Official Title: A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus GDC-0973 in Previously Untreated $BRAF^{V600}$-Mutation Positive Patients With Unresectable Locally Advanced or Metastatic Melanoma

NCT Number: NCT01689519

Document Date: Protocol Version 8: 20-October-2016

PROTOCOL

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB VERSUS VEMURAFENIB PLUS GDC-0973 IN PREVIOUSLY UNTREATED BRAF^{V600}-MUTATION POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA**
PROTOCOL NUMBER:	GO28141
VERSION NUMBER:	*8*
EUDRACT NUMBER:	2012-003008-11
IND NUMBER:	Vemurafenib (RO5185426): 109307 Cobimetinib (GDC-0973/RO5514041/XL518): 76798
TEST PRODUCT:	Vemurafenib (RO5185426) Cobimetinib (GDC-0973/RO5514041/XL518)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 3 August 2012; Version 2: 4 October 2012 Version 3: 24 April 2013 Version 4: 12 September 2013 Version 5: 24 February 2015 Version 6: 20 October 2015 Version 7: 30 March 2016 *Version 8:* See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	20-Oct-2016 17:24:10

PROTOCOL

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[redacted] MD PhD

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

Protocol GO28141 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:

- Language around cobimetinib approval has been clarified (Section 5.1).
- Safety language for rhabdomyolysis/CPK elevations and hemorrhage has been updated and moved to "identified risks associated with cobimetinib" (Section 5.1.2.1).
- Language around impaired fertility and developmental toxicity was clarified (Section 5.1.2.2).
- The term "non-serious adverse events of special interest" has been updated to "adverse events of special interest" to reflect standard Roche terminology (Sections 5.1.4.1, 5.2, 5.2.3, 5.3.5.6, 5.4, 5.4.2, 5.5.2, and 5.7).
- The dose modification table has been updated (Table 10 in Section 5.1.5.3).
- Suspected transmission of an infectious agent by the study drug has been added to the list of adverse events of special interest (Section 5.2.3).
- The title of Section 5.3.5.10 has been updated to Adverse Events Associated with an Overdose or Error in Drug Administration.
- It has been clarified that safety analyses will not be performed using patient-reported outcome data (Section 5.3.5.11).
- The term "spontaneous abortion" has been changed to "abortion" to reflect standard Roche terminology (Section 5.4.3.3).
- The term "adverse event of concern" has been changed to "adverse event of special interest" for clarity (Section 5.6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 8: SUMMARY OF CHANGES

GLOBAL CHANGES

The term “non-serious adverse event of special interest” and the term “adverse event of concern” have been changed to “adverse event of special interest.”

SECTION 5.1: Safety Plan

Cobimetinib ~~(~~for use with vemurafenib~~)~~ is approved in the United States*, Canada,* ~~and~~ *members of the* European Union*,* ~~as well as~~*and* other countries.

SECTION 5.1.2.1: *Important* Identