.3 Dose-Limiting Toxicity Assessment Window

For all patients enrolled in the vemurafenib and cobimetinib combination cohorts, DLTs will be assessed during a DLT assessment window of 28 days in Cycle 1. The 28-day DLT window will not apply for patients treated with single-agent cobimetinib.

Dose reductions are not allowed during the DLT window for a patient to count in dose-escalation decisions.

Patients who discontinue study treatment or miss 3 or more total days of either vemurafenib or cobimetinib prior to completing the DLT assessment window for any reason other than DLT will be replaced.

3.1.4 Rules for Dose-Escalation and Potential Dose De-Escalation; Changes in Dose Scheduling following Dose-Limiting Toxicity

Dose escalation will occur in accordance with the rules listed below. Intra-cohort dose escalation is not allowed.

- A minimum of 3 patients will be initially enrolled per cohort
- If 1 of the first 3 patients enrolled in a given cohort experiences a DLT, at least 3 additional patients will be enrolled in that cohort.
- If fewer than one-third of evaluable patients in a given cohort experiences a DLT (e.g., DLTs in fewer than 1 of 3 or 2 of 6 patients), escalation will proceed to the next higher dose cohort.
- If a DLT is observed in one-third or more of patients (e.g., 2 or more of up to 6 patients), the dose combination at which this occurs will be considered intolerable, and the MTD will have been exceeded.

- The highest dose level(s) at which fewer than one-third of patients (e.g., 1 out of 6) experiences a DLT will be declared the MTD(s). If only 3 patients were initially evaluated at that dose level, an additional 3 patients will be enrolled to evaluate for DLTs at that dose level. It is possible that more than one MTD combination may be determined, e.g., if the dose combinations in Cohorts 2 and 3 are both deemed to be safe and tolerable and the dose combination in Cohort 4 is not; or if there are different MTDs for the combination of vemurafenib with cobimetinib dosed on a 14/14, 21/7, or continuous daily schedule. In these cases, more than one combination MTD dose and schedule may be expanded. A minimum of two expansion cohorts (n= 20 per cohort) will be enrolled (see below), one consisting of patients who have progressed on vemurafenib monotherapy immediately preceding enrollment in this trial and the other consisting of previously untreated patients with locally advanced/unresectable or metastatic melanoma or those previously treated but without prior exposure to any BRAF or MEK inhibitor therapy.
- If the combination MTD is exceeded in Cohort 1 (in which cobimetinib is given on a 14/14 schedule), further dose escalation will be discontinued, and instead, dose de-escalation with Cohort -1, -2 and Cohort -3 may occur (see Table 6). If the combination MTD is exceeded in Cohort 1A (in which cobimetinib is given on a 21/7 schedule), dose de-escalation with Cohort -1A may occur. If the combination MTD is exceeded in Cohort 1B, 1C, or 1D, dose de-escalation in Cohort -1B, -1C,or -1D, respectively, may occur (see Table 7).
- After dosing has been completed in each cohort, data pertaining to dose-escalation decisions will be reviewed by a committee composed of the following Sponsor representatives: Roche/Genentech Medical Monitor, statistician, Roche/Genentech safety officer with consultation from the PK scientist and Global Studies Leader. Investigator input will be provided by the principal investigators.

This committee will review available relevant data on demographics, adverse events, laboratory assessments, 12-lead ECGs, and dose administration logs, as well as PK data. On the basis of a review of these data and in consultation with the participating investigators, a determination will be made as to whether dose escalation should continue, and if so, at what level and schedule. The selection of a recommended Phase II dose and schedule will depend upon results of the safety, activity, and PK evaluations from all patients treated in both the dose-escalation and cohort-expansion stages.

The overall vemurafenib and cobimetinib dose-escalation/de-escalation plan is depicted in Figure 4, Figure 5, Table 5, Table 6, and Table 7.

On the basis of a review of available safety and PK data during this and other studies with both agents, dose-escalation may be halted or modified by the Sponsor, in consultation with investigators as deemed appropriate for safety concerns.

3.1.5 Definition of Dose-Limiting Toxicity

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). A copy of this grading scale will be provided to the study sites upon request or can be accessed at **http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm**

DLT definitions reflect the known and expected toxicities of vemurafenib and cobimetinib.

A DLT definition is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to study treatment (per guidance in Section 7).

- Grade ≥ 3 non-hematologic, non-hepatic organ toxicity, EXCLUDING the following:
  a) Grade 3 nausea or vomiting that resolves to Grade ≤ 1 within 7 days of appropriate supportive therapy
  b) Grade 3 diarrhea that resolves to Grade ≤ 1 within 7 days with appropriate supportive therapy
  c) Grade 3 rash that resolves to Grade ≤ 2 within 7 days with appropriate supportive therapy
  d) Grade 3 photosensitivity that resolves to Grade ≤ 2 within 7 days with appropriate supportive therapy
  e) Grade 3 cuSCC that is subsequently resected
  f) Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days
  g) Grade ≥ 3 hyperuricemia that resolves to Grade ≤ 2 within 7 days
  h) Grade 3 fever
  i) Grade 3 or 4 elevation of serum CPK levels, which is asymptomatic (i.e., not accompanied by signs, symptoms, or other laboratory abnormalities associated with rhabdomyolysis or myocardial injury), deemed by the investigator to be clinically insignificant and that returns to Grade ≤2 within 14 days of cobimetinib treatment interruption.
- Grade ≥ 3 febrile neutropenia
- Grade ≥ 4 neutropenia (ANC <500/µl)
- Grade ≥ 4 thrombocytopenia
- Grade ≥ 4 anemia
- Grade ≥ 3 total bilirubin, hepatic transaminase (ALT or AST), ALP, with the following exceptions:

  Patients with Grade 2 hepatic transaminase or ALP elevation at baseline as a result of metastases; for these patients, hepatic transaminase or ALP elevation ≥10 x upper limits of normal (ULN) will be considered a DLT.

All DLTs will be reported by telephone to the Medical Monitor within 24 hours.

3.1.6 Dosing beyond Cycle 1

Treatment will continue until disease progression, unacceptable toxicity, or any other discontinuation criterion is met (Section 4.5). There may be circumstances in which one of the study drugs is discontinued (e.g., as outlined in dose modification, Section 6.1). In the case of permanent cobimetinib discontinuation, patients previously treated with vemurafenib should come off the study. In the case of permanent vemurafenib discontinuation, it will be possible for the patient to continue treatment with single-agent cobimetinib until disease progression, unacceptable toxicity, or any other discontinuation criterion is met (see Section 4.5). In patients without prior treatment for locally advanced and unresectable or metastatic melanoma, permanent discontinuation of either drug while continuing the other will not be grounds for study discontinuation.

3.2 Stage 2: Cohort-Expansion Stage

After a cohort is declared safe and tolerable, cohort-expansion may be instituted for that specific cohort. For a given vemurafenib/ cobimetinib dose and schedule, a minimum of 2 expansion cohorts will be enrolled, and each will consist of approximately 20 patients. Expansion Cohort 1 will be open to patients whose melanoma has progressed while on vemurafenib immediately preceding enrollment in this trial and Expansion Cohort 2 will enroll patients without prior treatment for locally advanced/unresectable or metastatic melanoma or those who are previously treated but without prior exposure to any BRAF or MEK inhibitor therapy. Expansion cohorts will allow for the gathering of additional safety and PK data and the opportunity to better describe the PD effects of the combination. The cobimetinib schedule(s) to be used in each expansion cohort (i.e., 14/14 vs. 21/7 vs. continuous daily schedule) will be based upon an evaluation of safety, activity, and PK results from all patients treated on these schedules during the dose-escalation stage.

Results from the cohort-expansion stage will further inform our choice of the optimal dose and schedule of cobimetinib in combination with vemurafenib for further clinical testing (Table 8).

Table 8 Cohort Expansion for Patients Receiving Vemurafenib and Cobimetinib

Cohort (patient number)	Vemurafenib/Cobimetinib dose, schedule	Eligible patients
1 (n=20)	Combination MTD at one or more dose/schedule	Vemurafenib progressors only
2 (n=20)	Combination MTD at one or more dose/schedule	(PUPs and PTPs)

PTPs: patients previously treated for locally advanced/unresectable or metastatic melanoma but without prior exposure to any BRAF or MEK inhibitor therapy.
PUPs: patients previously untreated for locally advanced/unresectable or metastatic melanoma.

All patients, whether enrolled in the dose-escalation or expansion stage of the study, will be required to provide melanoma tumor biopsy samples at baseline (pre-treatment), Day 14, and at disease progression for PD biomarker analyses. These lesions should have accessible melanoma tumors that may be biopsied with minimal risk and discomfort. In cases where there are no lesions amenable to biopsy, sample collection can be omitted. This should be discussed with the Medical Monitor.

Patients in the expansion stage (Stage 2) of the study will undergo the same tumor, safety, PD marker, biomarker, and PK assessments as those enrolled in the dose-escalation cohorts. Note: PK assessments upon disease progression, at the time of DLT, and at the time of dose reduction/treatment interruption due to adverse events were no longer required as of protocol amendment j.

If the frequency of Grade 3 or 4 toxicities or other unacceptable chronic toxicities in the cohort-expansion stage suggests that the MTD has been exceeded at that dose level, any remaining accrual at that dose level will be halted. Consideration will then be given to enrolling expansion cohorts at a lower dose combination level.

As noted above, it is possible that more than one MTD combination will be defined, consisting of different dose combinations and/or schedules of vemurafenib and cobimetinib that are deemed safe and tolerable. If this occurs, it is possible that more than two expansion cohorts will be enrolled to gather additional safety, PK, and PD data at these MTD combinations and schedules.

3.3 Rationale for Patient Selection

Patient with previously untreated, $BRAF^{V600E}$ mutation-positive, locally advanced and unresectable or metastatic melanoma OR those previously treated but without prior exposure to any BRAF or MEK inhibitor therapy are eligible. Additionally, those who exhibit documented evidence of asynchronous progression of melanoma during participation in a Phase I (PLX06-02, clinical pharmacology studies), Phase II (BRIM-2), or Phase III clinical trial of vemurafenib monotherapy (including the expanded access protocol) or while receiving vemurafenib in a postmarketing setting immediately prior to enrollment in this study will also be eligible.

The $BRAF^{V600E}$ mutation status for eligible patients must have been determined using the **cobas**® diagnostic test.

Patients previously treated with vemurafenib (either in a clinical trial or postmarketing setting):

The majority of patients with metastatic melanoma treated in Phase I and II clinical trials of vemurafenib have had asynchronous progression, where progression occurs in a subset of lesions (i.e., less than 30% of those identified as target lesions). This pattern of discordant/mixed progression suggests that there may be a benefit to continuing treatment with vemurafenib to maintain disease control in the non-progressing lesions.

The reason for this pattern of mixed progression in patients treated with vemurafenib is unclear. Preliminary review of data from Study PLX06-02 suggests that progressing patients maintain their BRAF mutation. It is likely that as melanomas progress, the functional redundancy between the numerous signaling pathways present in the tumor allows the tumor to overcome previously effective pathway blockade [15]. Overexpression of CRAF is hypothesized to play a role in the escape of $BRAF^{V600E}$-mutated tumors to vemurafenib treatment, for example.

In vitro and in vivo assessments of MEK inhibitors have shown that they can inhibit the growth of $BRAF^{V600E}$-mutated melanomas. In fact, the presence of BRAF mutations

appears to predict for sensitivity to MEK inhibition [25, 31]. This sensitivity may result from the suppression of the RAF/MEK/ERK pathway.

The additional RAS/RAF/MEK/ERK pathway suppression from cobimetinib in combination with vemurafenib may re-establish and enhance tumor control in the progressing lesions of patients experiencing discordant/mixed progression on treatment with vemurafenib.

Patients without prior treatment for locally advanced/unresectable or metastatic melanoma or those previously treated but without prior exposure to any BRAF or MEK inhibitor therapy:

Inclusion of this category of patient will allow a more expedient assessment of the optimal dose(s) and schedule(s) for the vemurafenib/ cobimetinib combination as well as a preliminary assessment of the activity of this combination in relationship to that observed historically with vemurafenib monotherapy.

3.4 Rationale for Starting Dose and Schedule

The starting dose of vemurafenib in this Phase Ib study will be 720 mg bid for 28 consecutive days of each 28-day cycle of combination dosing, which is one dose level below the single-agent MTD of 960 mg bid administered on this schedule as established in the vemurafenib Phase Ia trial (PLX06-02) and which has been utilized in all subsequent vemurafenib clinical trials. The 720 mg bid dose has been shown to be effective and tolerable in the subset of patients requiring dose reduction in the Phase I and II trials of vemurafenib. This dose should be adequate to maintain vemurafenib-mediated control of non-progressing lesions and, at the same time, allow for combination with cobimetinib. Patients in screening (written informed consent) for this study who were previously receiving 960 mg bid vemurafenib will be dose-reduced to 720 mg bid for 7–14 days prior to Cycle 1, Day 1 in Cohorts 1, 1A, 2, 2A or 1C. Patients receiving 960 mg bid vemurafenib prior to screening initiation (written informed consent) and assigned to Cohorts 1B, 1D, 3, 4, or 5 will continue receiving 960 mg bid vemurafenib throughout the screening period, assuming this dose has been adequately tolerated prior to starting the study. Patients in screening for this study who are naïve to prior treatment with vemurafenib at the time of consent will only start vemurafenib on Cycle 1, Day 1 once they are deemed eligible for enrollment. As soon as feasible after signing informed consent, patients should initiate vemurafenib treatment with study drug provided expressly for this particular study and discontinue their supply of study drug from the antecedent vemurafenib clinical study or commercial source.

The starting dose of cobimetinib in this Phase Ib trial will be 60 mg per day for 14 consecutive days of each 28-day cycle of combination therapy, which is two dose levels below the single-agent MTD of 100 mg per day administered on this schedule. cobimetinib dosing will be investigated in the current study on a 14/14, a 21/7, and a continuous daily schedule as it is unclear whether a schedule that may deliver higher peak concentrations of cobimetinib over a shorter treatment interval per cycle (i.e., the 14/14 schedule) will exhibit a better safety and tolerability profile than one associated with lower peak concentrations but longer duration of exposure per cycle (i.e., the 21/7 or continuous daily schedule). As noted, the safety and tolerability of

cobimetinib monotherapy on a 21/7 schedule (MTD–60 mg/day) has been established in the MEK 4592g study.

Review of nonclinical and available clinical data for vemurafenib and cobimetinib suggest that the risk for significant additive or overlapping toxicities or DDI potential is tolerable. In vivo combinations of vemurafenib and other MEK inhibitors or cobimetinib and other BRAF inhibitors in xenograft models have not demonstrated toxicities that impacted dosing. Therefore, it is anticipated that 720 mg bid of vemurafenib dosed daily for 28 days in combination with 60 mg of cobimetinib dosed daily for 14 days of a 28-day cycle are appropriate starting doses with which to evaluate this combination.

3.5 Rationale for Pharmacokinetic Evaluation Schedule

Vemurafenib and cobimetinib will be used in combination in metastatic melanoma patients for the first time in this study.

Historical PK data are available for both compounds as monotherapies. Data from the combination of both drugs used in this study will be compared with these historical controls to monitor any unexpected changes in pharmacokinetics that may occur following the co-administration of both drugs. Currently, no major concerns have been identified for any PK interaction between vemurafenib and cobimetinib. In vitro experiments indicate that vemurafenib may be a weak substrate and moderate inhibitor of Pgp. Cobimetinib is a substrate of Pgp and combination therapy with vemurafenib may lead to an alteration of plasma exposures of cobimetinib. Additional nonclinical and clinical data regarding the metabolism of vemurafenib suggest that the drug may be a mild inducer of CYP3A4. Preliminary information suggests that CYP3A and UGT2B7 are the enzymes responsible for cobimetinib metabolism. However, the fraction of cobimetinib metabolized by CYP3A is unknown. Thus, induction of CYP3A4 by vemurafenib may lead to decreased systemic exposures of cobimetinib.

In vitro CYP inhibition studies suggest that cobimetinib has a moderate potential to interact with drugs that are substrates for CYP2D6 (IC_{50} 1.8μM) or CYP3A (IC_{50} 5.9–1.7 μM; Ki 7.6 μM). It is unclear how cobimetinib may alter the pharmacokinetics of vemurafenib.

For patients who have progressed while receiving vemurafenib monotherapy immediately preceding enrollment in this trial only, an exposure time profile for vemurafenib will be taken at Day -1, spanning an 8-hour post-dose period to determine the exposure level of this drug prior to study start. Patients assigned to Cohorts 1, 1A, 2, 2A, and 1C who tolerated 960 mg bid vemurafenib prestudy will be dose reduced to 720 mg bid for at least 1 week prior to study start.

There will be no opportunity to evaluate the pharmacokinetics of cobimetinib monotherapy in this study except in those patients who are treated in the cobimetinib monotherapy arm. Cobimetinib will be combined with vemurafenib on Day 1, and for all patients, PK assessments will occur on Day 1 for cobimetinib (0, 0.5, 1, 2, 4, and 6 hours post-dose) and Day 14 (0, 0.5, 1, 2, 4, 6, and 8 hours post-dose) for both agents to characterize exposure for each drug after single dose and at steady state, respectively. A PK assessment will be made on Day 8 to characterize the approach to steady state. Additional PK samples will be collected during the 14-days off period for cobimetinib to evaluate the elimination properties (t1/2 clearance) of the drug in the presence of vemurafenib for those patients treated on a 14/14 schedule only.

Lastly, for both compounds, periodic steady-state PK samples will be collected in subsequent cycles to ensure patients are exposed to constant drug levels throughout the study. For additional information on PK sampling, refer to Table 10 and Table 11.

3.6 Rationale for Dosing beyond Cycle 1

The ethical conduct of studying cancer therapeutics requires that patients have the opportunity to continue study treatment for as long as the treatment is effective and tolerable. Therefore, patients enrolled in this study who comply with the requirements of the protocol and are tolerating study treatment may continue dosing until disease progression, unacceptable toxicity, or any other discontinuation criterion is met (Section 3.1.6).

3.7 Rationale for Collection of Patient Specimens for Molecular Analyses (Biopsies, Plasma, Blood)

Roche is committed to the collection of patient specimens in all clinical study protocols. The objective of molecular analyses (biomarker profiling) is to enable development of treatments specifically targeted for optimal patient benefit (personalized healthcare). The rationale of planned molecular analyses is explained below. However, since knowledge of the drug, the disease, new markers, and technologies are evolving, the definitive list of analyses may be modified based on new information as the information becomes available.

Investigation of Response/Resistance Markers

To identify causes for resistance, molecular analyses will be performed to investigate BRAF, CRAF, PTEN, RAS, and MEK, as well as further key pathway markers at the protein, mRNA, and genetic level.

As this study shall help to create new hypotheses of response/resistance mechanisms for this drug combination, genetic analyses of the whole genome of tumors is required and shall be performed if patient consents. These analyses allow us to identify mutations that have so far not been associated with drug resistance and help to answer the questions how to treat or further treat patients.

To assess mechanisms of response and resistance to the vemurafenib and cobimetinib combination therapy, baseline (the post-progression biopsy sample from the previous

vemurafenib study may be substituted), Day 10 to 14, and disease progression biopsies from melanoma tumors will be analyzed for all patient cohorts, if available.

$BRAF^{V600E}$ mutation will be evaluated retrospectively on tumor biopsies collected during this study and in plasma. It has been shown that tumor-specific mutations can be identified in serum/plasma of patients. Analysis and correlation of plasma and biopsy will help to further evaluate the option of using plasma for the detection of tumor specific mutations.

BRAF mutations have remained stable in previous analyses of melanoma tumors over time (data on file). Therefore, BRAF mutation testing of tumor samples will not be prioritized.

Molecular Characterization of SCC or Other Suspicious Neoplasms

The objective of molecular analyses using SCC or other suspicious neoplasm specimens is to further understand the mechanism and cause of SCC development in recipients of vemurafenib and to identify factors that may pre-dispose patients to develop drug-induced SCC (see Section 5.3.4.6).

Lesions that are suspicious for malignancy other than SCC may be submitted at the discretion of the investigator.

Genetic analysis of RAS, p53, and RAF, as well as analyses of MAPK pathway protein activation, will be performed using specimens from SCC or suspicious neoplasms, as well as paired normal skin. Normal skin will be needed as a control in order to be able to explore differences in MAPK pathway activation.

Molecular Analyses to Investigate Drug Effects of Vemurafenib and Cobimetinib

In vitro experiments on $BRAF^{V600E}$-positive melanoma cell lines have shown suppression of ERK and MEK phosphorylation in response to vemurafenib dosing. ERK and MEK phosphorylation will be investigated in melanoma tumor biopsies to assess the effect of the drug combination directly on the tumor. Other molecular analyses may be performed in light of emerging scientific information.

3.8 Rationale for Evaluating FDG-PET Changes

Serial FDG-PET scans are used routinely to monitor anti-tumor activity in patients with advanced cancer including metastatic melanoma. In addition, it is sometimes used as a non-invasive PD measure of drug activity.

a) In this study, FDG-PET imaging will be used to provide a non-invasive measurement of drug activity and a potential early readout of anti-tumor activity in patients receiving the vemurafenib and cobimetinib combination or cobimetinib monotherapy. All patients in the study who have PET-avid disease at screening will be asked to undergo FDG-PET imaging at three additional timepoints during study treatment:
   - Steady state in Cycle 1 (between Days 10–14)
   - Cycle 2, Day 14 ± 7 days (coinciding with first CT/MRI response assessment)

- Disease progression (for characterization of progression patterns; when available)

3.9 Outcome Measures

3.9.1 Safety Outcome Measures

Safety outcome measures for this study are as follows:

- Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to NCI CTCAE v4.0
- Incidence and nature of DLTs
- Changes in vital signs, ECGs, and clinical laboratory results during the course of study (see Section 5.3).

3.9.2 Pharmacokinetic and Pharmacodynamic Outcome Measures

The goal of PK sampling is to describe vemurafenib and cobimetinib pharmacokinetics when given in combination and in comparison with historic controls when the agents were given as monotherapy. The relationship between vemurafenib and cobimetinib concentrations and anti-tumor activity will also be described.

Vemurafenib and cobimetinib PK parameters will be determined in all patients who receive study treatment using non-compartmental analysis and/or population methods.

For both vemurafenib and cobimetinib, the following PK parameters will be estimated:

- Total exposure ($AUC_{0\text{-last}}$)
- Maximal plasma concentration (C_{max})
- Minimal plasma concentration (C_{min})
- Other PK parameters may be determined after visual inspection of observed concentration–time data.

The following PD outcome measures will be assessed:

- FDG-PET response rates based on modified definitions proposed by the European Organization for Research of Cancer (EORTC; [32]) and as assessed by an independent, blinded FDG-PET Image Reading Facility (IRF)

- Changes in effector molecules of the MAPK pathway that are directly or indirectly affected by BRAF and MEK inhibition (including but not limited to ERK and phosphorylated ERK and MEK) by IHC using biopsies at baseline, between Days 10–14 of Cycle 1, and at disease progression (when available).

3.9.3 Efficacy Outcome Measures

The following activity outcome measures will be assessed (see Section 5.3.2 for methods of assessments):

- Objective response (OR)
- PFS
- DOR

- OS

3.9.4 Exploratory Outcome Measures

To evaluate the relationship between anti-tumor activity (objective response rate, PFS, DOR, etc.) and changes in PD biomarkers or other genetic alterations when vemurafenib and cobimetinib are administered in combination.

3.10 Safety Plan

Measures will be taken to ensure the safety of patients participating in this trial, in particular, the use of stringent inclusion and exclusion criteria (Sections 4.2 and 4.3) and close monitoring of patients as indicated below and in Section 3.10.

Because this is the first time vemurafenib and cobimetinib will be administered to humans in combination, all patients will be monitored closely for toxicity. All adverse events will be recorded during the trial and for up to 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever comes first. The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

As with other vemurafenib studies, the risk for SCC will be mitigated by utilization of the Risk Management Plan (RMP) that is described in Section 5.3.4.6 of this protocol.

3.10.1 Risks Associated with Vemurafenib

The toxicity profile for vemurafenib has been documented from safety data derived from seven studies of more than 600 treated patients with locally advanced unresectable or metastatic melanoma. The most common toxicities observed were rash, fatigue, arthralgia, myalgia, headache, nausea, photosensitivity, alopecia, and pruritus. The most common laboratory abnormalities reported as adverse events included elevations of liver function tests (i.e., GGT, ALP, ALT, AST, and bilirubin). *Other safety events for vemurafenib used in monotherapy include new primary malignancies such as cutaneous malignancies, non-cutaneous squamous cell carcinoma, and other malignancies; tumor promotion in BRAF wild-type malignancies; hypersensitivity reactions; hepatotoxicity; ophthalmologic reactions; embryo-fetal toxicity; radiation sensitization and radiation recall; and renal failure. Please refer the vemurafenib IB for additional safety information.*

The majority of adverse events reported in conjunction with Phase I through III clinical trials were of mild or moderate severity. Approximately one-half of all patients treated with vemurafenib required interruption and/or reduction of dose on at least one occasion, although treatment discontinuation due to adverse events has been rare.

Approximately 20% of vemurafenib recipients developed one or more localized cuSCCs (mainly KA type). The majority of these were observed within the first 16 weeks of vemurafenib exposure and were not treatment limiting. The risk for cuSCC will be mitigated through the use of a Risk Management Plan as outlined in Section 5.3.4.6. This plan has been utilized across all clinical studies of vemurafenib to date.

Analysis of ECG data from the Phase II NP22657 study of vemurafenib in metastatic melanoma patients (Genentech, data on file) revealed a risk of QT interval prolongation without associated clinical symptomatology.

Two cases of SCC of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled on a clinical trial. In addition, 2 cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for >2 years.

As of the second quarter of 2014, an adverse drug reaction of pancreatitis has been identified in patients being treated with vemurafenib. Seventeen cases of pancreatitis with no strong risk factors or alternative explanations were reported. Eight of the 17 cases were assessed as likely associated with vemurafenib use based on event onset latency and rechallenge/dechallenge information. The clinical presentation, including mild to moderate severity, was consistent with the clinical picture of drug-induced pancreatitis [18].

The Sponsor recommends that serum amylase and lipase testing be conducted as part of the workup of any suspected case of pancreatitis in addition to other appropriate testing (e.g., CT of the abdomen).

An adverse drug reaction of acute kidney injury, including interstitial nephritis following vemurafenib administration, has been identified in patients being treated with vemurafenib. The majority of these cases were characterized by mild to moderate increases in serum creatinine (some observed in the setting of dehydration events) with recovery after dose modification. Approximately 2% of acute kidney injury cases were biopsy–proven interstitial nephritis, and approximately 3% of acute kidney injury cases were acute tubular injury/necrosis. No fatal cases were related to acute kidney injury.

Renal function should be monitored in patients who are undergoing vemurafenib treatment. Vemurafenib dose modification guidelines should be utilized when applicable, and it is recommended to routinely monitor serum creatinine levels in all patients undergoing vemurafenib therapy.

Please refer the vemurafenib IB for additional safety information.

3.10.2 Risks Associated with Cobimetinib

3.10.2.1 *Identified Risks Associated with Cobimetinib*

Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with Cotellic. In clinical studies with cobimetinib, events of cerebral hemorrhage, gastrointestinal tract hemorrhage, reproductive tract hemorrhage, and hematuria, have been reported.

In the Phase III study GO28141, Grade 1-4 hemorrhagic events were reported in 13.0% of patients treated with cobimetinib plus vemurafenib, and in 7.3% of patients treated with placebo plus vemurafenib. The majority of hemorrhagic

events were Grade 1 or 2 and non-serious. Grade 3-4 hemorrhage events were reported in 1.2% of patients receiving cobimetinib plus vemurafenib and 0.8% of patients receiving placebo plus vemurafenib.

Caution should be used in patients with additional risk factors for bleeding, such as brain metastases, and/or in patients that use concomitant medications that increase the risk of bleeding (including antiplatelet or anticoagulant therapy).

Instructions for Dose Modification for hemorrhage events are included in Table 12 in Section 6.1.1.

Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK inhibitors, including cobimetinib [33]. Manifestations of serous retinopathy include visual disturbances, findings of retinal detachment, and retinopathy. Serous retinopathy events may also be asymptomatic.

Serous retinopathy has been characterized in the Phase III Study GO28141. The study incorporated prospective serial ophthalmic examinations for all enrolled patients. Serous retinopathy was reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (25.5% vs. 2.8%, respectively), and approximately half of the events were asymptomatic Grade 1 events. Few patients treated with cobimetinib plus vemurafenib experienced Grade≥3 ocular adverse events (2.8%); the majority of these were managed with dose modification of both cobimetinib and vemurafenib.

To address serous retinopathy with cobimetinib treatment, all patients are required to undergo a baseline ophthalmologic examination to assess for history or evidence of retinal pathology that is considered to be a risk factor for or indicative of neurosensory retinal detachment, central serous chorioretinopathy, neovascular retinopathy, or retinopathy of prematurity. Patients will also undergo ophthalmologic examinations at specified timepoints throughout the study (see the schedule of assessments and procedures in Section 5). Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 5.3.4.4.

Guidelines for management of patients who develop Grade≥2 visual disorders or retinopathy are provided in Section 6.1.1.

Left Ventricular Dysfunction

Decreases in LVEF from baseline have been reported in patients receiving cobimetinib. Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in LVEF events may be asymptomatic.

Left ventricular dysfunction has been characterized in the Phase III Study GO28141, which incorporated prospective serial LVEF evaluation in all patients. With active surveillance, measured reductions in LVEF were observed more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (26% vs. 19%,

respectively, of Grade 2 or 3 decrease). Of the patients treated with cobimetinib plus vemurafenib, 2 patients (0.8%) had symptomatic reduction in LVEF, and the remaining patients were asymptomatic. Most LVEF reduction events in patients on cobimetinib plus vemurafenib (62%) improved or resolved with management according to the dose-modification guidelines (see Section 6.1.1).

Rhabdomyolysis and CPK Elevations

Elevations in CPK have been observed in patients who received cobimetinib monotherapy as well as when administered with other agents. The majority of CPK elevations reported were asymptomatic, non-serious, and resolved with or without study drug interruption. One event of rhabdomyolysis was reported in the Phase III study GO28141 (cobimetinib plus vemurafenib), and rhabdomyolysis has been reported in postmarketing experience.

In Study GO28141, elevated CPK was reported as an adverse event more frequently in patients treated with cobimetinib plus vemurafenib (32.4% all grades, 11.3% Grade ≥ 3 events) than placebo plus vemurafenib (8.1% all grades, 0% Grade ≥ 3 events).

CPK will be monitored at baseline and monthly during treatment or as clinically indicated. Instructions for Dose Modification for elevated CPK and rhabdomyolysis are included in Table 12 in Section 6.1.1.

Photosensitivity (when Administered with Vemurafenib)

No evidence of phototoxicity has been observed with cobimetinib as a single agent. However, photosensitivity was observed on Study GO28141 with a higher frequency in the cobimetinib plus vemurafenib arm versus the placebo plus vemurafenib arm (46% vs. 35%, respectively). The majority of events were Grades 1 or 2, with Grade≥3 events occurring in 4% of patients in the cobimetinib plus vemurafenib arm versus 0% in the placebo plus vemurafenib arm. Grade≥3 photosensitivity events in the cobimetinib plus vemurafenib arm were treated with primary topical medication in conjunction with interruption of study agents. Refer to Section 6.1.1 for photosensitivity management guidelines.

Pneumonitis

Events of pneumonitis have been reported in cobimetinib clinical studies. Most reported events were considered non-serious and of low-severity grade. In the Phase III Study GO28141, pneumonitis events were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (1.6% vs. 0.4%, all grades). There were no reported Grade≥3 events in either study arm. Serious adverse events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib.

3.10.2.2 *Potential Risks Associated with Cobimetinib*

Liver Laboratory Abnormalities and Severe Hepatotoxicity

Liver laboratory test abnormalities, including increases in ALT, AST, and ALP, have been reported as adverse events and serious adverse events in patients treated with cobimetinib plus vemurafenib.

In the Phase III Study GO28141, liver laboratory test abnormalities reported as Grade≥3 adverse events occurred more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (20.5% vs. 15.1%, respectively).

Generally, elevations in liver laboratory tests were managed effectively with dose modification guidelines. In both study arms, the majority of Grade≥3 liver laboratory test abnormalities resolved.

Impaired Female Fertility

There is a potential for effects on fertility and embryo-fetal toxicity based on results from nonclinical studies.

While no dedicated fertility studies have been conducted with cobimetinib in animals, degenerative changes observed in reproductive tissues included increased apoptosis/necrosis of corpora lutea and seminal vesicle, epididymal and vaginal epithelial cells in rats, and epididymal epithelial cells in dogs. These changes were reversible upon discontinuation of cobimetinib administration.

Teratogenicity and Developmental Toxicitiy

In a dedicated nonclinical embryo-fetal toxicity study, cobimetinib produced fetal toxicity (resorptions and reductions in fetal weight), and teratogenicity (malformations of the great vessels and skull) at similar systemic exposures in rat to those observed in patients administered the 60 mg dose.

3.10.2.3 *Other Risks Associated with Cobimetinib*

Rash

In the Phase III Study GO28141, combined rash events of all types and grades were reported more frequently in patients treated with cobimetinib plus vemurafenib than placebo plus vemurafenib (71.7% vs. 66.7%, respectively), although Grade≥3 events (approximately 16% of patients) and types of rash reported were similar between study arms. Specific events in patients treated with cobimetinib plus vemurafenib included rash (39% all grades, 5.9% Grade≥3, 1.6% serious adverse events) and rash maculo-papular (14.6% all grades, 6.3% Grade≥3, 1.2% serious adverse events).

Generally, Grade≥3 rash events were effectively managed with dose modification guidelines. In GO28141, approximately 90% of Grade≥3 rash events resolved in both arms.

Gastrointestinal Toxicity

A range of gastrointestinal adverse events, including nausea, vomiting, and diarrhea, have been reported in all cobimetinib studies in adult cancer patients.

In the Phase III Study GO28141, diarrhea was the most common adverse event reported. Diarrhea events of all severity grades were reported in 59.9% of patients and Grade 3 or 4 events were reported in 6.5% of patients treated with cobimetinib plus vemurafenib versus 30.9% and 0.8%, respectively, in the patients treated with placebo plus vemurafenib. No Grade 5 events of diarrhea have been reported. Serious adverse events of diarrhea were reported in 1.2% of patients treated with cobimetinib plus vemurafenib.

Nausea and vomiting have been reported in association with cobimetinib. Most nausea and vomiting events were considered non-serious and low-severity grade. In the Phase III Study GO28141, nausea and vomiting events were reported more frequently in the active cobimetinib arm than the control arm (nausea 39.0% vs. 23.8% and vomiting 21.3% vs. 12.1%, respectively). However, of patients treated with cobimetinib plus vemurafenib, few experienced Grade 3 events (nausea 0.8%, vomiting 1.2%).

In the Phase I single-agent study (MEK4592g), all grades of nausea and vomiting were reported at rates of 33.9% with 0.9% reported for Grade≥3 nausea and no Grade≥3 events reported for vomiting.

The combination of diarrhea, nausea, and vomiting has the potential to contribute to clinically significant volume depletion/dehydration from the combination of fluid losses with decreased oral intake. In the majority of cases, diarrhea has been effectively managed with antidiarrheal agents and supportive care. Routine antiemetic prophylaxis is not recommended.

Hypersensitivity

There have been few reports of hypersensitivity and/or anaphylaxis in clinical trials with patients who have been exposed to cobimetinib monotherapy or cobimetinib when used with other agents. These have appeared to be isolated reports and, in some cases, occurred in patients with histories of drug allergies. Thus, the relationship of cobimetinib to these events is unclear.

In the Phase III Study GO28141, Grade 3 hypersensitivity events were reported in 3 patients in the cobimetinib and vemurafenib arm compared with no such events in the placebo plus vemurafenib arm. All events required hospitalization and treatment with steroids.

Investigators should promptly evaluate and treat patients who are suspected of experiencing a hypersensitivity reaction.

Please refer to the cobimetinib IB for additional safety information.

3.10.3 General Plan to Manage Safety Concerns

Eligibility Criteria

Eligibility criteria for this study were selected to guard the safety of patients in this trial. A number of exclusion criteria are specifically based on nonclinical and clinical safety data observed following exposure to cobimetinib and vemurafenib as single agents. The exclusion criteria for safety (see Section 4.3 for a complete list and description of exclusion criteria) include, but are not limited to, the following: history of prior significant toxicity from exposure to another RAF or MEK inhibitor requiring discontinuation of treatment; known brain metastases that are untreated, symptomatic, or require therapy to control symptoms; major surgical procedure or significant traumatic injury within 4 weeks prior to first dose of study drug treatment; pregnancy or lactation; clinically significant cardiovascular disease; history of congenital long QT syndrome or QTc > 450 msec; inadequate bone marrow function; inadequate hepatic or renal function; uncontrolled ascites requiring weekly large volume paracentesis; and history of malabsorption or other clinically significant metabolic dysfunction; history of RVO; evidence of visible retinal pathology that is considered a risk factor for retinal vein thrombosis; factors predisposing to RVO including uncontrolled hypertension (Grade ≥ 2 at screening), diabetes (e.g., untreated or inadequately treated Grade ≥ 2 glucose intolerance), hyperlipidemia (e.g., untreated or inadequately treated Grade ≥ 2 hypercholesterolemia or hypertriglyceridemia) or hypercoagulable state; and evidence of intraocular pressure >21 mm Hg as measured by tonometry.

Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, which are defined and graded according to NCI CTCAE v4.0.

Patients will be monitored weekly for safety during the first 8 weeks and then every 4 weeks starting with Cycle 3 and also as needed until 28 days after the last dose of study treatment or until initiation of other anti-cancer therapy, whichever occurs first. All unresolved adverse events and serious adverse events will be followed until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the adverse event or serious adverse event. Dermatologic, head and neck evaluations, and chest CT scans will be conducted according to the local standard of care after patient discontinues study treatment, withdraws consent, dies or is lost to follow-up, whichever occurs earliest. Please see Section 5.3.4.6.

Definitions of DLTs have been designed to keep the degree and frequency of severe toxicity observed in this study within acceptable limits for Phase I trials in oncology.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Section 5.3.4, Table 9 for the list and timing of study assessments).

All serious adverse events, protocol-defined adverse events of special interest, DLTs, and Grade 3 and 4 adverse events during the DLT assessment window will be reported in an expedited fashion (see Section 7.1.1.4). In addition, the Medical Monitor and the investigators will review and evaluate observed adverse events on a regular basis.

Patients who have an ongoing treatment-related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

See Table 9 and Section 5.3.4 (Assessment of Safety) for complete details of the safety evaluation for this study.

3.11 End of Study

Study treatment will be discontinued in patients who experience disease progression or unacceptable toxicity and are not eligible for single-agent cobimetinib treatment or are not compliant with the study protocol.

Upon study treatment discontinuation or withdrawal from study treatment, patients are required to continue the following assessments as indicated in the Schedule of Assessments:

- *A study completion visit will be performed 28 days after the last dose of study treatment for all patients.*
- *Survival will be collected via telephone calls and/or clinic visits every 12 weeks until death, weithdrawal of consent of loss to follow-up.*

All patients will be followed for survival information unless a patient requests to be withdrawn from follow up; this request must be documented in the patient's medical record and signed by the investigator. If the patient withdraws from study follow up, the study staff may use a public information source (such as county records) to obtain information about survival status only. Survival follow-up can be conducted via telephone.

3.12 Number of Patients/Assignment to Treatment Groups

It is estimated that approximately 3-6 patients per cohort will be enrolled during the dose-escalation stage. Additional patients may be enrolled in a previously cleared vemurafenib/cobimetinib dose combination (Section 3.1.1). Approximately twenty patients who have progressed on vemurafenib monotherapy immediately preceding enrollment in this trial as well as approximately 20 patients previously untreated or treated (but without prior exposure to any BRAF or MEK inhibitor therapy) patients in each expansion cohort will be enrolled during the cohort-expansion stage.

The single-agent cobimetinib cohort will enroll up to 20 patients who meet one of the following criteria:

- Had previously tolerated only 480 mg bid on a prior study of vemurafenib and had progressed at this dose

- Had previously tolerated 720 mg bid or 960 mg bid of vemurafenib and for whom a treatment slot does not exist in the currently enrolling, dose escalation cohort(s) and who are unable to wait for the next available cohorts to open.

3.13 Centers

Approximately 7–10 centers from two countries (United States and Australia) will participate in this study.

4. STUDY POPULATION

4.1 Overview

Patients with $BRAF^{V600E}$ mutation-positive melanoma who are previously untreated for locally advanced/unresectable or metastatic disease OR those previously treated but without prior exposure to any BRAF or MEK inhibitor therapy OR those who have progressed during treatment with vemurafenib monotherapy immediately prior to enrollment in this study will participate. Patients who progress while on vemurafenib may include those who participated in any of the current Phase I trials (including clinical pharmacology studies), the Phase II clinical trial (BRIM-2), the Phase III pivotal study (BRIM-3) and the Expanded Access Protocol (EAP) study OR those who progress while receiving vemurafenib in a postmarketing setting.

All eligible patients will have had their $BRAF^{V600E}$ mutation status confirmed using the **cobas**® test prior to study enrollment.

4.2 Inclusion Criteria

A patient may be included if the answer to all of the following statements is "yes."

Disease-Specific Inclusion Criteria:

1. Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by AJCC
2. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Appendix 1)
3. ECOG performance status of ≤ 1 (see Appendix 2)

General Inclusion Criteria:

4. Male or female patient age ≥ 18 years
5. Able to participate and willing to give written informed consent prior to performance of any study-related procedures and to comply with the study protocol
6. Patients must
   a.) be previously untreated for locally advanced/unresectable or metastatic melanoma OR
   b.) previously treated but without prior exposure to any BRAF or MEK inhibitor therapy OR

c.) progressed on vemurafenib while participating in a Phase I (including clinical pharmacology studies), II, or III clinical study or EAP immediately prior to enrollment in this study OR

d.) progressed on vemurafenib administered in a postmarketing setting immediately prior to enrollment in this study.

Note: Participants in an antecedent vemurafenib clinical trial or those who progress while receiving the drug in a postmarketing setting should exhibit evidence of discordant/mixed progression and not have received intervening antimelanoma therapy except with vemurafenib. The presence of V600E mutation in melanoma tumor tissue must be documented using the **cobas** $BRAF^{V600}$ mutation test in all patients.

7. Life expectancy ≥ 12 weeks
8. Patients must have fully recovered from the effects of any major surgery or significant traumatic injury within 14 days from the first dose of study treatment.
9. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 2 weeks prior to first dose of study drug treatment:
    - ANC ≥ 1.5 X 10^9/L
    - Platelet count ≥ 100 X 10^9/L
    - Hemoglobin ≥ 9 g/dL
    - Albumin ≥ 2.5 g/dL
    - Bilirubin ≤ 1.5 X ULN
    - AST, ALT, and ALP ≤ 2.5 X ULN, with the following exceptions:
    - Patients with documented liver metastases: AST and /or ALT ≤ 5 X ULN
    - Patients with documented liver or bone metastases: ALP ≤ 5 X ULN
    - Serum creatinine ≤ 1.5 X ULN or creatinine clearance ≥ 50 ml/min on the basis of measured creatinine clearance from a 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation: <u>(140-age) x (weight in kg) x (0.85 if female)</u>
        1. 72 x (serum creatinine in mg/dL)
10. INR and aPTT ≤ 1.5 X ULN
11. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use an effective form(s) of contraception during the course of this study and for at least 6 months after completion of study therapy.
    - Females of childbearing potential are defined as sexually mature women without prior hysterectomy who have had any evidence of menses in the past 12 months. In order to be considered NOT of childbearing potential, amenorrhea for a period of 12 months or longer must have occurred in the absence of chemotherapy, anti-estrogens, or ovarian suppression.
    - Effective forms of contraception includes surgical sterilization, a reliable barrier method with spermicide, birth control pills, or contraceptive hormone implants
12. Negative serum pregnancy test within 7 days prior to commencement of dosing in women of childbearing potential; women of non-childbearing potential may be included if they are either surgically sterile or have been naturally menopausal

for ≥ 1 year. Women of non-childbearing potential need not undergo the pregnancy test.

13. Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.
14. Consent to provide archival tissue (either a paraffin-embedded tissue block or up to 15 unstained slides) for molecular analyses to investigate BRAF, CRAS, CRAF, PTEN, RAS, and MEK, as well as other pathway markers on the protein, epigenetic, and genetic level. See Table 9 for details.
15. Consent to undergo tumor biopsies of accessible lesions for PD biomarker and molecular analyses including BRAF, CRAF, PTEN, RAS, and MEK, as well as other pathway markers on the protein, mRNA, and genetic level. See Table 9 for details.

4.3 Exclusion Criteria

A patient will be excluded if the answer to any of the following statements is "yes."

Cancer-Related Exclusion Criteria:

1. History of prior significant toxicity from another RAF or MEK pathway inhibitor requiring discontinuation of treatment
2. Allergy or hypersensitivity to components of the cobimetinib or vemurafenib formulations
3. Palliative radiotherapy within 2 weeks prior to first dose of study drug treatment in Cycle 1, Day 1
4. Experimental therapy within 4 weeks prior to first dose of study drug treatment in Cycle 1, Day 1 except vemurafenib
5. Major surgical procedure or significant traumatic injury within 14 days prior to first dose of study drug treatment in Cycle 1, Day 1 or anticipation of the need for major surgery during the course of study treatment
6. a) For patients who participated in an antecedent vemurafenib study or progressed while receiving vemurafenib in a postmarketing setting: administration of any systemic anti-melanoma therapy other than vemurafenib during the interval between documentation of progression coincident with their vemurafenib exposure and consideration for this study will render the patient ineligible.
   b) For previously untreated patients: no prior systemic, anti-cancer therapy (e.g., biologic or other targeted therapy, chemotherapy or hormonal therapy) for unresectable, locally advanced or metastatic melanoma disease. Note: Prior treatment in the adjuvant setting for previously resected melanoma is allowed.
   c) For previously treated patients: no prior exposure to any BRAF or MEK inhibitor therapy; prior treatment with systemic chemotherapy or ipilumumab is allowed.
7. Active malignancy other than melanoma that could potentially interfere with interpretation of the PD or efficacy measures

Exclusion Criteria Based on Organ Function

Ocular:

8. Evidence of visible retinal pathology, as assessed by ophthalmologic examination, that is considered a risk factor for retinal vein thrombosis
9. Intraocular pressure > 21 mm Hg as measured by tonometry
10. History of RVO
11. Predisposing factors to RVO, including uncontrolled hypertension (Grade ≥ 2 at screening), uncontrolled diabetes (e.g., untreated or inadequately treated Grade ≥ 2 glucose intolerance), uncontrolled hyperlipidemia (e.g., untreated or inadequately treated Grade ≥ 2 hypercholesterolemia or hypertriglyceridemia) or hypercoagulable state

Cardiac:

12. History of clinically significant cardiac or pulmonary dysfunction, including the following:
    - Grade ≥ 2 hypertension (treated or untreated) or unstable angina
    - Current Grade ≥2 dyspnea or hypoxia or need for supplemental oxygen
    - History of symptomatic congestive heart failure of New York Heart Association ≥ Class II (see Appendix 4) or serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia
    - History of myocardial infarction within 6 months prior to first dose of study drug treatment in Cycle 1
    - Current dyspnea at rest due to complications of advanced malignancy or any requirement for supplemental oxygen to perform activities of daily living
    - History of congenital long QT syndrome or QTc > 450 msec.

Central Nervous System:

13. Patients with active CNS lesions are excluded (i.e., those with radiographically unstable, symptomatic lesions). However, patients treated with stereotactic therapy or surgery are eligible if they remain without evidence of disease progression in the brain for ≥ 3 weeks. Whole brain radiotherapy is not allowed with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal brain lesions.

General Exclusion Criteria:

14. The patient has not recovered to Grade ≤ 1 from adverse events due to investigational or other agents administered more than 28 days prior to enrollment except for alopecia.
15. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary or metabolic disease)
16. Inability or unwillingness to swallow pills

17. History of malabsorption or other condition that would interfere with enteral absorption of study drug
18. History of clinically significant liver disease (including cirrhosis), current alcohol abuse, or known infection with HIV, hepatitis B virus, or hepatitis C virus
19. Any condition requiring therapeutic anticoagulation (e.g., for chronic atrial fibrillation) with either warfarin, or unfractionated heparin. Note: Patients receiving anticoagulation with low-molecular weight heparin, and low-dose aspirin are eligible, as long as INR and aPTT are ≤ 1.5X ULN
20. Use of thrombolytics to establish patency of obstructed indwelling venous catheters is allowed.
21. Prophylactic anticoagulation to maintain patency of venous access devices is allowed as long as INR and aPTT are ≤ 1.5 X ULN.
22. Active autoimmune disease (e.g., systemic lupus erythematosis, autoimmune vasculitis, inflammatory bowel disease)
23. Uncontrolled ascites requiring weekly large volume paracentesis for 3 consecutive weeks prior to enrollment
24. Pregnancy, lactation, or breast feeding
25. Unwillingness or inability to comply with study and follow-up procedures
26. No other history of or ongoing malignancy that would potentially interfere with the interpretation of the PD or efficacy assays
27. Need to take a concomitant medication, dietary supplement, or food that is prohibited during the study (as described in Sections 4.4.1 and 4.4.2)

4.4 Concomitant Medication and Treatment

4.4.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient within 7 days before screening through the study completion visit. Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria (see Sections 4.2 and 4.3). Patients who experience toxicities may be treated symptomatically as clinically indicated. All concomitant medications should be recorded on the appropriate electronic Case Report Form (eCRF).

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drug.

Hematopoietic growth factors (e.g., erythropoietin and granulocyte colony-stimulating factors) and pain medications administered as dictated by standard practice are acceptable while the patient is enrolled in the study. However, growth factors should not be administered prophylactically before initial treatment with study drug; nor should they be used during the DLT observation period.

4.4.2 Excluded Therapy and Food

Use of the following foods and therapies is prohibited during the study (i.e., from 7 days before screening through the study completion visit):

- Grapefruit juice
- St. John's wort or hyperforin
- Any concomitant therapy intended for the treatment of cancer (approved by health authorities or experimental), including chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy, investigational agents, or herbal therapy; after Cycle 1, certain forms of radiation therapy may be considered for pain palliation if patients are deriving benefit. Study treatment may be suspended during radiation therapy with agreement by the Medical Monitor.
- Warfarin, anti-thrombotic therapy (except low-molecular weight heparin), or anti-platelet drugs (except low-dose aspirin), prophylactic anticoagulation and/or local application of thrombolytics for patency of venous access devices are allowed as long as INR and aPTT are ≤ 1.5 ULN.
- Quinidine or other anti-arrthymic agents
- Chronic systemic corticosteroid use (≥ 10 mg of prednisone or equivalent dose of other anti-inflammatory corticosteroids for >7 days) or use of immunosuppressants. However, treatment with systemic corticosteroids during the course of the study for management of toxicity related to vemurafenib and /or cobimetinib (e.g., allergic rash) is allowed.

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever comes first.

4.4.3 Medication Precautions in Case of Drug–Drug Interactions

Vemurafenib:

On the basis of nonclinical data, vemurafenib may have the potential to cause DDI with concomitant medications that are primarily eliminated by CYP2C9. Patients should be advised to consult with their physician before taking any of the listed medications:

- Non-steriodal anti-inflammatory drugs (e.g., ibuprofen, diclofenac, meloxicam)
- Oral hypoglycemic agents (e.g., tolbutamide, glipizide, glyburide, glimepiride)
- Antihypertensives (e.g., losartan, irbesartan, torsemide)
- Anticonvulsants (e.g., phenytoin)
- Anticoagulants (e.g., warfarin)
- Lipid-lowering drugs (e.g., fluvostatin)

In a CYP450 in vivo metabolism study (NP22676), vemurafenib inhibited CYP1A2 and induced CYP3A4 activity in melanoma patients by approximately 3-fold and 2-fold, respectively. If CYP1A2 substrates must be co-administered with vemurafenib, investigators should assess the safety risk associated with a potential increase in plasma

concentrations of CYP1A2 metabolized drugs. If CYP3A4 substrates must be co-administered with vemurafenib, investigators should monitor the signs of reduced benefit of CYP3A4 metabolized drugs due to a potential decrease in their plasma concentration. Doses of concomitant CYP1A2 and CYP3A4 drugs, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

For CYP2C9, data suggested that the relatively strong nonclinical signal inhibition, (IC_{50} = 5.9 μM in vitro in hepatic microsomes) did not translate to a DDI with this CYP450 isoform. However, vemurafenib was associated with a decrease in clearance of warfarin from plasma, and a 19% increase in the mean exposure (AUC) that did not fall outside of the equivalence boundary.

Little metabolism of vemurafenib (< 10%) was detected in nonclinical studies and in data from a human mass balance study with ^{14}C- vemurafenib in patients with melanoma (Study NP25158). Nonclinical studies suggest that CYP3A4 metabolism and subsequent glucuronidation are responsible for the metabolism of vemurafenib. No clinical data are currently available evaluating the effects of CYP3A4 inducers or inhibitors on vemurafenib exposure.

Appendix 10 includes a non-exhaustive list of typical examples of CYP1A2, CYP3A4, and CYP2C9 substrates and CYP3A4 inducers and inhibitors. A more extensive list of medications can be found online at the following link: http://medicine.iupui.edu/clinpharm/ddis/Table.asp. For further information see the Investigator's Brochure.

Cobimetinib:

On the basis of in vitro data showing that cobimetinib is metabolized by the hepatic cytochrome CYP3A4, the drugs listed below should be avoided. If use of one of these drugs is necessary, the risks and benefits and potential alternatives should be discussed with the Medical Monitor prior to its concomitant use with cobimetinib.

- Strong CYP3A4/5 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, and voriconazole
- Strong CYP3A4/5 inducers such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, and Phenobarbital

4.4.4 Medications Affecting QT Interval

Certain medications could affect the results of QT intervals on ECG measurements required in this study. Specifically, anti-emetics other than those belonging to the 5-HT_3 receptor antagonist class (i.e., granisetron, ondansetron, dolasetron, palanosetron) are preferred since the latter has the potential to prolong the QTc interval (see Section 3.10.1). We encourage and recommend that investigators avoid or take precautions in closely monitoring patients who are on medications or herbal and vitamin supplements that may increase QTc interval. Alternative treatment options for medications known to affect QT interval should be discussed with each patient prior to

their inclusion into this study. A complete list of medications that may cause QT interval prolongation is provided in Appendix 6. Please refer to http://www.azcert.org/ for additional information and references.

4.5 Criteria for Premature Withdrawal and Discontinuation

Patients have the right to withdraw from the study at any time for any reason.

In cases where the patient decides to prematurely discontinue study treatment ("refuses treatment"), he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. The investigator may withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure or any reason where it is felt by the investigator that it is in the best interest of the patient to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient. Any patient who discontinues will be encouraged to return to the study center for a study completion visit.

Additionally, patients must discontinue study treatment if they experience any of the following:

- Disease progression per investigator assessment using RECIST v1.1
- Intolerance of vemurafenib and cobimetinib combination therapy or cobimetinib monotherapy after discussion with the Medical Monitor
- Pregnancy

Patients should return to the clinic for a study completion visit 28 days after study treatment discontinuation (see Section 5 for assessments that are to be performed at that visit). The primary reason for discontinuation must be recorded on the appropriate eCRF.

Study Discontinuation

Roche has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- All enrolled patients have discontinued study treatment.
- The incidence or intensity (severity) of adverse events in this or other studies indicates a potential health hazard to patients.

Post-Trial Access

Roche does not intend to provide vemurafenib or cobimetinib or other interventions to patients after the conclusion of the study or any earlier withdrawal (see Section 3.11).

4.6 Withdrawal of Patients from the Roche Clinical Repository

Patients who give consent to long-term storage of biomarker specimens for further research in the RCR have the right to withdraw their consent to long-term storage of the samples at any time for any reason. If a patient wishes to withdraw his/her consent to the long-term storage of his/her specimen(s), the investigator must inform the Medical Monitor in writing of the patient's wishes using the withdrawal form provided and enter the date of withdrawal in the patient's eCRF. A patient withdrawal from the trial does not by itself constitute withdrawal from long-term storage of sample(s) in the RCR; likewise, withdrawal from the long-term storage of samples(s) in the RCR does not constitute a withdrawal from the main trial.

4.7 Replacement Policy (Ensuring Adequate Numbers of Evaluable Patients)

4.7.1 For Patients

No patient prematurely discontinued from the study for any reason, after having completed the first cycle (first 28 days on the study), will be replaced. Patients who discontinue study treatment or have missed 3 or more days in total of either study drug in the first 28-day cycle for reasons other than a DLT will be replaced.

4.7.2 For Centers

A center may be replaced or closed for the following administrative reasons:

– Poor protocol adherence

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 9 Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort)

	Screening Period (28 Days)		Combination (Vemurafenib and Cobimetinib) Treatment Period or Cobimetinib Monotherapy Treatment Period																		Follow-Up after Study Treatment		
Cycle			**Cycle 1**						**Cycle 2**				**Cycle 3**				**Cycle 4+**						
Cycle Day	**-28 to -1 Days[1]**	**-1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Disease Progression/ Final Visit**	**28 Days Post- Dose**	**Every 12 Weeks**
Informed consent[1]	x																						
Medical history and demographics	x																						
Tumor tissue for $BRAF^{V600E}$ Mutation screening[1]	x																						
Physical exam[2]	x		x		x		x	x	x	x	x	x	x				x						
Vital signs, height, weight[3]	x		x		x		x	x	x	x	x	x	x				x						
ECOG status[3]	x		x		x		x	x	x	x	x	x	x				x						
12-lead ECG[4]	x[4]	x[4]	x	x		x		x	x				x				x[4]						
Ophthalmic exams[5]	x																						
Hematology[6]	x		x		x	x		x	x	x	x	x	x				x						
Chemistry[7]	x		x		x	x		x	x	x	x	x	x				x						
Coagulation tests[6]	x																						
Pulse oximetry	x																						
Urinalysis[8]	x																						
Serum pregnancy tests[9]	x		x						x				x				x						

Table 9: Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort) (Cont.)

	Screening Period (28 Days)		Combination (Vemurafenib and Cobimetinib) Treatment Period or Cobimetinib Monotherapy Treatment Period																		Follow-Up after Study Treatment		
Cycle			**Cycle 1**						**Cycle 2**				**Cycle 3**				**Cycle 4+**						
Cycle Day	**-28 to -1 Days[1]**	**-1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Disease Progression/ Final Visit**	**28 Days Post-Dose**	**Every 12 Weeks**
CT/MRI of the head[10]	x																						
Tumor assessment (CT/MRI)[10]	x										x												
FDG-PET[11]	x[11]					x					x[11]												
PK blood samples[12]			PLEASE REFER TO Table 10 and Table 11 FOR PK SAMPLING SCHEDULE																				
Vemurafenib administration[13]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Cobimetinib administration[14]			x	x	x	x	x[14]	x[14]	x	x	x[14]	x[14]	x	x	x[14]	x[14]	x	x	x[14]	x[14]			
Concomitant medications[15]	x	x	x	x	x	x	x	x	x	x	x	x	x				x				x		
Adverse events[16]	x	x	x	x	x	x	x	x	x	x	x	x	x				x				x	x	
Drug accountability					x		x	x	x	x	x	x	x				x				x		
Survival assessment[17]																							x
ASSESSMENTS FOR SCC RISK MANAGEMENT																							
Dermatology evaluation[18]	x								x														
Head and neck SCC examination[19]	x																x						
Chest CT for SCC RMP[20]	x										x						x						

Table 9: Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort) (Cont.)

	Screening Period (28 Days)		Combination (Vemurafenib and Cobimetinib) Treatment Period or Cobimetinib Monotherapy Treatment Period																		Follow-Up after Study Treatment		
Cycle			**Cycle 1**						**Cycle 2**				**Cycle 3**				**Cycle 4+**						
Cycle Day	**-28 to -1 Days[1]**	**-1**	**1**	**2**	**8**	**14**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Disease Progression/ Final Visit**	**28 Days Post-Dose**	**Every 12 Weeks**
ASSESSMENTS FOR BIOMARKERS																							
Tumor biopsy for biomarker analyses [21]			x			x															x		
Whole blood samples for biomarker			x																				
Plasma for biomarker analysis			x																				
Squamous cell carcinoma tumor tissue or other suspicious malignant lesions and normal skin[22]	x		**Ongoing throughout trial, according to local standard of care**																		x	According to local standard of care	

Schedule of Assessments – Footnotes

ECOG=Eastern Cooperative Oncology Group; **INR**=international normalized ratio; **PK**=pharmacokinetic; **pretreat**=pretreatment period

Notes: Assessments scheduled on the day of study drug administration should be performed prior to study drug dosing, unless otherwise specified.

Table 9: Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort) (Cont.)

Unless otherwise specified, assessments that are done weekly, should be performed within a ± 1 day window except PK assessments. Those performed monthly, should be performed within a window of ± 3 days. Patients are NOT required to visit the clinics on Days 15, and 22 of Cycle 3, Cycle 4, and subsequent cycles if no assessments are scheduled on these days. In addition, a clinic visit should be scheduled any time there is a safety issue or any unscheduled assessments need to be performed.

1. Informed consent must be obtained before any study specific screening assessments are performed. Screening assessments are to be performed within 28 days prior to Day 1 of Cycle 1 unless otherwise noted. Assessments performed as standard of care within the screening window may be used for screening. Screening exams for ECG, hematology, chemistry, coagulation, urinalysis, and pulse oximetry must be performed within 14 days of first dose. Note: All study patients who were not previously treated with vemurafenib must have melanoma tissue tested for $BRAF^{V600}$ mutation using the cobas® 4800 BRAF V600 Mutation Test. Testing requires a formalin-fixed paraffin-embedded (FFPE) tumor block or unstained sections. A screening window of 42 days prior to Cycle 1, Day 1 will be allowed to test for the $BRAF^{V600E}$ mutation in patients without prior exposure to vemurafenib only. Other screening assessments can commence only after a positive test result is documented and a slot is available in an open cohort of either the dose-escalation or cohort-expansion phase. For patients without prior exposure to vemurafenib, the 28-day window (Day –28 to Day –1) for performing screening assessments begins at the time the first screening assessment is performed after documentation of $BRAF^{V600E}$ mutation–positive tumor tissue.
2. Physical exam will be performed during screening and subsequently at each study visit. The frequency of each study visit should be performed in accordance with the local standard of care. After initial screening physical exam, a limited physical exam, a symptom-directed exam that contains an evaluation of the oropharynx, lungs, heart, abdomen, and skin will be performed. Patients will be asked about skin and vision changes at each symptom-directed physical exam. Assessments must be done before study drug dosing, where applicable.
3. ECOG, weight, and vital signs, which include temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures while the patient is in a seated position, will be collected when a physical exam is performed in accordance with standard of care. Height will be collected only at screening/baseline.
4. Triplicate 12-lead ECG should be performed at screening (within 14 days); Day –1, Hour 0 (pre-vemurafenib dose); Cycle 1, Day 1, Hour 4 (4 hours post-cobimetinib dose); Day 2, Hour 0 (pre-dose); Day 14, Hour 0 (pre-dose) and Hours 2, 4, and 8 post-dose; Day 22, Hour 0 (pre-vemurafenib dose); Cycle 2, Day 1; Cycle 3, Day 1; Cycle 4, Day 1. Following Cycle 4, the frequency of ECG monitoring should be performed in accordance with the local standard of care, and triplicate ECGs are not longer required. Triplicate 12-lead ECG monitoring should be performed more frequently if clinically indicated. ECG on Day -1 is not required for previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma patients. Follow the guidelines in Table 11 for ECG monitoring in the setting of vemurafenib interruption and dose reduction due to QTc interval prolongation. For all ECGs, patients should be resting in a supine position for ≥ 10 minutes prior to ECG collection
5. Complete ophthalmologic exams will be performed at screening and subsequently as clinically indicated if a patient notes any visual disturbances. Complete ophthalmologic examination will be performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. Ophthalmologic examination may be performed up to 42 days prior to starting study treatment.

Table 9: Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort) (Cont.)

6. Hematology includes hemoglobin, hematocrit, WBC count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes), and platelet count. Coagulation tests include INR and aPTT and are required only at screening. Frequency of hematology assessments after Cycle 4 should be performed in accordance with the local standard of care.
7. Chemistry includes glucose, BUN, creatinine, sodium, potassium, chloride, magnesium, bicarbonate, phosphate, calcium, total protein, albumin, total bilirubin, direct bilirubin, ALP, LDH, CPK, uric acid, AST, and ALT. Note: Patients who exhibit CPK elevation coincident with cobimetinib treatment should have measurement of MB fraction, if there is a clinical suspicion of possible myocardial
injury or in the case of prolongation of the QTc interval. Frequency of chemistry asssessments after Cycle 4 should be performed in accordance with the local standard of care.
8. Urinalysis is required only at screening and includes specific gravity, pH, glucose, protein ketones, blood, and microscopics (RBC, WBC, casts, and crystals).
9. For women of childbearing potential, including premenopausal women who have had a tubal ligation, a serum pregnancy test is required at screening (within 7 days prior to C1D1) and should be performed in accordance with the local standard of care while the patient is receiving study treatment.
10. All patients must have a screening head CT and/or MRI to assess for brain metastasis, and subsequently only as clinically indicated. Radiographic tumor assessments (CT or MRI scans) will be obtained to assess extent of disease at the following timepoints: screening (any time within 28-day period of Cycle 1, Day 1) and thereafter tumor assessments should be performed in accordance with the local standard of care while the patient is receiving study treatment. If at any time during the treatment phase there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled tumor assessment should be performed. If a PET scan is used for preliminary assessment of progressive disease or for SCC follow-up assessment, a corresponding CT scan is required to be completed. A documented standard-of-care tumor assessment performed within 28 days of Cycle 1, Day 1 may be used for the screening assessment (must contain a chest CT scan).
11. FDG-PET imaging will be done at screening (≤ 14 days prior to Cycle 1, Day 1). If the patient has FDG-PET avid disease, he/she will undergo subsequent FDG-PET imaging. This will be scheduled once during mid-Cycle 1 (anytime between Days 10 and 14) and once on Cycle 2, Day 14±7 days to coincide with the first CT/MRI response assessment. FDG-PET scan must be performed fasting (patients must not have consumed any food or glucose/sugar-containing fluid) at least 4 hours prior to FDG-PET scan. Blood glucose level will be obtained immediately prior to FDG administration either by fingerstick test or by serum glucose assay on a blood sample obtained by venipuncture and processed in the local laboratory.
12. PK samples should be obtained according to the schedule provided in Table 10 and Table 11 for patients who progressed while on vemurafenib immediately prior to enrollment in this study and those previously untreated or treated (but without prior exposure to any BRAF or MEK inhibitor therapy) for locally advanced/unresectable or metastatic melanoma, respectively. Document date and time of all PK draws.
13. Patients who have progressed on vemurafenib will continue daily treatment with vemurafenib during the screening period pending cohort assignment. Confirm dose with study site monitor as a dose reduction may be required. During this study, patients will be treated with an oral dose of vemurafenib daily in a 28-day cycle. Patients available for enrollment in this study who were receiving 960 mg bid vemurafenib will be dose reduced to 720 mg bid for 7–14 days prior to enrollment in Cohorts 1, 1A, 2, 2A, and 1C. Patients assigned to Cohorts 1B, 1D, 3, 4, or 5 will continue receiving 960 mg bid vemurafenib throughout the screening period, assuming this dose has been adequately tolerated prestudy.

Table 9: Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort) (Cont.)

14. Patients will receive cobimetinib on a 14-days on/14-days off schedule, on a 21-days on/7 days off schedule, or on a continuous schedule (qd) in a 28-day cycle. For study evaluations performed earlier than the scheduled day, patients cannot restart cobimetinib until they have had the minimum number of days without cobimetinib dosing. For patients on the 14/14 and 21/7 dosing schedules of cobimetinib, the minimum numbers of days without cobimetinib are 14 and 7, respectively. For both investigational drugs, dosing will continue until disease progression, consent withdrawal, or unacceptable toxicity. Dispense a sufficient number of vemurafenib and cobimetinib capsules/tablets to last until the next visit and provide a medication diary. Extra capsules/tablets may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance of patient's home from study center). Instruct patient to record the time and date they take each study drug dose in the diary and to return all unused capsules/tablets at each study visit to assess compliance. Collect and review medication diary, collect unused capsules/tablets, and assess compliance at each subsequent visit.
15. Review and capture of all concomitant medications will be performed at each study visit. Concomitant medications are defined as any prescription medications or over-the-counter preparations used by a patient within 7 days before screening and continuing through the study completion visit.
16. After signing the informed consent, adverse events will be collected as detailed in Section 7.1.2. All adverse events will be recorded until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first.
17. During long-term follow-up, survival assessments should be performed every 12 weeks until *death* after last study treatment.
18. Dermatology evaluation: screening (up to 28 days prior to Cycle 1, Day 1), after 22−30 days on study treatment (Cycle 2, Day 1); thereafter, dermatology evaluation should be performed in accordance with the local standard of care while the patient is receiving study treatment and after completion of study treatment. If patients develop SCC (cutaneous or non-cutaneous) or any primary neoplasms as per the RMP after withdrawal from study, this information must be collected and reported as a serious adverse event to the Sponsor whether deemed related or unrelated to study drug. Any other adverse events or serious adverse events occurring after study discontinuation will only be collected up to 28 days after the last dose of study medication or as per serious adverse event guidelines.
19. A head and neck exam for SCC (cutaneous or non-cutaneous) or any primary neoplasms risk management will be done by the treating physician at screening; thereafter, head and neck exams should be performed in accordance with the local standard of care while the patient is receiving study treatment and after completion of study treatment.
20. The routinely scheduled radiologic assessment for tumor burden can be used as the chest CT for the Risk Management Plan of SCC (cutaneous or non-cutaneous) or any primary neoplasms while the patient is on study drug. Following cessation of study drug, surveillance of SCC should be performed in accordance with the local standard of care.

Table 9: Schedule of Assessments (All Cohorts Including Cobimetinib Monotherapy Cohort) (Cont.)

21. For all patients—previously treated with vemurafenib and those either previously untreated or treated (but without prior exposure to any BRAF or MEK inhibitor therapy) for locally advanced/unresectable or metastatic melanoma—biopsies of accessible tissue are mandatory upon patient's consent to participate in the trial. Fresh-frozen and paraffin-embedded tumor biopsy for molecular analyses will be obtained within 28 days of Cycle 1, Day 1 (unless progression biopsy tissue was submitted in previous study within 3 months of screening). Biopsies should be completed at least 48 hours before the initiation of study drug therapy on Cycle 1, Day 1. Biopsies (both formalin-fixed and fresh-frozen samples) will be collected at time of progressive disease. A biopsy of tumor tissue must be obtained during Cycle 1 while the patient is receiving cobimetinib; Day 10 to 14 is the required timing for this biopsy. It is highly recommended that the biopsy at disease progression be collected within 3 days after last study treatment. Lesions with the greatest change in dimensional size, based on interval evaluation, are the lesions to be biopsied. Excisional biopsies, punch biopsies, or multiple (2 or more), 14-gauge core needle biopsies are acceptable. **Fine needle aspiration (FNA) biopsies will not be accepted**.
22. For patients who develop any cutaneous lesion(s) suspicious for squamous cell carcinoma (SCC) or keratoacanthoma (KA) during treatment with vemurafenib and/or cobimetinib, biopsy tissue and a paired normal skin biopsy must be obtained for biomarker analyses (mandatory sample). Only one normal skin biopsy is required per patient, regardless of the number of SCC lesions identified and biopsied during the study. Suspicious lesions not thought to represent cutaneous SCC may also be sent for central pathological review at the discretion of the investigator and may undergo molecular characterization.

5.1 Screening Examination and Eligibility Screening Form

All patients must provide written informed consent before any study-specific assessments or procedures are performed.

A pre-screening log needs to be completed and sent to the study leader or Medical Monitor for attribution of the slot.

An Eligibility Screening Form documenting the investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator.

A screen failure log must be maintained by the investigator.

A screening examination should be performed between Day –28 and Day –1, except for ophthalmologic examination. The ophthalmologic examination may be performed up to 42 days prior to starting study treatment. Patients who meet all the inclusion and exclusion criteria will be enrolled into the study treatment phase. All screening and baseline assessments are outlined in the Schedule of Assessments, Table 9.

For patients previously treated with vemurafenib, examinations and biopsies performed during the previous study of vemurafenib in which the patient was enrolled may be substituted for screening examinations and biopsies in this study, provided they were performed within 3 months of screening for the current study (see Section 5.3.1).

5.2 Procedures for Enrollment of Eligible Patients

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study treatment. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

All patients at all participating sites will be registered with the Sponsor/designee. Investigators will submit an Enrollment Form and the fully executed Eligibility Screening Form to the Sponsor/designee. The Principal Investigator will be notified of the enrollment/cohort assignment upon receipt. Assignment of a patient number and treatment doses for vemurafenib and cobimetinib will be generated and provided back to the investigator at the time of patient registration.

Under no circumstance will patients who enroll in this study and have completed treatment as specified be permitted to re-enroll in the study with the exception of patients allowed to receive single-agent cobimetinib (after having failed the combination of vemurafenib and cobimetinib, with the Medical Monitor's permission. Such patients are not required to undergo a second screening evaluation prior to initiation of cobimetinib monotherapy.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening window may be used; such tests do not need to be repeated for screening. Screening local laboratory assessments performed ≤ 96 hours prior to Day 1 do not have to be repeated.

A patient Enrollment and Identification Code List must be maintained by the investigator.

5.3 Clinical Assessments and Procedures

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the study completion visit, and during the survival follow-up period. After signing the informed consent, adverse events will be collected as detailed in Section 7.2.1. Patients will be assessed for adverse events weekly during the first two cycles, prior to each subsequent cycle, and as necessary throughout the study. All adverse events will be recorded until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Visits are based on the 28-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday and/or other scheduling conflict that precludes the visit, the visit should be scheduled on the date nearest to the date in question, which may be earlier or later.

5.3.1 Screening and Pre-Treatment Assessment

All study patients who were not previously treated with vemurafenib must have melanoma tissue tested for $BRAF^{V600E}$ mutation using the cobas® 4800 BRAF V600 Mutation Test. Testing requires a formalin-fixed paraffin-embedded (FFPE) tumor block or unstained sections. A screening window of 42 days prior to Cycle 1, Day 1 will be allowed to test for the $BRAF^{V600E}$ mutation in patients without prior exposure to vemurafenib only. Other screening assessments can commence only after a positive test result is documented by the central reference laboratory and a slot is available in an open cohort of either the dose-escalation or cohort-expansion phase. For patients without prior exposure to vemurafenib, the 28-day window (Day –28 to Day –1) for performing screening assessments begins at the time the first screening assessment is performed following documentation of $BRAF^{V600E}$ mutation–positive tumor tissue.

Any patient who has melanoma progression either on an antecedent clinical trial of vemurafenib monotherapy or while receiving the drug in a postmarketing setting immediately prior to enrollment in this study should continue to receive vemurafenib during the screening evaluation until it has been determined that he/she is ineligible for the current study.

Screening assessments will include a CT or MRI scan of the brain, chest, abdomen, and pelvis and all other known and suspected sites of disease. A bone scan should also be performed, if clinically indicated. Subsequent tumor assessments should include a CT or MRI of the chest, abdomen, and pelvis and all other sites of disease documented at baseline. The same imaging methods used at screening must be used throughout the study for each patient.

The following clinical assessments and procedures will be performed during the screening period after the written informed consent has been obtained (see Table 9).

- Review of eligibility criteria
- Medical, surgical, and cancer histories

- Demographic data (sex, age, self-reported race/ethnicity)
- Documentation of previous and current concomitant medications (prescribed and over-the-counter preparations)
- Complete physical examination
- Height
- Weight
- Vital signs
- Pulse oximetry, resting (≤ 14 days prior to Day 1 of Cycle 1)
- ECOG performance status (see Appendix 2)
- 12-lead ECG (in triplicate), resting (≤ 14 days prior to Day 1 of Cycle 1 and also on Day –1)
- Screening complete ophthalmologic examinations: Screening assessments must be performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography.
- Local laboratory assessments (≤ 14 days prior to Cycle 1, Day 1)
  - Hematology (hemoglobin, hematocrit, WBC count with differential [neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes]) and platelet count
  - Serum chemistries (glucose, BUN, creatinine, sodium, potassium, chloride, magnesium, bicarbonate, phosphate, calcium, total protein, albumin, total bilirubin, direct bilirubin, ALP, LDH, CPK, uric acid, AST, and ALT)
  - Coagulation (aPTT and INR)
  - Urinalysis
  - Serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation) within 7 days prior to C1D1
- Pre–FDG-PET blood glucose test: Blood glucose levels will be obtained immediately prior to FDG administration either by fingerstick test or by serum glucose assay on a blood sample obtained by venipuncture and processed in the local laboratory. Patients should not have consumed food for 4 hours prior to this test.
- FDG-PET scan

The following procedures must be performed only after patient eligibility has been confirmed and informed consent has been obtained.

- Thorough head and neck evaluation (completed by treating physician)
- CT scan of chest (for SCC risk management; can use routinely scheduled radiologic assessment for tumor burden while patient is in the study)
- Dermatology evaluation
- Fresh-frozen and paraffin-embedded tumor biopsy for molecular analyses to investigate response or resistance, as well as pharmacodynamics (unless progression biopsy tissue was submitted in previous study within 3 months of screening).
- Plasma samples for molecular analyses
- Whole blood for molecular analyses including genetic analyses of germline mutations
- Listed PK samples (see Table 10 and Table 11)

5.3.2 Tumor Response Criteria

Tumor response will be evaluated according to RECIST v1.1 (see Appendix 1).

Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. The frequency of post-baseline tumor assessments will be conducted in accordance to the local standard of care. At the investigator's discretion, CT/MRI scans may be repeated at any time if progressive disease is suspected. In addition, an OR must be confirmed by repeat assessments ≥ 4 weeks after initial documentation. In the case of stable disease (SD), tumor measurements must have met the SD criteria at least once after study entry at a minimum interval of not fewer than 6 weeks.

The extent of disease will be determined by reproducible radiographic techniques, either the CT or MRI scan. All known and suspected areas of disease will be evaluated as deemed appropriate by the investigator. If more than one method of assessment is used at screening, select the most accurate method according to RECIST v1.1 when recording data; in addition, this method should again be used in all subsequent evaluations. The preferred method for radiologic tumor response assessment(s) is a CT or MRI scan. PET scan is not adequate for RECIST response assessment. If a PET scan is used for determination of disease progression, then a corresponding CT and/or MRI scan is required. CT and/or MRI scans will be compared against PET scans.

The use of radiographic contrast (intravenous contrast) is required unless medically contraindicated (see Appendix 1). Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible. The results of the second FDG-PET scan (performed 10–14 days after the start of the cobimetinib and vemurafenib combination dosing in Cycle 1) will not be used to make response assessments.

Only superficial lesions (skin nodules, palpable lymph nodes/adenopathy) are considered to be measurable on physical examination. In the case of skin lesions, the use of color photography, including a ruler/calliper, must be used for documentation of response.

Tumor assessment scans may be assessed by an independent IRF. As of Protocol Version K *and future amendments*, central collection of scans is no longer required.

Scheduling of Tumor Assessments

Baseline total tumor burden must be assessed within 4 weeks before Cycle 1, Day 1. The frequency of post-baseline tumor assessments will be conducted in accordance to the local standard of care. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed. If an unscheduled evaluation shows clear evidence of progression by standard RECIST criteria and the patient is not a candidate for treatment beyond progression (see Section 5.8), the treatment will be discontinued and the patient will be defined as a treatment failure.

5.3.3 Performance Status

Performance status will be measured using the ECOG Performance Status Scale (see Appendix 2). It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study. Please refer to Table 9 for details on when ECOG performance statuses are collected.

Performance status will be assessed at multiple points throughout the trial (Table 9) to see if the performance status score changes.

5.3.4 Clinical Safety Assessments

NCI CTCAE v4.0 will be used to characterize the toxicity profile of the study treatment. All patients will be assessed for adverse events. After signing the informed consent, adverse events will be collected as detailed in Section 7.2.1. Patients will be assessed for adverse events weekly during the first two cycles, prior to each subsequent cycle, and as necessary throughout the study. All adverse events will be recorded until 28 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. Prolonged follow-up is required for any occurrence of SCC as outlined in the RMP (Section 5.3.4.6).

A complete medical history (including demographics) will be performed at screening.

A limited physical examination will be performed as indicated. Please refer to the Schedule of Assessments (Table 9) for specific details and timepoints pertaining to clinical assessments and procedures outlined below.

5.3.4.1 *Medical History*

Medical history includes clinically significant diseases within the last 5 years, smoking history, prior cancer history, prior cancer therapies and procedures, and all medications used by the patient within 28 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

5.3.4.2 *Vital Signs and Oxygen Saturation*

Vital signs will include measurements of heart rate, respiratory rate, and systolic and diastolic blood pressures while the patient is in a seated position and oral or tympanic temperature (°C). Oxygen saturation will be assessed by pulse oximetry at rest.

5.3.4.3 *Physical and Symptom-Directed Examinations*

A complete physical examination should include the evaluation of head, eye, ear, nose and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems, weight, as well as height at screening. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

As part of tumor assessments, physical examinations should include evaluation of the presence of enlarged lymph nodes, hepatomegaly, and splenomegaly. Some visits allow symptom-directed examination (physical examinations relevant to patient's symptoms). As part of each symptom-directed examination in this study, patients will be asked about skin and vision changes.

5.3.4.4 *Ophthalmologic Examinations*

All patients will have complete ophthalmologic examinations performed and interpreted by a qualified ophthalmologist, including visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. These examinations will be performed at baseline and subsequently as clinically indicated, if patients note any visual disturbances. Changes from baseline findings should be recorded at each subsequent ophthalmologic examination. The ophthalmologic examination may be performed up to 42 days prior to starting study treatment.

5.3.4.5 *ECG*

Triplicate 12-lead ECG should be performed in all patients at following timepoints:

- Screening
- Day -1, Hour 0 (pre-vemurafenib dose)*
  Day -1 ECG is not required for previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma patients.
- Cycle 1, Day 1, Hour 4 (4 hours post–cobimetinib dose and ±1 hour)
- Cycle 1, Day 2, Hour 0 (pre-dose)
- Cycle 1, Day 14, Hour 0 (pre-dose) and Hours 2 (±15 minutes), 4 (±1 hour) and 8 (±1 hour) post-dose
- Cycle 1, Day 22, Hour 0 (pre-vemurafenib dose)
- Cycle 2, Day 1
- Cycle 3, Day 1
- Cycle 4, Day 1

*Day -1 ECG is not required for Previously Treated (but without Prior Exposure to BRAF or MEK Inhibitor Therapy) or Previously Untreated for Locally Advanced/Unresectable or Metastatic Melanoma patients.

Following Cycle 4, ECG monitoring should be performed in accordance with the local standard of care, and triplicate ECGs are no longer required. As of Protocol Version K *and future amendments*, central collection of ECGs is no longer required.

Additional ECGs should be performed when clinically indicated. To minimize postural variability, it is important that patients are resting and in a supine position for ≥ 10 minutes prior to each ECG assessment. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability due to the effects of physical stress. If QTc interval prolongation (>500 msec) is noted on ECG while on study treatment, please refer to the guidelines provided in Table 12 for modification of vemurafenib dosing and subsequent ECG monitoring.

5.3.4.6 *Dermatologic Evaluation, Surveillance of Second Primary Malignancies, and Risk Management Plan*

Patients will be followed for SCCs (cutaneous and non-cutaneous) and development of any new primary malignancies according to the Risk Management Plan outlined below.

Dermatologic Evaluation

A dermatological evaluation performed by a dermatologist will be conducted pre-dose (up to 28 days prior to Cycle 1, Day 1), after 22–30 days on study treatment (Cycle 2, Day 1); thereafter, dermatology evaluation should be performed in accordance with the local standard of care while patients are receiving study treatment and after completion of study treatment. During study treatment and up to 6 months after treatment completion, patients and investigators must record the occurrence of any new primary malignancy, including but not limited to squamous cell carcinomas (cutaneous or non-cutaneous) according to NCI CTCAE v4.0. Patients should see their physicians as needed for any new skin lesions while on study drug. An unscheduled dermatology examination may be done during treatment as needed and if SCC or any second primary cutaneous malignancy is suspected.

- A designated dermatologist will perform skin evaluations to monitor for SCC, BCC, actinic keratosis, and KA (Table 9).
- A complete history of prior dermatologic medications and SCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions and phototherapy for psoriasis) must be collected.
- Any lesions suspected of representing a new SCC, BCC, new primary melanoma, actinic keratosis, or KA should be appropriately mapped and photographed (with images stored digitally and made available to the Sponsor upon request).
- Any suspicious lesions not thought to represent SCC, BCC, new primary melanoma or keratoacanthoma identified either at baseline or while on study drug may be biopsied/excised and sent for pathological examination at the discretion of the investigator. Available specimen block/sections should also be sent to a designated central pathology laboratory for confirmation of diagnosis.
- Available specimen block/sections of SCC or other suspicious lesions, should be sent to the designated central pathology laboratory for confirmation of diagnosis
- Residual biopsy tissue (if available) will be analyzed for further molecular characterization.

Suspicious lesion submitted to central pathology must be accompanied by a biopsy of normal skin as reference for molecular characterization of the lesion. Only one normal skin sample is required per patient, regardless of the number of SCC lesions identified.

- Actinic keratosis, KA, or other skin conditions identified by the dermatologist should be treated as per local standards of care.
- If a patient develops SCC after withdrawal from study, this information must be collected and reported as a serious adverse event to the Sponsor, whether it is deemed related or unrelated to study drug.
- The occurrence of any skin changes, including rash and photosensitivity, should be reported to the study investigator, and patients will be referred to the dermatologist as required.

Additional Assessments for Second Primary Malignancy Surveillance
(Treating Physician or Other Qualified Physician):

- A thorough examination of the head and neck must be performed by the treating physician at baseline for all patients enrolled; thereafter, head and neck exams should be performed in accordance with the local standard of care while the patient is receiving study treatment and after the completion of study treatment.
- The routinely scheduled chest CT/MRI scan performed as part of the assessment of tumor burden will be used as the chest CT for SCC surveillance while the patient is on study treatment. Following cessation of study drug, surveillance of SCC should be performed in accordance with the local standard of care.

Patients who previously developed cuSCC and are already participating in a skin surveillance program must restart the process upon enrollment into this study with a dermatologic examination performed within 28 days prior to the initiation of therapy and after 22–30 days on study treatment (Cycle 2, Day 1). Thereafter, dermatology evaluation should be performed in accordance with the local standard of care while the patient is receiving study treatment and after the completion of study treatment.

5.3.5 FDG-PET Imaging

Patients on this study are required to undergo FDG-PET imaging.

FDG-PET imaging will be done at baseline (≤14 days prior to first dose of study treatment). If the patient has FDG-PET avid disease, he/she will undergo subsequent FDG-PET imaging. This will be scheduled during Cycle 1 between Days 10 to 14 and Cycle 2, Day 14±7 days (coinciding with first CT/MRI response assessment). FDG-PET images should be obtained per procedures outlined in the separate imaging manual. FDG-PET scans will be assessed by an independent IRF.

Given the exploratory nature of FDG-PET changes at Cycle 1, Day 14 (e.g., FDG-PET flares), the results of this scan should not be utilized to determine a patient's disease status during treatment with vemurafenib and cobimetinib.

- Pre–FDG-PET blood glucose test
  Blood glucose levels will be measured immediately prior to FDG administration either by fingerstick test or by serum glucose assay on a blood sample obtained by venipuncture and processed in the local laboratory. Patients should not have consumed food for 4 hours prior to this test.

- FDG-PET scan
  Follow-up FDG-PET scans should be performed at the above-mentioned timepoints only in patients who have FDG-PET avid disease at baseline (i.e., with one or more evaluable lesions detected on the baseline scan). Procedures for obtaining FDG-PET scans are described in detail in the imaging manual.

5.4 Laboratory Assessments

A series of laboratory assessments will be made throughout the course of this study. These assessments are being performed to monitor patient safety.

Normal ranges for the study laboratory parameters, where available, must be supplied to Roche/designee before the study starts.

The total volume of blood collected for safety laboratory assessments will be approximately 10 mL.

5.4.1 Laboratory Assessments List

The laboratory assessments listed will be performed at a local laboratory:

- Hematology: WBC count, hemoglobin, hematocrit, platelet count, WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, and monocytes)
- Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphate, magnesium, total and direct bilirubin, total protein, albumin, AST, ALT, LDH, ALP, CPK, and uric acid. Note: Patients who exhibit CPK elevation coincident with cobimetinib treatment should have measurement of MB fraction if there is a clinical suspicion of possible myocardial injury or in case of prolongation of the QTc interval.
- Coagulation screening studies (aPTT, INR)
- Urinalysis: specific gravity, pH, glucose, protein, blood, ketones, microscopics (RBC, WBC, casts and crystals)
- Serum pregnancy test (for women of childbearing potential including premenopausal women who have had a tubal ligation)

5.4.2 Assessments during Treatment

For patients on the 14/14 and 21/7 dosing schedule of cobimetinib, the minimum numbers of days per cycle without cobimetinib dosing are 14 and 7, respectively.

Please see Table 9 for the Schedule of Assessments.

5.4.3 Dose-Escalation (Cohorts 1 through 5), Dose–De-escalation, and Dose-Expansion Cohorts

Day 1 is the day of the first combined administration of vemurafenib and cobimetinib.

Patients in the dose–de-escalation and dose-expansion cohorts will follow the same schedule of assessments and procedures as required for patients in the dose-escalation stage.

Cobimetinib Monotherapy Cohort

Patients in this cohort will follow the same schedule of assessments and procedures as patients in the dose-escalation stage.

5.4.4 Study Completion/Early Termination Visit

Patients who complete the study or discontinue early from the study will be asked to return to the clinic within 28 days after their last dose of vemurafenib and/or cobimetinib or before starting new non-protocol therapy (whichever is earlier) for a study completion visit. The visit at which a response assessment showed disease progression may be used as the study completion/early termination visit. The following assessments will be performed:

- Concomitant medications
- Adverse events

Please refer to Table 9 for assessments to be performed at the study completion or early termination visit.

5.4.5 Follow-Up Assessments

After the study completion visit, ongoing adverse events thought to be related to study treatment will be followed until the event has resolved to baseline grade, is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse events.

After the study completion visit, investigators should report only serious adverse events that are deemed related to study treatment (See Section 7.2.1).

5.5 Pharmacokinetic Assessments

Plasma samples for measurements of vemurafenib and cobimetinib concentrations and possible metabolites will be collected to characterize the pharmacokinetics of vemurafenib and cobimetinib.

For each PK blood sample collection, venous blood (2 mL in a heparin tube for vemurafenib and 3 mL in an EDTA tube for cobimetinib) will be collected to measure concentrations of vemurafenib and cobimetinib. When ECG recordings are obtained at the same visit, the collection of PK samples should be time-matched to the collection of ECG recordings (plasma samples collected after ECG recording) to investigate any potential relationship of systemic levels of vemurafenib and cobimetinib with ECG findings.

Plasma samples for the determination of vemurafenib and cobimetinib levels will be collected as outlined in Table 10 and Table 11 for patients who have progressed while receiving vemurafenib immediately prior to enrollment on this study and those either previously untreated or treated (but without prior exposure to any BRAF or MEK inhibitor therapy) for locally advanced/unresectable or metastatic melanoma, respectively. For cobimetinib, the sampling will allow determination of the total exposure (AUC_{0-24}), C_{max}, and C_{min}. For vemurafenib, plasma exposures will be assessed before (for patients previously treated with vemurafenib only) and during (all patients) co-administration with cobimetinib. Plasma concentrations will be compared with historical exposures observed in previous studies with vemurafenib.

Potential correlations of relevant PK parameters with dose, safety or efficacy outcomes, and other covariates will be explored.

Changes in PD markers will be listed by dose, exposure, cohort, mutation status, and response status. Additional PK and PD analyses will be conducted as appropriate.

5.5.1 Assay Methods

Concentrations of vemurafenib and cobimetinib will be determined in plasma using validated liquid chromatography tandem mass spectroscopy methods.

Table 10 Schedule of PK Sampling for Patients Previously Treated with Vemurafenib [a,b]

Day of Assessment	-1					1						2	8	14							15	16	17	C2 D1	C2D8	C3D8
Time (hr)	0	2	4	6	8	0	0.5	1	2	4	6	0	0	0	0.5	1	2	4	6	8	0	0	0	0	0, 2hr post-dose	0
Vemurafenib	x	x	x	x	x	x						x	x	x	x	x	x	x	x	x	x	x[b]	x[b]		x	x
Cobimetinib 14/14						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Cobimetinib 21/7						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x
Cobimetinib continuous						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x

[a] *Vemurafenib plasma levels samples shall be collected on Days 16 and 17 of C1 only when cobimetinib is given on a 14/14 schedule.*

[b] *Patients on cobimetinib monotherapy will undergo PK sampling based on their assigned cobimetinib dosing schedule.*

Table 11 Schedule of PK Sampling for Patients Either Previously Treated (but without Prior Exposure to BRAF or MEK Inhibitor Therapy) or Previously Untreated for Locally Advanced/Unresectable or Metastatic Melanoma [a]

Day of Assessment	1						2	8	14							15	16	17	C2 D1	C2D8	C3D8
Time (hr)	0	0.5	1	2	4	6	0	0	0	0.5	1	2	4	6	8	0	0	0	0	0, 2hr post-dose	0
Vemurafenib	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[b]	x[b]		x	x
Cobimetinib 14/14	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Cobimetinib 21/7	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x
Cobimetinib Continuous	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			x	x	x

[a] Vemurafenib plasma levels samples shall be collected on Days 16 and 17 of C1 only when cobimetinib is given on a 14/14 schedule.

5.6 Exploratory Molecular Assessments (Biomarker Assessments)

Samples collected for PD and biomarker assessments will be analyzed with the objective of understanding mechanisms of action and pharmacodynamics and to identify biomarkers that are predictive of response to the vemurafenib and cobimetinib combination or to cobimetinib alone or to explain mechanisms of resistance. Additional markers might be measured in case a strong scientific rationale for these analyses develops.

Specimens for dynamic (non-inherited) and genetic (inherited) biomarker discovery and validation will be collected from all patients participating in the trial.

The total volume blood loss for plasma, serum, and whole blood biomarker assessments will be approximately 18 mL.

For all samples, dates of consent and specimen collection should be recorded on the eCRF. For sampling procedures, storage conditions and shipment instructions, see the Sample Handling and Logistics Manual.

5.6.1 Plasma Samples

Blood (two approximately 6.0-mL samples in EDTA) for plasma isolation will be obtained at baseline. These samples will be used for biomarker assays, which may include BRAF mutations and other candidate biomarkers (including somatic mutations of the tumor).

5.6.2 Whole Blood for Biomarker Analyses

A blood sample (approximately 6 mL in K3 EDTA) for biomarker analysis will be collected as described in the laboratory manual.

The following assessments may be performed on whole blood:

- Analysis of new mutations (not described so far) detected in tumor tissue in order to verify the somatic nature of this mutation
- Single nucleotide polymorphisms (SNPs) in case evidence develops that SNPs might be associated with safety, efficacy, or pharmacokinetics of vemurafenib

5.6.3 Tissue Samples

For all patients tumor biopsies of accessible tissue are required.

5.6.3.1 *Tumor Tissue*

A final biopsy is requested at the time of progression. A lesion with the greatest change in dimension based on interval evaluation should be excised at time of progressive disease. As stated above, the scheduling of this tumor biopsy should not interfere with the scheduling of the FDG-PET scan.

Tumor biopsies will be obtained from patients with accessible progressing tumors at baseline following the patient's consent to participate in the trial. Failure to obtain

sufficient tumor sample after making best efforts to biopsy the tumor will not be considered a protocol deviation. If a biopsy at progression was submitted to Roche from an antecedent vemurafenib study within 3 months of enrollment, no baseline biopsy is required. For previously untreated patients only, the diagnostic tumor specimen may be substituted as baseline tumor sample.

If archival tumor tissue was not collected during the previous trial, or was inadequate for testing, then archival tumor tissue (formalin-fixed paraffin-embedded archival block or 20 unstained slides) may also be requested. Fine needle aspiration (FNA) biopsies are not acceptable.

In addition to the biopsies noted above, patients will be required to provide tumor biopsies approximately 10–14 days after the start of dosing with vemurafenib and cobimetinib in Cycle 1. The patient must be taking cobimetinib at the time of the Day 10–14 biopsy.

Scheduling of the tumor biopsy should not interfere with the scheduling of the first, post-baseline FDG-PET scan. The FDG-PET scan should not occur within 1 week following a study-mandated biopsy unless the biopsy is obtained from a site that is not a region of interest on the FDG-PET. Ideally, tumor biopsies at screening and during Days 10 to 14 of Cycle 1 should be performed after the mandated PET scans.

See the guidance below regarding the logistics for tumor biopsy and FDG-PET scanning in the case of multiple or single lesions.

- Multiple lesions: The tumor biopsy will be obtained from a lesion other than the one of interest being scanned for FDG-PET and should be obtained 1–4 hours after study drug dosing in Week 2 of Cycle 1, either before or after the scan.
- Single lesion: For patients with only one lesion for both the FDG-PET and the tumor biopsy, the timing of the FDG-PET scan is more important and the biopsy should be obtained after the second FDG-PET scan. The second FDG-PET scan (performed 10 to 14 days after start of dosing with vemurafenib and cobimetinib in Cycle 1) will be completed first (approximately 1–4 hours after dosing) and the tumor biopsy will then be obtained.

Formalin-fixed tumor tissue embedded in paraffin blocks (FFPE biopsy) and, if feasible, fresh-frozen tumor tissue will be collected at baseline, between Days 10 and 14, and at disease progression. The biopsy at disease progression should be taken from an enlarging lesion. Biopsies at progression should be obtained within 3 days of study drug discontinuation (i.e., continue study treatment for several days beyond documentation of progression, if necessary, in order to coordinate the timing of biopsy to occur within 3 days of study drug discontinuation).

Biopsies will be collected and immediately transferred into provided vials filled with formalin. The biopsies will then be fixed for 24± 2 hours, transferred into 70% ethanol, and then (in ethanol) shipped to a central pathology laboratory for paraffin embedding. In cases where a reasonable-sized biopsy (e.g., excisional biopsy, 5-mm punch or more than

one 14-gauge core biopsy) can be collected with formalin fixation, every effort should also be made to collect a fresh-frozen biopsy.

Fresh-frozen tumor (baseline, between Days 10 and 14, and at disease progression) may be used for whole genome analysis; other techniques such as reverse phase protein array or mRNA quantitation may also be performed.

FFPE tumor from baseline and disease progression biopsies will be used to perform the following assessments:

- IHC for molecules known to be relevant for activity of the MAPK pathway (ERK and MEK protein phosphorylation)
- IHC for molecules potentially related to response/resistance including BRAF, CRAF, and PTEN
- BRAF mutations (including V600E) and other somatic mutations affecting PI3K, RAS, RAF, and ERK

The following assessments are planned using the FFPE biopsy taken under treatment (Days 10–14):

- IHC for molecules that are potential PD biomarkers for vemurafenib and cobimetinib (e.g., ERK and MEK phosphorylation).

5.6.3.2 *Presumed or Suspected Squamous Cell Carcinoma, Second Primary Melanoma, and Normal Skin*

Formalin-fixed tissue embedded in paraffin blocks will be collected from patients who develop lesions presumed or suspected to be SCC or second primary melanomas during screening, the treatment period, and during follow-up. Tumor blocks will be returned after biomarker analyses have been performed. Unstained slides are acceptable if, despite all efforts, tumor blocks cannot be sent. Biopsies of suspicious malignant lesions not thought to represent SCC or second primary melanoma may be submitted at the discretion of the investigator.

Normal skin punch biopsies will be obtained under local anesthesia from all patients who develop SCC. Skin biopsies should be collected at the time the SCC lesion is excised in an area of normal skin (with hair follicles present) to the level of subcutaneous tissue. These samples may be obtained by using a 3- to 4-mm punch biopsy device, which should not require suturing. The skin biopsies will be formalin fixed on site and will be shipped in 70% ethanol.

FFPE samples from paired biopsies of SCC (or suspicious neoplasms) and normal skin will be used to perform immunohistochemical analyses of pathway markers (pERK, pMEK, p53), as well as somatic mutation analyses (including mutations of RAS, RAF, CDKN2A, and p53).

5.6.4 Storage of Pharmacodynamic and Exploratory Biomarker Samples

All PD and exploratory biomarker samples (plasma and/or tissue) will be stored for up to 5 years after completion of the study. Patients will have the option to consent that samples remaining after the protocol-defined analyses can be stored up to 15 years in the RCR.

If the patient consents to long-term storage, the RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The implementation and use of the RCR specimens is governed by the RCR policy to ensure the appropriate use of specimens. If no consent has been given for long-term storage, all samples will be destroyed no later than 5 years after the initial freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.

The specimens in RCR will also be made available for future biomarker research towards further understanding of vemurafenib and cobimetinib treatment of advanced metastatic melanoma, related diseases, and adverse events and for the development of potential associated diagnostic assays.

Plasma and tumor specimens will be single coded as for all other clinical samples (labeled and tracked using the patient's study identification number).

5.7 Patients Who Have Discontinued Study Drug

All patients who discontinue vemurafenib and cobimetinib or cobimetinib monotherapy treatments will be followed for survival. Survival status will be assessed every 12 weeks until withdrawal of consent, death, or loss to follow-up, whichever occurs first.

5.8 Dosing beyond Progression

Dosing beyond progression is not recommended. Only under special circumstances when it is felt that the patient may clinically benefit by continued therapy should dosing beyond progression be considered. If it is judged by the investigator, in consultation with the Sponsor, that it is in the best interest of the patient, the patient may continue dosing of both vemurafenib and cobimetinib at the current dose or on cobimetinib alone. All patients who continue cobimetinib monotherapy dosing beyond progression will be dosed at 60 mg daily on a 21/7 schedule and will continue to be followed in their previously assigned cohort. Patients, who prior to progression could only tolerate a dose of cobimetinib below 60 mg daily, may continue dosing at their previously tolerated dose and schedule.

Special circumstances can be defined by, for example, cystic lesions, mixed responses, and new brain metastases that are treatable during the study with stereotactic radiotherapy or surgery but that do not require whole brain radiotherapy. If brain metastases are to be treated with stereotactic radiotherapy/gamma knife, vemurafenib and cobimetinib should be held 1 day prior to the procedure and may resume 1 day after the procedure is completed.

Patients who receive study therapy beyond progression must continue to undergo study visits, laboratory assessments and safety assessments and tumor assessments as specified in Sections 5.3 and 5.4. Tumor assessment scans collected post-progression will not be sent to ICON and the tumor assessment forms in the eCRF does not need to be completed.

Patients who receive study therapy beyond progression may stop study therapy anytime the investigator judges that the patient is no longer benefiting from the study therapy. Patients are required to stop study therapy if continued disease progression is documented in subsequent tumor assessments.

6. INVESTIGATIONAL MEDICINAL PRODUCT

This is an open-label study. Assignment of patients to specific dose cohorts will be tracked manually by the Sponsor. Study drug assignment will be handled manually by the Sponsor.

6.1 Dose and Administration Schedule of Vemurafenib and Cobimetinib

Patients enrolled in a given cohort will receive vemurafenib and cobimetinib at a specified dose combination as described in Section 3. Vemurafenib will be dosed orally bid and cobimetinib will be dosed orally qd.

Patients in screening (written informed consent) for this study who were previously receiving 960 mg bid vemurafenib will be dose-reduced to 720 mg bid for 7–14 days prior to Cycle, 1 Day 1 in Cohorts 1, 1A, 2, 2A, or 1C. Patients receiving 960 mg bid vemurafenib prior to screening initiation (written informed consent) and assigned to Cohorts 1B, 1D, 3, 4, or 5 will continue receiving 960 mg bid vemurafenib, assuming this dose has been adequately tolerated prior to starting the study. Patients in screening (written informed consent) for this study who are treatment naive to vemurafenib at the time of consent will only start vemurafenib on Cycle 1, Day 1 once they are deemed eligible for enrollment.

Vemurafenib will be dosed daily and cobimetinib will be dosed on a 14/14 schedule, a 21/7 schedule, or a continuous daily schedule in a 28-day cycle.

On study visit days, the daily doses of cobimetinib will be taken in the clinic after pre-dose assessments have been performed. After establishing patient eligibility for continued administration of study drugs, patients will be given a sufficient number of tablets and/or capsules to last until the next visit. In some cases, extra tablets and/or capsules may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., due to inclement weather or distance of patient's home from study center).

Cobimetinib should be taken at approximately the same time each day, preferably in the morning, and no later than 4 hours after the scheduled time. Each dose of cobimetinib should be taken with a glass of water.

For vemurafenib, patients will receive study medication bottles, each containing tablets that are 240 mg each. The number of tablets for the morning and evening dose will

depend on the cohort assignment, with at least 8 hours between doses. Each dose of vemurafenib should be taken with a glass of water. As soon as feasible after signing informed consent, patients previously treated with vemurafenib should continue vemurafenib treatment with study drug provided expressly for this particular study and discontinue their supply of drug derived either from their antecedent vemurafenib study or a pharmacy.

Both cobimetinib and vemurafenib will be taken at the same time in the morning.

On PK sample collection days, patients will be required to come into the clinic and have vemurafenib and cobimetinib administered as part of the scheduled study visit after pre-dose assessments have been performed. Vemurafenib and cobimetinib may be taken with or without food, including on PK sampling days.

Patients will be instructed as to the number and strength of the tablets and/or capsules to take according to their assigned dose cohort. The cobimetinib and vemurafenib tablets and/or capsules should never be chewed or opened.

If a dose is missed (not taken within 4 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

Patients will be asked to record the time and date they take each dose in a medication diary. Missed doses should be recorded in a patient diary. Patients will be instructed to bring all unused study medication and their medication diaries to each study visit for assessments of compliance.

The protocol requires a study evaluation to occur on Day 1 of every cycle but allows a period of ± 3 days. Patients on the 14/14 and 21/7 dosing schedule of cobimetinib are required to have the minimum number of days per cycle without cobimetinib dosing 14 and 7 days, respectively. Patients are still expected to return for PK blood draws according to the schedule outlined in Table 10 and Table 11. For example, if a patient on a 21/7 cobimetinib dosing schedule has a study evaluation 2 days earlier than the nominal study day, the patient cannot restart cobimetinib until he/she has had at least 7 days without cobimetinib dosing.

6.1.1 Vemurafenib and Cobimetinib Dose Modification

Dose modifications, interruptions, and delays of vemurafenib and/or cobimetinib study treatment during and after the DLT assessment window should be made on the basis of the guidelines provided in Table 12. Recognizing that new knowledge will be acquired and unforeseen safety issues may arise in the course of the study, the guidelines are not exhaustive and do not represent the full spectrum of care or treatment options described. The dose modification guidelines are not intended to replace clinical judgment or dictate care of individual patients.

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines

Adverse Event	Action
A) Rash/desquamation: **Grade ≥ 3**	a) The appearance of rash must be characterized as acneiform or non-acneiform. b) Acneiform rash • Initiate supportive measures per site guidelines. • Delay cobimetinib dosing until Grade ≤2. • Vemurafenib dosing may continue when cobimetinib is interrupted. • Reduce cobimetinib by one dose level (e.g., 60 to 40 mg at assigned dosing schedule). If after restarting at reduced dose, the patient experiences skin toxicity grade ≥ 3, further reduce cobimetinib by another dose level (e.g., 40 to 20mg at assigned dosing schedule). Permanently discontinue cobimetinib if restarting after second dose reduction, the patient experiences skin toxicity grade ≥ 3. • If rash Grade ≥ 3 persists for > 28 days despite adequate supportive care, cobimetinib may be resumed if in the investigator's judgement, the benefit-risk of treatment remains favorable. c) Non-acneiform, maculo-papular rash • Initiate supportive measures per site guidelines. • Delay vemurafenib dosing until Grade≤2. • Cobimetinib dosing may continue when vemurafenib is interrupted. • For Grade 3 rash, reduce vemurafenib by one dose level (e.g., 960 to 720 mg or 720 to 480 mg). If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3, further reduce vemurafenib by 1 dose level. Permanently discontinue vemurafenib if restarting after second dose reduction, the patient experiences skin toxicity Grade ≥ 3. • For Grade 4 rash, reduce vemurafenib by two dose levels (e.g., 960 to 480 mg or 720 to 240 mg). Permanently discontinue vemurafenib if after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3.

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines (Cont.)

Adverse Event	Action
B) Photosensitivity: Grade ≥ 3	a) In cases of Grade 2 photosensitivity, treatment with vemurafenib and cobimetinib may be continued for up to 1 week with the initiation of supportive measures. If the photosensitivity does not resolve to Grade ≤ 1 during this time or if the photosensitivity worsens to Grade ≥ 3, then both vemurafenib and cobimetinib treatment must be interrupted until the photosensitivity resolves to a Grade ≤ 1. If this occurs within 28 days, treatment may be re-initiated with vemurafenib dose reduced by one level (e.g., 720 to 480 mg). b) If the photosensitivity does not resolve to Grade ≤ 1 by 28 days, then the therapy with vemurafenib and cobimetinib should be discontinued. c) If the photosensitivity recurs to Grade ≥ 3 with vemurafenib and cobimetinib, re-initiation despite prophylactic measures and the dose reduction of vemurafenib, then both agents should be held until the photosensitivity resolves to Grade ≤ 1 or less. Cobimetinib should be dose reduced by one level when treatment is re-initiated (e.g., 80 to 60 mg on a 14/14 day schedule; from 60 to 40 mg on a 21/7 or a continuous schedule). The dose of vemurafenib should be maintained at the previously reduced dose. d) If photosensitivity recurs a second time to Grade ≥ 3 despite prophylactic measures and the aforementioned dose reductions of vemurafenib and cobimetinib, either one or both study treatments may resume if in the investigator's judgement, the benefit-risk of treatment remains favorable.
C) New skin lesion, suggestive of SCC; SCC is considered a Grade 3 event in NCI CTCAE v4.0	a) Follow SCC Risk Management Plan detailed in protocol (Section 5.3.4.6) b) Interrupt vemurafenib and cobimetinib for 48 hours before and after excisional biopsy. This period of interruption may be altered based upon experience in this study. c) If lesion is diagnosed as SCC, treatment may be re-instituted with vemurafenib and cobimetinib at pre-event dose levels after the lesion is excised. If the lesion is not excised, vemurafenib treatment may be resumed if in the investigator's judgement, the benefit-risk of treatment remains favorable. d) If the lesion is not an SCC, then treatment with vemurafenib and cobimetinib may be restarted at the most recent dose level.

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines (Cont.)

Adverse Event	Action
D) Ocular toxicity or visual symptoms **Grade ≥ 2**	a) For any treatment-emergent Grade ≥ 2 visual symptoms or ocular toxicity, cobimetinib and vemurafenib must be interrupted pending diagnostic evaluation, including a complete ophthalmologic examination performed and interpreted by a qualified ophthalmologist, visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography. b) If RVO is diagnosed, vemurafenib and cobimetinib dosing should be permanently discontinued and the RVO treated per institutional guidelines. c) If RVO is not present, but the visual symptoms are not completely resolved by 28 days, either one or both study treatments may resume if in the investigator's judgement, the benefit-risk of treatment remains favorable. d) If visual symptoms have completely resolved and findings consistent with RVO or neurosensory retinal detachment are not present, the patient may resume use of vemurafenib and cobimetinib with cobimetinib dose reduced by one level (e.g., 80 to 60 mg on a 14/14 day schedule; 60 to 40 mg on a 21/7 or a continuous schedule). e) If ocular toxicity of Grade ≥2 recurs a second time, both vemurafenib and cobimetinib should be permanently discontinued.
E) Diarrhea (Grade ≥3)	a) No change in vemurafenib and cobimetinib dosing will be implemented for Grade 2 diarrhea; patients should receive maximal supportive care per institutional guidelines. b) If Grade ≥ 3 diarrhea occurs despite supportive care, then both drugs should be held until the diarrhea has improved to Grade ≤ 1. If this occurs within 28 days, vemurafenib and cobimetinib may be restarted with cobimetinib dose reduced by one level (e.g., 80 to 60 mg on a 14/14 day schedule; 60 to 40 mg on a 21/7 or a continuous schedule). c) If the diarrhea is not completely resolved by 28 days, then either one or both study treatments may resume if in the investigator's judgement, the benefit-risk of treatment remains favorable. d) If Grade ≥ 3 diarrhea recurs despite supportive care and cobimetinib dose reduction, vemurafenib and cobimetinib should be held until the diarrhea resolves to Grade < 1. If this occurs within 28 days, then therapy may be re-initiated with vemurafenib dose reduced by one level (e.g., 720 to 480 mg). The cobimetinib dose may be maintained at the previously reduced dose. e) If the diarrhea recurs at Grade ≥ 3 despite supportive care and dose reductions in both drugs, then either one or both study treatments may resume if in the investigator's judgement, the benefit-risk of treatment remains favorable.

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines (Cont.)

Adverse Event	Action
F) ***Rhabdomyolysis or symptomatic CPK elevations***	*a) Interrupt cobimetinib treatment. If severity is improved by at least on grade within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when cobimetinib treatment is modified, if clinically indicated.* *b) If rhabdomyolysis or symptomatic CPK elevation do not improve within 4 weeks, permanently discontinue cobimetinib treatment.*
G) Asymptomatic CPK elevations	*a) Grade ≤ 3: cobimetinib dosing does not need to modified or interrupted to manage asymptomatic Grade ≤ 3 CPK elevations.* *b) Grade 4: Interrupt cobimetinib treatment. If improved to Grade ≤ 3 within 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. Vemurafenib dosing can be continued when cobimetinib treatment is modified, if clinically indicated. If CPK elevations do not improve to Grade ≤ 3 within 4 weeks following dose interruption, permanently discontinue cobimetinib treatment.*
***H*) Liver function test (LFT) elevations**	a) If Grade 1 or 2, continue current dose of vemurafenib and cobimetinib. b) If Grade 3 or 4, hold vemurafenib. Continue current dose of cobimetinib. Upon resolution of LFT to Grade ≤ 1, resume vemurafenib at one lower dose level (e.g., 960 to 720 mg, or 720 to 480 mg). c) If Grade 3 or 4, LFT elevation recurs after one dose reduction, vemurafenib may be reduced by another dose level (e.g., 720 to 480 to 240 mg). Permanently discontinue vemurafenib if Grade 4 LFT elevation recurs when vemurafenib is at a dose of 240 mg bid and continue current dose of cobimetinib.

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines (Cont.)

Adverse Event	Action
***I*) QTc interval prolongation on ECG**	On-study QTc interval prolongation to >500 ms but <60 ms increment compared with baseline OR prolongation of QTc interval to ≥60 ms compared with baseline (regardless of absolute QTc): a) Rule out other risk factors for arrhythmia (e.g., myocardial ischemia); check for electrolyte disturbances (particularly potassium and magnesium levels) in all cases. b) Evaluate concomitant medications to determine if there is co-administration of drugs that prolongs QTc interval in all cases (e.g., 5-HT_3 receptor antagonist anti-emetics), see Appendix 6. c) Interrupt dosing of vemurafenib and perform ECG and electrolyte monitoring weekly during period of vemurafenib interruption until QTc improves and electrolytes are corrected in all cases; continue dosing with cobimetinib at the current dose if otherwise tolerated. d) If QTc interval does not improve within 28 days after interruption of vemurafenib dosing, permanently discontinue vemurafenib; continue dosing with cobimetinib at the current dose. e) If QTc improves within 28 days, restart dosing of vemurafenib at one reduced dose level (e.g., 960 to 720 mg bid). f) Repeat 12-lead ECG monitoring at Week 2 and Week 4 of the new, lower vemurafenib dose, at Day 1 of each subsequent Cycle×3, and every 3 months thereafter. g) If second increase in QTc interval to >500 ms occurs at the lower dose of vemurafenib, follow Guidelines a through c above, reduce dose of vemurafenib by 1 more dose level (e.g., 720 to 480 mg bid), and follow Guidelines d and e. On-study QTc interval prolongation to >500ms AND >60 ms increment compared with baseline: a) Patient may continue cobimetinib at his/her current dose level. Vemurafenib treatment may resume if in the investigator's judgement, the benefit-risk of treatment remains favorable.
J) Hemorrhage	*Grade 3 events: Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib treatment. Vemurafenib dosing can be continued when cobimetinib treatment is interrupted, if clinically indicated.* *Grade 4 events or cerebral hemorrhage (all grades): Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib.*

Table 12 Vemurafenib and Cobimetinib Dose Modification Guidelines (Cont.)

Adverse Event	Action
***K*) Other Grade 4, non-hematologic adverse events related to study drug**	a) Interrupt dosing of vemurafenib and cobimetinib. b) If adverse event resolves to Grade ≤ 1 within 28 days, then (at investigator discretion) restart dosing of vemurafenib and *cobimetinib*. Both should be decreased by one dose level of the pre-event dose (e.g., 960 to 720 mg for vemurafenib; 80 to 60 mg for cobimetinib on a 14/14 day schedule). c) If the adverse event does not resolve to Grade ≤ 1 within 28 days, discontinue study treatment. d) If the adverse event recurs after 1 dose reduction, either one or both study treatments may resume if in the investigator's judgement, the benefit-risk of treatment remains favorable.

bid = twice daily; LFT = liver function test; QTc = corrected QT interval; RVO = retinal vein occlusion; SCC = squamous cell carcinoma.

6.2 Accountability and Patient Compliance for Investigational Medicinal Product

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipts (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. Patients will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance.

Accountability and patient compliance will be assessed by maintaining adequate "drug dispensing" and return records.

Accurate records must be kept for each study drug provided by the Sponsor. These records must contain the following information.

- Documentation of drug shipments received from the Sponsor (date received and quantity
- Disposition of unused study drug not dispensed to patient

A Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study medication was dispensed
- The date(s) and quantity of the study medication dispensed to the patient.
- The date(s) and quantity of the study medication returned by the patient.

All records and drug supplies must be available for inspection by the study monitor at every monitoring visit.

All study drug required for completion of this study will be provided by Sponsor. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Study drug will either be disposed of at the study site according to study site's institutional standard operating procedures or returned to Roche and/Genentech with the appropriate documentation, as determined by the study site. If the study site chooses to destroy the study drug, the method of destruction must be documented.

Roche and/or Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.3 Formulation, Storage, Packaging, and Labeling

Study drug packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature.

Local packaging in some countries may be different.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals, and temperature conditions and report any deviations or product complaints to the study monitor upon discovery.

6.3.1 Vemurafenib

Vemurafenib is supplied in 240-mg film-coated tablets packed in bottles for oral administration. For additional batch specific instructions and information for vemurafenib film-coated tablets, see the packaging.

Vemurafenib will be stored at the clinical site under the recommended storage conditions of "Do Not Store above 25°C" as indicated on the study drug label. Patients will be requested to store the vemurafenib at the recommended storage conditions noted on the label, out of the reach of children or other co-inhabitants.

Vemurafenib will be labeled in compliance with Good Manufacturing Procedures. The drug label will include the contents, protocol number, batch number, and storage conditions, as well as any required statements that the drug is "For Investigational Use Only."

6.3.2 Cobimetinib

Cobimetinib will be supplied in two forms: capsules and tablets.

While supplies last, cobimetinib will be supplied as 5-mg, 25-mg, and 100-mg capsules that are differentiated by color. The 5-mg capsules are light blue (Size 1), the

25-mg capsules are orange (Size 1), and the 100-mg capsules are flesh colored (Size 0). The capsule formulation contains no excipients other than the hard gelatin capsule. The capsules should be stored at the clinical site under recommended storage conditions: 15°C–30°C/59°F–86°F, as indicated on the study drug label.

After the capsule supplies are used up or have expired, cobimetinib will be administered in tablet format. The tablet formulation of cobimetinib (GDC-0973) will be a 20-mg film–coated, immediate-release tablet. The tablet formulation consists of the cobimetinib and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate (non-bovine), and Opadry White film coat.

All excipients used in the tablet formulation are compendial (USP/NF and/or EP) grade with the exception of the film coating. The tablet coating consists of polyvinyl alcohol part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. The ingredients in the film coating are compendial. The tablets should not be stored above 25°C (77°F).

The tablet/capsule dose administered to each patient will be based on cohort assignment. Doses will be administered at the clinical site for the initial dose and on subsequent dosing days that coincide with clinical site visits. Patients will be given instructions for self-administration on dosing days that do not coincide with clinical site visits. Any unused study drug must be returned to the study site for disposal. Patients will be asked to store the cobimetinib at the recommended storage conditions noted on the label, out of reach of children or other co-inhabitants.

Cobimetinib packaging will be overseen by the Roche clinical trial supplies department and bear a label with the identification required by local law as well as the protocol number. The packaging and labeling of the study drugs will be in accordance with the Sponsor's standards and local regulations. Local packaging and labeling requirements may differ in some countries.

Upon delivery of the investigational products to the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals, and temperature conditions. Site personnel should report any deviations or product complaints to the study monitor upon discovery.

For further details, see the cobimetinib (GDC-0973) IB.

6.4 Blinding and Un-blinding

This is not applicable as this study is open-labeled.

6.5 Accountability of Investigational Medicinal Product and Assessment of Compliance

6.5.1 Accountability of Investigational Medicinal Product

All records and drug supplies must be available for inspection by the study monitor at every monitoring visit.

Patients will be asked to return all used and unused drug supply containers at the end of the treatment as a measure of compliance. All supplies, including partially used or empty containers and copies of the dispensing and inventory logs, must be returned to the Roche/Genentech monitor at the end of the study, unless alternate destruction has been

authorized by Roche/Genentech or required by local or institutional regulations (Section 6.5.2).

6.5.2 Assessment of Compliance

Patient compliance will be assessed by maintaining adequate study drug dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.

Destruction of the Investigational Medicinal Product (IMP)

Local or institutional regulations may require immediate destruction of unused IMP for safety reasons, e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers or patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of its institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical Adverse Events

According to the International Conference of Harmonization (ICH), an adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Preexisting conditions that worsen during a study are to be reported as adverse events.

7.1.1.1 *Intensity*

Intensity of all adverse events will be graded according to the NCI CTCAE v4.0 on a 5-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Adverse events not listed on the CTCAE should be graded as follows:

CTC Grade[a,b]	Equivalent to:	Definition
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[c]
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[d]
Grade 4	Life threatening/ disabling	Life-threatening consequences; urgent intervention indicated
Grade 5[e]	Death	Death related to AE

[a] Semi-colon indicates 'or' within the description of the grade; a single dash (-) indicates a grade is not available.
[b] Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.
[c] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[d] Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not being bedridden.
[e] Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

7.1.1.2 *Drug–Adverse Event Relationship*

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the study medication, i.e., there are facts (evidence) or arguments to suggest a causal relationship, drug–event relationship should be assessed as Yes.

The following criteria should be considered in order to assess the relationship as Yes:

- Reasonable temporal association with drug administration
- It may or may not have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as No:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

7.1.1.3 *Serious Adverse Events (Immediately Reportable to Roche)*

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect, or precaution. It is any adverse event that at any dose fulfils at least one of the following criteria:

- Is fatal (results in **death**; NOTE: death is an outcome, not an event)
- Is life threatening (NOTE: The term life threatening refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused a death had it been more severe.)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above

****The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably**.

The study will comply with all local regulatory requirements and adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2** (see Appendix 3).

7.1.1.4 *Adverse Events of Special Interest*

The following events are adverse events of special interest and will need to be reported to the Sponsor expeditiously (see Section 7.2.1 for instructions on expedited reporting), irrespective of regulatory seriousness criteria:

- Grade ≥ 1 retinal vein occlusion
- Grade ≥ 2 visual disturbances
- cuSCC of any grade
- Grade ≥3 QTc interval prolongation
- Grade ≥3 photosensitivity
- Grade 4 elevations in liver function tests (serum ALT, AST and/or bilirubin)

7.1.1.5 *Other Adverse Events Requiring Expedited Reporting*

The following events are adverse events that will need to be reported to the Sponsor expeditiously, irrespective of regulatory seriousness criteria:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which 35% is direct bilirubin)

- Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with clinical jaundice.

- Suspected transmission of an infectious agent by the study drug, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

7.1.1.6 *Progression of Underlying Malignancy*

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an adverse event or serious adverse event.

7.1.2 Treatment and Follow-Up of Adverse Events

After the discontinuation of therapy with vemurafenib and/or cobimetinib, continue following up of adverse events as follows:

Related adverse events: Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Start of new anti-cancer regimen
- Investigator confirms no further improvement can be expected
- Clinical or safety data will no longer be collected; or final database closure

Unrelated severe or life-threatening adverse events: Follow until one of the following occurs:

- Resolved or improved to baseline

- Intensity (severity) improved to Grade 2 *or lower*
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected; or final database closure

Unrelated Grade 1 or Grade 2 adverse events: Follow as clinically indicated.

The final outcome of each adverse event must be recorded on the eCRF

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eform of the eCRF or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event should be reported as such, in addition to being recorded as an adverse event in the eCRF.

Any treatment-emergent abnormal laboratory result that is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

This applies to any protocol and non-protocol–specified safety and efficacy laboratory result from tests performed after the first dose of study medication that falls outside the laboratory reference range and meets the clinical significance criteria.

7.1.3.1 *Follow-Up of Abnormal Laboratory Test Values*

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed-up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Serious Adverse Events (Immediately Reportable)

Investigators will seek information on adverse events at each patient contact.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). **The**

exception to this is if the patient is on commercial Zelboraf (vemurafenib) during this time; in such cases, adverse events are to be reported to Roche, and spontaneous reporting criteria will apply.

After initiation of study drug any clinical adverse event or abnormal laboratory test value that is serious and that occurs during the course of the study (as defined in Section 7.1.1.3) must be reported to Roche immediately (i.e., no more than 24 hours after learning of an event). The investigator must complete the SAE Reporting Form [SRD-0115310] and forward it to the person in charge of processing the serious adverse events at Roche (SAE Responsible).

Related serious adverse events **MUST** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated serious adverse events must be collected and reported during the study and for up to 28 days after the last dose of study medication.

Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the SAE Reporting Form [SRD-0115310] rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an adverse event or serious adverse event. If a diagnosis is subsequently established, it should be reported as follow-up information.

Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an adverse event or serious adverse event.

However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately.

For the purposes of this study, the following will not be considered a serious adverse event:

- Elective hospitalizations or surgical procedures that are a result of a patient's preexisting condition(s) that have not worsened since receiving trial medication; examples may include, but are not limited to, cholecystectomy for gallstones, joint replacement surgery, and diagnostic testing. Such events should still be recorded as medical procedures in the eCRF.

7.2.2 Pregnancy

A female patient must be instructed to stop taking the test "drug" and immediately inform the investigator if she becomes pregnant during the study. The investigator should report

all pregnancies within 24 hours to the Sponsor using the Clinical Trial Pregnancy Reporting Form, [SRD-0115311] for any pregnancies that occur within 6 months of last dose of study treatment. The investigator should counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a male patient participating in the study should be reported to the investigator and the Sponsor. The partner should be counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

NOTE: The investigator should fill out a Pregnancy Reporting Form, [SRD-0115311], only if the pregnant partner has signed a Pregnant Partner Data Release Form.

7.3 Warnings and Precautions

7.3.1 Vemurafenib Warnings and Precautions

Investigators and patients should be aware of the risks of photosensitivity reactions, cutaneous neoplasms, non-cutaneous neoplasms, potentiation of radiation toxicities, hypersensitivity reactions, severe dermatologic reactions, liver injury, QTc interval prolongation, and potential DDIs during treatment with vemurafenib. For details pertaining to these risks, please refer to Section 1.2.4 and Section 1.2.5.

7.3.2 Cobimetinib Warnings and Precautions

Investigators and patients should be aware of the risks of serous retinopathy and left ventricular dysfunction during treatment with cobimetinib. For details pertaining to the risk of serous retinopathy and left ventricular dysfunction, please refer to Section 1.3.7.2 and Section 1.3.7.3, respectively, for details pertaining to these risks.

7.3.3 Other Precautions

Given the biopsy requirements in this study, risks such as infection of the surgical site, excessive bleeding, or injury to adjacent tissues should be considered for patients who undergo tumor tissue biopsies.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Variable

This study is designed to evaluate the safety and tolerability of vemurafenib and Cobimetinib when administered in combination in patients with previously untreated or treated (but without prior exposure to any BRAF or MEK inhibitor therapy), $BRAF^{V600E}$ mutation-positive, locally advanced/unresectable or metastatic melanoma as well as those who have progressed after treatment with vemurafenib immediately prior to enrollment on this study and to identify a recommended dose and schedule for the combination of vemurafenib and cobimetinib for further clinical testing. Safety and tolerability will be described through DLTs and MTDs for vemurafenib and cobimetinib.

8.1.2 Secondary Variables

Evidence of objective tumor response following vemurafenib and cobimetinib treatment or cobimetinib monotherapy will be documented and summarized. Potential alterations in the RAS/RAF/MEK pathway (such as RAS, RAF, and MEK mutations) will be assessed to identify potential tumor response and resistance mechanisms. $BRAF^{V600E}$ mutation status of progressing patients will be assessed as well. Predisposing factors for SCC development will be analyzed using specimens from SCC or suspicious neoplasms, as well as paired normal skin.

The steady-state pharmacokinetics of vemurafenib and cobimetinib will be characterized. PD effects of vemurafenib and cobimetinib combination therapy and cobimetinib monotherapy (up to 12 patients) will be measured by changes in FDG-PET and changes in biomarkers from pre- and during-treatment samples.

Secondary efficacy endpoints include the following:

OR is defined as a complete or a partial response confirmed $\geq$ 4 weeks after initial documentation on the basis of investigator assessment using the RECIST v1.1 criteria.

DOR is defined as the interval (days) between the date of the earliest qualifying response and the date of progressive disease or death for any cause. This will be calculated only for patients who had an OR. Patients with no documented progression after a complete or partial response will be censored at the date of the last evaluable tumor assessment.

PFS is defined as the interval (days) between the start date of treatment and the date of progression or death for any cause, whichever comes first. Patients who have neither progressed nor died will be censored on the date of last evaluable tumor assessment. Patients who had no post-baseline assessments and did not have an event will be censored at Day 1. PFS will be calculated on the basis of investigator assessment according to RECIST v1.1.

OS is defined as the interval between the start date of treatment and the date of death for any cause.

Tumor assessment scans may be assessed by an independent IRF.

8.1.3 Safety

Safety of the treatment will be evaluated by adverse events, laboratory tests, vital signs, ECGs, performance status, and ophthalmic and dermatological evaluations.

All patients who received any amount of treatment will be included in the safety evaluation.

8.2 Statistical and Analytical Methods

8.2.1 Statistical Model

No statistical model will be used in the efficacy analysis and no formal hypothesis testing is planned. Descriptive statistics will be used to summarize the clinical activity, pharmacokinetics, and PD effect of vemurafenib and cobimetinib as described in the section on study objectives.

DLTs that occur in the first 28 days after initial dose of vemurafenib and cobimetinib will be used to determine the recommended dose. Subsequent DLTs will be reported and summarized as well.

The safety and efficacy (e.g., ORR, duration of response) will be presented by assigned dose cohort in the dose escalation stage and treatment group (patients previously treated with vemurafenib; patients previously untreated or treated [but without prior exposure to any BRAF or MEK inhibitor therapy] for locally advanced/unresectable or metastatic disease) in the dose expansion stage. The final analysis will be performed on all patient data collected through the 28 days after last patient's last dose of study drug or at least 12 months after last patient in, whichever occurs later. For all patients who completed 6 months SCC follow-up after end of treatment prior to protocol amendment j, an additional analysis will be performed to summarize any SCC findings per the RMP.

8.2.2 Hypothesis Testing

Descriptive statistical analyses will be performed for all analyses. Any statistical testing performed will be exploratory in nature and will be used to demonstrate the mechanism of action of vemurafenib and cobimetinib.

8.2.3 Analysis Populations

The treated population is defined as all patients who receive any amount of study medication. All safety analyses will use the treated population. Patients who enroll in the dose escalation stage who complete the DLT assessment window (Day 28) or experience a DLT in the assessment window and are withdrawn from study will be evaluable for determination of the recommended dose.

8.2.4 Safety Data Analyses

Safety will be assessed through summaries of DLTs, adverse events, changes in laboratory test results, changes in vital signs, and vemurafenib and cobimetinib exposures. Descriptive statistics will be used to summarize all safety data. Summary tables and listings will be presented by assigned dose cohort.

Adverse event data will be reported in listings and presented in frequency tables by Medical Dictionary for Regulatory Affairs (MedDRA) terms. All adverse events occurring on or after treatment on Cycle 1, Day 1 will be summarized. Summaries of adverse event by grade, seriousness, and relationship to study treatment will be presented, as well as summaries of adverse events leading to death or to premature withdrawal from study treatment. Serious adverse events, including deaths, will be listed separately and summarized.

Relevant laboratory and vital signs (temperature, heart rate, and blood pressure) data will be presented using summary statistics.

Laboratory data will be presented as summary tables for worst toxicity grade compared with baseline using Standard Internationale units. Descriptive statistics will be used to summarize ECOG performance status. Vital signs, ECGs, and ophthalmologic and dermatologic test results will be reported in the listings.

Exposure to study medication will be summarized by total duration of study medication, number of cycles started, and cumulative dose using descriptive statistics. Dose interruptions/modifications and their reasons will be presented.

8.2.5 Exploratory Analyses

Pharmacogenetic Analysis

In order to explore the potential role of polymorphisms in drug metabolism enzyme and gene transporters in the PK disposition and safety profile of vemurafenib and cobimetinib, gene mutations may be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other appropriate methods. PK parameters, including dose-normalized AUC and C_{max}, would be compared between genotypes and, where possible, predicted phenotypes.

8.2.6 Determination of Maximal Tolerated Dose

Patients who withdraw from the study or who miss more than the allowed number of vemurafenib or cobimetinib doses prior to Cycle 1, Day 28 for reasons other than a DLT will be considered unevaluable for DLTs and will not be included in the determination of the MTD of the vemurafenib and cobimetinib combination. The MTD of the vemurafenib and cobimetinib combination will be determined according to the rules described in Section 3.1.4. In the event dose escalation does not continue until the MTD can be determined (e.g., because of PK futility), the MTD will be reported as "undetermined."

8.2.7 Other Analyses

8.2.7.1 *Pharmacokinetic Analysis*

Several PK parameters derived from the blood PK samples will be analyzed using descriptive statistics (means, standard deviations, coefficients of variation, median). They will include C_{max}, C_{min}, and AUC. Additional parameters such as apparent CL, volume of distribution, and $t_{1/2}$ will be estimated if the concentration data are sufficient.

Estimation of the PK parameters will be performed using standard non-compartmental methods. Actual sampling times will be used to calculate PK parameters.

Steady-state pharmacokinetics of vemurafenib and cobimetinib will be summarized descriptively. Relevant PK parameters will be correlated with dose, safety, or efficacy variables.

8.2.7.2 *Exploratory Biomarker Analyses*

The aim of exploratory biomarker analyses is to explore the potential to predict efficacy (response, PFS, and survival) and/or toxicities by each marker separately and/or by suitable combinations.

Given the explorative nature of these analyses, no fixed analysis schedule can be specified. Exploratory analyses of individual biomarkers and combinations of markers will be conducted using appropriate statistical methods in a data-dependent way. The results might generate hypotheses on how biomarker observation could predict for benefit. Validation of the hypotheses will require a new set of independent data.

Additional biomarker data may become available from other studies prior to finalizing this study. Testing of biomarkers to support or confirm results from other studies will be specified in an analysis plan prior to closing this study.

FDG-PET response as defined by the EORTC will be used as a potential early readout of anti-tumor activity.

8.3 Sample Size

Design considerations were not made with regard to explicit power and type I errors but to obtain preliminary safety, PK, and PD information in this patient population. The number of patients expected to be treated with combination therapy in this two-stage study is approximately 130, assuming approximately 30–60 patients enroll in the dose-escalation stage (i.e., 10 dose cohorts) and at least 40 patients enroll in at least two expansion cohorts (one consisting of patients previously treated with vemurafenib, the other consisting of patients previously treated [but without prior exposure to BRAF or MEK inhibitor therapy] or previously untreated for locally advanced/unresectable or metastatic melanoma). This estimate does not include up to 20 patients who may enroll in the cobimetinib monotherapy cohort.

The sample size for this trial is based upon the dose-escalation rules described in Table 13, which describes the properties of the dose-escalation rules with different underlying rates of DLT.

Patients who withdraw from the study prior to completing the DLT assessment window for reasons other than DLTs will be replaced.

Table 13 Properties of the Dose-Escalation Rules with Different Underlying Rates of DLT

Underlying Rates of Dose-Limiting Toxicity	Probability of Enrolling an Additional 3 Patients	Probability that the Dose Is Determined to be Tolerated
0.10	0.24	0.91
0.20	0.38	0.71
0.33	0.44	0.43
0.40	0.43	0.31
0.50	0.38	0.17
0.60	0.29	0.08

An expansion cohort of approximately 20 patients treated at the recommended dose will provide a reasonable chance (87.8%) of observing at least one or more adverse events when the true frequency of the adverse event is 10% at a given dose level. Table 14 provides probabilities of seeing at least one adverse event among 20 patients for probabilities ranging from 0.001 to 0.20 (i.e., adverse event frequencies of 0.1% to 20%). For example, if the true probability of an adverse event is 0.20 or greater, there is a more than an (98.8%) chance of seeing at least one such event in an expansion cohort of 20 patients.

Table 14 Probability of Safety-Signal Detection with an Expansion Cohort of 20 Patients

True Underlying Probability of an Adverse Event	Probability of Observing At Least One Adverse Event in 20 Patients
0.001	0.020
0.01	0.182
0.05	0.642
0.10	0.878
0.15	0.961
0.20	0.988

Preliminary evaluation of activity in the RAS/RAF-mutant population is an important study objective. With an expansion cohort of 20 patients RAS/RAF-mutant patients, if the true response rate is at least 20%, the chance of seeing at least one response is >98.8%.

9. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

Data for this study will be recorded via an electronic data capture system using eCRFs and will be transcribed by the site from the paper source documents onto the eCRFs. **In no case is the eCRF to be considered as source data for this trial.**

Accurate and reliable data collection will be assured by verification and crosschecking of the eCRFs against the investigator's records by the study monitor (source document verification) and the maintenance of a drug-dispensing log by the investigator. Data management will be performed by [redacted] at the following address;

[redacted]

A comprehensive validation check program verifies that the data and discrepancy reports will be generated accordingly for resolution by the investigator.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF using the most up-to-date version of the MedDRA terminology for adverse events and diseases and the International Non-Proprietary Name Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. STUDY COMMITTEES

A Data Safety Monitoring Board (DSMB) has been utilized to ensure patient safety and will consist of external clinicians who are experts in the disease area and 1 external statistician. The DSMB reviewed available safety data approximately every 3 months. The DSMB had the option to change the data review schedule as deemed needed. Details of the DSMB's responsibilities and logistics were outlined in the charter. Safety monitoring by an independent DSMB has ceased following the results of the primary efficacy analysis of the Phase III study, GO28141.

11. REFERENCES

1. Ries LAG, et al, eds. SEER Cancer Statistics Review, 1975-2000, Bethesda, MD : National cancer Institute ; 2003 : Table XVI-1–9.

2. Lucas, R. Global Burden of Disease of solar Ultraviolet Radiation, Environmental Burden of Disease Series, July 25, 2006; No. 13. News release, World Health Organization.

3. http://www.sunsmart.com.au/browse.asp?ContainerID=1752/ SUNSMART Cancer Council Victoria (2007).

4. http://www.skincancer.gov.au/internet/skincancer/publishing.nsf/Content/fact -2 Australian Government Dept. of Health and Ageing (2008).

5. Beeram M, Patnaik, et al., Raf: a strategic target for therapeutic development against Cancer. J Clin Oncol 2005; (23):6771–90.

6. Maldonado JL, Fridlyand J, Patel H, et al., Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst 2003; (95): 1878–90.

7. Lang J, Mackie RM, Prevalence of exon 15 BRAF mutations in primary melanoma of the superficial spreading, nodular, acral, and lentigo maligna subtypes. J Invest Dermatol. 2005; (125): 575-9.

8. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005; (353): 2135-47.

9. http://www.sanger.ac.uk/genetics/CGP/cosmic/.

10. Gray-Schopfer V, Wellbrock C and Marais R.Melanoma biology and new targeted therapy. Nature, 2007; (445):851–7.

11. Hingorani SR, Jacobetz MA, et al, Integrating BRAF/MEK inhibitors in combination therapy for melanoma. Cancer Research, 2003; (63):5198–5202

12. Sumimoto H, Miyagishi M, Miyoshi H, et al., Inhibition of growth and invasive ability of melanoma by invasion of mutated BRAF with lentivirus-mediated RNA interference. Oncogene, 2004; (23):6031–9.

13. Smalley KSM, Herlyn M, et al., Targeting BRAF/MEK in melanoma: new hope or another false dawn? Expert Tev. Dermatol., 2007;(2):179–90.

14. Ascierto P, Streicher HZ, and Sznol M. Melanoma: A model for testing new agents in combination therapies. J of Translational Med., 2010;(8):38.

15. Flaherty KT, Puzanov I. Kim KB et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 2010; (363):809:819.

16. Callahan MK, Rampal R, Harding JJ, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. N Engl J Med. 2012 367:2316–21.

17. Grey A, Cooper A, McNeil C, et al. Progression of KRAS mutant pancreatic adenocarcinoma during vemurafenib treatment in a patient with metastatic melanoma. Intern Med J 2014;44:597–600.

18. Lankisch PG, Gottesleben DF. Drug induced acute pancreatitis: incidence and severity. M Gut 1995; 37: 565–7.

19. Harding JJ, Lacouture ME, Pulitzer M, et al. Hypersensitivity skin reactions in melanoma patients treated with vemurafenib after ipilimumab therapy J Clin Oncol 30, 2012 (suppl; abstr 8515).

20. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89:806–15.

21. Ribas a, Hodi FS, Callahan M, et al. Correspondence: hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med. 2012 368:1365–6.

22. Chapman PB, Hauschild A, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. (2011), 364, 2507–16.

23. Murad, A, et al., Cutaneous Squamous Cell Carcinoma., New Engl. J Med., (2001), 13, 975–983.

24. Smalley KS, Hass NK, et al., Multiple signaling pathways must be targeted to overcome drug resistance in cell lines derived from melanoma metastases. Molec. Cancer Therapy, 2006; (5):1136–44.

25. Solit DB, Garraway LA, et al., BRAF mutation predicts sensitivity to MEK inhibition. Nature, 2006; (439):358–62.

26. Haass NK, Sproesser K, et al., The mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel. Clin Cancer Res., 2008; (14):230–9.

27. Poulikos IP, Zhnag C, Bollag G, et al Raf inhibitors transactivate RAF dimers and ERK signaling in cells with wild-type BRAF. Nature, 2010; (464):427–30.

28. Hatzivassiliou G, Song K, Yen I, et al., Raf inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. Nature., 2010;(464): 431.

29. Heidorn SJ, Milagre C, Whittaker S, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF , Cell, (2010), 140, 209–21.

30. Daouti S, Higgins B, et al., Preclinical in vivo evaluation of efficacy, pharmacokinetics, and pharmacodynamics of a novel MEK1/2 kinase inhibitor RO5068760 in multiple tumor models. Mol. Cancer Ther. (2010), 9, 134–44.

31. Leboeuf R, Baumgartner JE, et al, BRAF V600E mutation is associated with preferential sensitivity to MEK inhibition in thyroid cancer cell lines. (2008), J Clin, Endocrinol. and Metab. 93, 2194–2201.

32. Young H, Baum R, et al,. Measurement of clinical and subclinical tumor response using [18F]-flurodeoxyglucose and positron emission tomography: review. Eur.J Cancer. (1999), 35, 1773–82.

33. Flaherty KT, Robert C, Hersey P, et al; METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107–14.

34. Lynch TJ Jr, Kim ES, et al Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. Oncologist, (2007), 12, 610–21.

PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the subject. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

In other countries where "Guideline for Good Clinical Practice" exists, Roche and the investigators will strictly ensure adherence to the stated provisions.

Patients who comply with the requirements of the protocol, are tolerating study treatment, and have not developed disease progression may be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to continue RO8155426 in combination with cobimetinib for up to 1 year as long as the above-mentioned conditions are met. If the study is terminated (see Section 4.7), however, study drugs may not be offered after study termination.

12.2 Informed Consent

Written Informed Consent from Subjects:

12.2.1 Main Study Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The Case Report Forms (CRFs) for this study contain a section for documenting subject informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For the subject not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

For US-IND studies: In a life-threatening situation where a subject is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the subject's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the subject under protocol with consent of both the investigator and another physician not involved in the study, with appropriate documentation submitted to the IRB within 5 days. If this collaboration is not immediately possible, there must be a written evaluation by a physician independent of the study and the appropriate documentation be submitted to the IRB within 5 days of treating the subject. In addition, the subject or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

For non-US-IND studies: In a life-threatening situation where a subject is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the subject's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the subject under protocol with consent of the investigator, with appropriate documentation that the IEC had approved the procedures used to enroll subjects in such situations. In addition, the subject or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

12.2.2 Roche Clinical Repository Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to have their samples stored long term for future research in the RCR after adequate explanation of the aims, methods, objectives and potential hazards. Subjects must receive an explanation that they are completely free to refuse long term storage of their samples for future research and may withdraw his/her sample at any time and for any reason during the 15 year storage period of the specimen(s). The Informed Consent for an **optional** long term storage of specimen(s) donation will be incorporated as a specific section into the main Clinical Trial [or Experimental Research study] Informed Consent Form (ICF). A second, separate, specific signature consenting to long term storage will be required to document the study participant's agreement to provide an optional specimen for long-term storage of their samples for future research; if the participant declines, he/ she will check a "no" box in the appropriate section and not provide a second signature.

The CRF for the associated clinical study contains a page for documenting subject informed consent to the RCR, and this must be completed appropriately.

12.2.3 Death or Loss of Competence of Participant who has Donated a Specimen(s) that is Stored in the Roche Clinical Repository

In case the Informed Consent Form and/or the Study Protocol do not provide any specific provisions for death or loss of competence, specimen and data will continue to be used as part of RCR research.

In the event of the death of a participant of a Roche Clinical Trial or Experimental Medicine Research study or if a participant is legally incompetent at the time of the specimen and data procurement, or becomes legally incompetent thereafter, applicable provisions as stated for such situations in the respective Informed Consent Form and/or the Study Protocol shall become effective and be followed accordingly.

Additional procurement of assent from legally incompetent persons and minors shall take place according to local laws and international best practice, as it applies to the specific case

12.3 Independent Ethics Committees (IEC)/Institutional Review Board (IRB)

The protocol, informed consent and any accompanying material provided to the subject in the U.S. will be submitted by the investigator to an IRB for review. For EEA member states, the sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the subject. In both the US and EEA member states, the accompanying material may include subject information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the subject as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, informed consent or material provided to the subject after receipt of the IEC/IRB approval must also be submitted by the investigator in the U.S. and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.

Long term storage of samples in the RCR is contingent on review and approval of the exploratory biomarker assessments and written informed consent by an appropriate regulatory body (depending on the country where the study is performed) and a site's Institutional Review Board (IRB) / Ethics Committee (EC). If a regulatory authority or site's IRB/EC do not approve the long term storage of samples for the exploratory assessments, the section on biomarker sampling will only be applicable for 5 year storage of samples.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

12.4 Role of the Science and Ethics Advisory Group (SEAG)

A Science and Ethics Advisory Group consisting of experts in the fields of biology, ethics, sociology and law will advise Roche regarding the use of specimens stored in the RCR and on the scientific and ethical aspects of handling genetic information. The SEAG is independent of Roche.

12.5 Financial Disclosure

The investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the investigator [investigator representative[s] in the case of a multicenter trial]. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Clinical Science Leader/Clinical Pharmacologist and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change[s] involves only logistical or administrative aspects of the trial [e.g. change in monitor[s], change of telephone number[s].

14. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Regulatory Agencies should be informed accordingly.

15. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

15.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: 1) Investigator's Study File, and 2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, eCRF and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the study the investigator will receive the subject data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.

Subject clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs] would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrollment logs. The Investigator must keep the two categories of documents as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator can not guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

ICH GCP guidelines require that Investigators maintain information in the study subject's records which corroborate data collected on the eCRF(s). Completed eCRF will be forwarded to Roche.

15.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

15.4 Case Report Forms or Electronic Case Report Forms

Data for this study will be captured directly onto the electronic case report form (eCRF) after logging onto the secure InForm database which is web based. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change.

For each subject enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study [even during a pre-randomization screening period if an eCRF was initiated]. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

16. MONITORING THE STUDY

It is understood that the responsible Roche monitor [or designee] will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial [CRFs and other pertinent data] provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the subject received the dose and schedule of study drugs assigned. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Roche Clinical Repository specimens will at all times be tracked in a manner consistent with Good Clinical Practice, by a quality controlled, auditable and validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in the study protocol and ICF, respectively. Roche monitors and auditors will have direct access to appropriate parts of records relating to subjects participating in this study for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, and regulatory inspections by providing direct access to source data and documents related to the RCR Research Project.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names and addresses.

The investigator should maintain documents not for submission to Roche, e.g., Roche already maintains rigorous confidentiality standards for clinical studies by "coding" (i.e. assigning a unique subject ID number at the investigator site) all subjects enrolled in Roche clinical studies. This means that subject names are not included in data sets that are transmitted to any Roche location. Given the sensitive nature of genetic data, Roche has implemented a number of additional processes to assure subject confidentiality. All specimens taken for inherited genetic research that will be stored in the RCR (see Section 5.5.1) undergo a second level of "coding". At Roche, the specimen is transferred to a new tube and labeled with a new random number. This is referred to as "Double Coding (De-Identification)". Data generated following the use of these specimens and all clinical data transferred from the clinical study database and considered relevant, will also be labeled with this same code. The "linking key" between the participant's identification number and this new independent code will be stored in a secure database system. Access to the table linking the participant identification number to the specimen code will be strictly limited and monitored by audit trial. Legitimate operational reasons for accessing the "linking key" will be documented in a standard operating procedure. Access to the "linking key" for any other reason will require written approval from the Governance Committee responsible for the specimen(s).

18. CLINICAL STUDY REPORT (CSR)

A clinical study report has been written and distributed to Health Authorities as required by applicable regulatory requirements.

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the study in which input of Roche personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Data derived from RCR specimen analysis on individual subjects will not be provided to study investigators, except where explicitly stipulated in a study protocol (e.g. if the result is an enrollment criterion). Exceptions may be granted (e.g. if biomarker data would be linked to safety issues). The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements and / or know- how originating from the use of the RCR will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009)

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm).

10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

Bone scan, PET scan or x-rays are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u>

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Target lesions that become 'too small to measure': while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assign(Cohorts 1C and 1D)ing an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy**. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

When the patient has only non-measurable disease: this circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).

This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Timepoint Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1 Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2 Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Appendix 1: New Response Evaluation Criteria in Solid Tumors – Version 1.1–Excerpt From Original Publication with Addition of Supplementary Explanations (Eisenhauer et al. 2009) (Cont.)

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Best Overall Response: All Timepoints

The best overall response will be determined by statistical programming once all the data for the patient is known.

Appendix 2: ECOG Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described below:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649–655, 1982.

Appendix 3: ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

– is fatal; [results in death] [NOTE: death is an outcome, not an event]

– is life-threatening [NOTE: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].

– required in-patient hospitalization or prolongation of existing hospitalization;

– results in persistent or significant disability/incapacity;

– is a congenital anomaly/birth defect;

– is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

– Pre-existing/Underlying disease–specify

– Study treatment–specify the drug(s) related to the event

– Other treatment (concomitant or previous)–specify

– Protocol-related procedure

– Other (e.g., accident, new or intercurrent illness)–specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug", should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor

See attached Protocol Administrative and Contact Information & List of Investigators Form,[gcp_for000227], for details of administrative and contact information.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations/Clinical Science

See attached Protocol Administrative and Contact Information & List of Investigators form,[gcp_for000227], for details of administrative and contact information

24 HOUR MEDICAL COVERAGE (Roche Emergency Medical Call Center Help Desk): Within the US, weekends, holidays and after 5:00 pm, call: [redacted] and ask for the physician on call. **From Australia,** call [redacted] **and ask for the physician on call. (Note: the number for Australia cannot be dialed from a mobile phone.)**

Appendix 4: New York Heart Association Classification of Functional Cardiac Capacity

Class	
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix 5: AJCC TNM Staging for Melanoma

Tumor (T) classification	
TX	Primary tumor cannot be assessed (e.g., shave biopsy, regressed primary)
Tis	Melanoma in situ
T1	< or = 1.0 mm
	a: without ulceration and level II/III*
	b: with ulceration or level IV or V*
T2	1.01-2.0 mm
	a: without ulceration
	b: with ulceration
T3	2.01-4.0 mm
	a: without ulceration
	b: with ulceration
T4	>4.0 mm
	a: without ulceration
	b: with ulceration
Node (N) classification	
N1	One lymph node
	a: micrometastases (clinically occult)
	b: macrometastases (clinically apparent)
N2	2-3 lymph nodes
	a: micrometastases
	b: macrometastases
	c: in-transit met(s)/satellite(s) without metastatic lymph nodes
N3	4 or more metastatic lymph nodes, or matted lymph nodes, or in-transit met(s)/satellite(s) with metastatic lymph node(s)
Metastasis (M) classification	
M1a	Distant skin, subcutaneous, or lymph node metastases, normal LDH
M1b	Lung metastases, normal LDH
M1c	All other visceral metastases, normal LDH Any distant metastases, elevated LDH

* Clark's levels: level II: invades the papillary dermis; level III: invades to the papillary-reticular dermal interface; level IV: invades the reticular dermis; level V: invades subcutaneous tissue.

Micrometastases are diagnosed after elective or sentinel lymphadenectomy.

Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

Appendix 6: Medications Affecting QT Interval (Information Available on http://www.azcert.org)

Albuterol	Doxepin	Lithium	Quinidine
Alfuzosin	Droperidol	Mesoridazine	Ranolazine
Amantadine	Ephedrine	Metaproterenol	Risperidone
Amiodarone	Epinephrine	Methadone	Ritodrine
Amitriptyline	Erythromycin	Methylphenidate	Roxithromycin
Amphetamine	Felbamate	Mexiletine	Salmeterol
Arsenic trioxide	Fenfluramine	Midodrine	Sertindole
Astemizole	Flecainide	Moexipril	Sertraline
Atazanavir	Fluconazole	Moxifloxacin	Sibutramine
Atomoxetine	Fluoxetine	Nicardipine	Sibutramine
Azithromycin	Foscarnet	Nilotinib	Solifenacin
Bepridil	Fosphenytoin	Norepinephrine	Sotalol
Chloral hydrate	Galantamine	Nortriptyline	Sparfloxacin
Chloroquine	Gatifloxacin	Octreotide	Sunitinib
Chlorpromazine	Gemifloxacin	Ofloxacin	Tacrolimus
Ciprofloxacin	Granisetron	Ondansetron	Tamoxifen
Cisapride	Halofantrine	Oxytocin	Telithromycin
Citalopram	Haloperidol	Paliperidone	Terbutaline
Clarithromycin	Ibutilide	Paroxetine	Terfenadine
Clomipramine	Imipramine	Pentamidine	Thioridazine
Clozapine	Indapamide	Perflutren lipid microspheres	Tizanidine
Cocaine	Isoproterenol	Phentermine	Tolterodine
Desipramine	Isradipine	Phenylephrine	Trimethoprim-Sulfa
Dexmethylphenidate	Itraconazole	Phenylpropanolamine	Trimipramine
Disopyramide	Ketoconazole	Pimozide	Vardenafil
Dobutamine	Lapatinib	Probucol	Venlafaxine
Dofetilide	Levafloxacin	Procainamide	Voriconazole
Dolasetron	Levalbuterol	Protriptyline	Ziprasidone
Domperidone	Levomethadyl	Pseudoephedrine	
Dopamine	Lisdexamfetamine	Quetiapine	

Appendix 7: Plasma Pharmacokinetic Sample Collection Schedule for Patients Previously Treated with Vemurafenib [a,b]

Study Visit	Time	Event
Cycle 1, Day -1	0-4 hours before vemurafenib AM dose. Record exact time of vemurafenib dose administration	Plasma sample for vemurafenib
	2 hours (± 15 minutes) after vemurafenib morning dose	Plasma sample for vemurafenib
	4 hours (± 30 min) after vemurafenib morning dose	Plasma sample for vemurafenib
	6 hours (± 1 hour) after vemurafenib morning dose	Plasma sample for vemurafenib
	8 hours (± 1 hour) after vemurafenib morning dose	Plasma sample for vemurafenib
Cycle 1, Day 1	0-4 hours before cobimetinib dose. Record exact time of cobimetinib dose administration	Plasma sample for cobimetinib and vemurafenib
	0.5 hour (± 10 minutes) after cobimetinib dose	Plasma sample for cobimetinib
	1 hour (± 15 minutes) after cobimetinib dose	Plasma sample for cobimetinib
	2 hours (± 15 minutes) after cobimetinib dose	Plasma sample for cobimetinib
	4 hours (± 1 hour) after cobimetinib dose	Plasma sample for cobimetinib
	6 hours (± 1 hour) after cobimetinib dose	Plasma sample for cobimetinib
Cycle 1, Day 2	0-2 hours before the second cobimetinib dose (24 hours from first dose of cobimetinib) Record exact time of cobimetinib dosing	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 8	0-4 hours before cobimetinib and vemurafenib dose. Record exact time of dosing	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 14	0-4 hours before cobimetinib and vemurafenib dose. Record exact time of dosing	Plasma sample for cobimetinib and vemurafenib
	0.5 hour (± 10 minutes) after cobimetinib dose	Plasma sample for cobimetinib and vemurafenib
	1 hour (± 15 minutes) after cobimetinib dose	Plasma sample for cobimetinib and vemurafenib

Appendix 7: Plasma Pharmacokinetic Sample Collection Schedule for Patients Previously Treated with Vemurafenib [a,b] (Cont.)

Study Visit	Time	Event
	2 hours (± 15 minutes) after cobimetinib dose	Plasma sample for cobimetinib and vemurafenib
	4 hours (± 1 hour) after cobimetinib dose	Plasma sample for cobimetinib and vemurafenib
	6 hours (± 1 hour) after cobimetinib dose	Plasma sample for cobimetinib and vemurafenib
	8 hours (± 1 hour) after cobimetinib dose	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 15	0-2 hours before vemurafenib dose	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 16[a]	0-2 hours before vemurafenib dose (48 hours from Day 14 dose of cobimetinib)	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 17[a]	0-2 hours before vemurafenib dose (72 hours from Day 14 dose of cobimetinib)	Plasma sample for cobimetinib and vemurafenib
Cycle 2, Day 1	0-4 hours before cobimetinib dose Record exact time of cobimetinib dosing.	Plasma sample for cobimetinib
Cycle 2, Day 8	0-4 hours before cobimetinib dose Record exact time of cobimetinib dosing.	Plasma sample for cobimetinib and vemurafenib
Cycle 2, Day 8	2-4 hours after cobimetinib dose Record exact time of cobimetinib dosing for Day 8 of Cycle 2.	Plasma sample for cobimetinib and vemurafenib
Cycle 3, Day 8	0-4 hours before cobimetinib dose Record exact time of cobimetinib dosing.	Plasma sample for cobimetinib and vemurafenib

[a] Vemurafenib plasma levels samples shall be collected on Days 16 and 17 of C1 only when cobimetinib is given on a 14/14 schedule

[b] Patients on cobimetinib monotherapy will undergo PK sampling based on their assigned cobimetinib dosing schedule.

Appendix 8: Plasma Pharmacokinetic Sample Collection Schedule for Patients Either Previously Untreated or Treated (but without Exposure to BRAF or MEK Inhibitor Therapy) for Locally Advanced/Unresectable or Metastatic Melanoma[a]

Study Visit	Time	Event
Cycle 1, Day 1	0-2 hours before cobimetinib and vemurafenib AM dose. Record exact time of cobimetinib and vemurafenib dose administration.	Plasma sample for cobimetinib and vemurafenib
	0.5 hour (± 10 minutes) after morning dose	Plasma sample for cobimetinib and vemurafenib
	1 hour (± 15 minutes) after morning dose	Plasma sample for cobimetinib and vemurafenib
	2 hours (± 15 minutes) after morning dose	Plasma sample for cobimetinib and vemurafenib
	4 hours (± 1 hour) after morning dose	Plasma sample for cobimetinib and vemurafenib
	6 hours (± 1 hour) after morning dose	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 2	0-2 hours before the second cobimetinib dose (24 hours from first dose of cobimetinib) Record exact time of cobimetinib dosing	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 8	0-4 hours before cobimetinib and vemurafenib dose. Record exact time of dosing	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 14	0-4 hours before cobimetinib and vemurafenib dose. Record exact time of dosing	Plasma sample for cobimetinib and vemurafenib
	0.5 hour (± 10 minutes) after morning dose of vemurafenib and cobimetinib	Plasma sample for cobimetinib and vemurafenib
	1 hour (± 15 minutes) after morning dose of vemurafenib and cobimetinib	Plasma sample for cobimetinib and vemurafenib
	2 hours (± 15 minutes) after morning dose of vemurafenib and cobimetinib	Plasma sample for cobimetinib and vemurafenib
	4 hours (± 1 hour) after morning dose of vemurafenib and cobimetinib	Plasma sample for cobimetinib and vemurafenib

Appendix 8: Plasma Pharmacokinetic Sample Collection Schedule for Patients Either Previously Untreated or Treated (but without Exposure to BRAF and MEK Inhibitor Therapy for Locally Advanced/Unresectable or Metastatic Melanoma (Cont.) [a]

Study Visit	Time	Event
	6 hours (± 1 hour) after morning dose of vemurafenib and cobimetinib	Plasma sample for cobimetinib and vemurafenib
	8 hours (± 1 hour) after morning dose of vemurafenib and cobimetinib	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 15	0-2 hours before cobimetinib dose (24 hours from Day 14 dose of cobimetinib)	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 16[a]	0-2 hours before vemurafenib dose (48 hours from Day 14 dose of cobimetinib)	Plasma sample for cobimetinib and vemurafenib
Cycle 1, Day 17[b]	0-2 hours before vemurafenib dose (72 hours from Day 14 dose of cobimetinib)	Plasma sample for cobimetinib and vemurafenib
Cycle 2, Day 1	0-4 hours before cobimetinib dose Record exact time of cobimetinib dosing.	Plasma sample for cobimetinib
Cycle 2, Day 8	0-4 hours before cobimetinib dose Record exact time of cobimetinib dosing for Day 7 and Day 8 of Cycle 2.	Plasma sample for cobimetinib and vemurafenib
Cycle 2, Day 8	2-4 hours after cobimetinib dose Record exact time of cobimetinib dosing for Day 8 of Cycle 2.	Plasma sample for cobimetinib and vemurafenib
Cycle 3, Day 8	0-2 hours before cobimetinib dose Record exact time of cobimetinib dosing for Day 7 and Day 8 of Cycle 2.	Plasma sample for cobimetinib and vemurafenib

[a] Vemurafenib plasma levels samples shall be collected on Days 16 and 17 of Cycle 1 only when cobimetinib is given on a 14/14 schedule.

Appendix 9: Cobas® 4800 BRAF V600 Mutation Assay Information

The cobas® 4800 BRAF V600 Mutation Assay is a real-time polymerase chain reaction (PCR) test intended to be used to identify melanoma patients whose tumors carry the $BRAF^{V600E}$ mutation for treatment with vemurafenib monotherapy. Its primary use is the detection of the $BRAF^{V600E}$ mutation in DNA isolated from formalin-fixed, paraffin-embedded human melanoma and colorectal cancer (CRC) tumor tissue.

A prototype version of this test, designed to run on the **cobas**® TaqMan® 48 Analyzer, was used to select melanoma and CRC patients for the Phase 1 extension cohorts. The **cobas**® 4800 System uses the same technology as that used in the **cobas**® TaqMan® 48 Analyzer.

Analytical performance studies have been conducted to characterize the **cobas**® 4800 BRAF V600 Mutation Assay for analytical sensitivity, limits of sample input, accuracy and reproducibility for detection of the $BRAF^{V600E}$ mutation in DNA from melanoma. Based upon these studies, the **cobas**® 4800 BRAF V600 Mutation Assay has been approved by the US FDA for investigational use to select adult patients with metastatic melanoma for treatment with vemurafenib in the Phase 2 and Phase 3 clinical trials of vemurafenib in locally-advanced/uresectable or metastatic melanoma (Investigational Device Exemption G070126).

Based on preliminary findings that the BRAF mutation is preserved in patients with tumors that escape vemurafenib-mediated suppression of the RAS/RAF pathways, BRAF mutation status will be confirmed retrospectively by the **cobas**® 4800 BRAF V600 Mutation Assay in the proposed clinical trial of vemurafenib and cobimetinib combination, NO25395.

Patients with a positive test for the mutation will be eligible for treatment in the clinical drug trial if they meet other eligibility criteria.

Appendix 10: Impact of Vemurafenib on Concomitant Medications

Impact of RO5185426 on Concomitant Medications		
Substrates		
CYP 1A2[1]	CYP 2C9[1]	CYP3A4[2]
amitriptyline	**NSAIDs:**	**Macrolide antibiotics:**
caffeine	diclofenac	clarithromycin
clomipramine	ibuprofen	erythromycin
clozapine	lornoxicam	telithromycin
cyclobenzaprine	meloxicam	Anti-arrhythmics:
estradiol	S-naproxen_Nor	quinidine_3OH
fluvoxamine	piroxicam	
haloperidol	suprofen	**Benzodiazepines:**
imipramine N-DeMe		alprazolam
mexilletine	**Oral Hypoglycemic:**	diazepam_3OH
naproxen	tolbutamide	midazolam
olanzapine	glipizide	triazolam
ondansetron	Angiotensin II	
phenacetin	Blockers:	**Immune Modulators:**
acetaminophen	losartan	cyclosporine
propranolol	irbesartan	tacrolimus (FK506)
riluzole	Sulfonylureas:	HIV Antivirals:
ropivacaine	glyburide	indinavir
tacrine	glibenclamide	nelfinavir
theophylline	glipizide	ritonavir
tizanidine	glimepiride	saquinavir
verapamil	tolbutamide	Prokinetic:
(R)warfarin	amitriptyline	cisapride
zileuton	celecoxib	
zolmitriptan	fluoxetine	**Antihistamines:**
	fluvastatin	astemizole
	glyburide	chlorpheniramine
	nateglinide	terfenadine
	phenytoin-4-OH2	
	rosiglitazone	**Calcium Channel Blockers:**
	tamoxifen	amlodipine
	torsemide	diltiazem
	S-warfarin	felodipine
		lercanidipine
		nifedipine2
		nisoldipine
		nitrendipine
		verapamil

Appendix 10: Impact of Vemurafenib on Concomitant Medications (Cont.)

CYP 1A2[1]	CYP 2C9[1]	CYP3A4[2]
		HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone **Miscellaneous:** alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-Ndemethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone salmeterol

Appendix 10: Impact of Vemurafenib on Concomitant Medications (Cont.)

		sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

1 Exposure of these drugs may be increased following vemurafenib treatment.
2 Exposure of these drugs may be decreased following vemurafenib treatment.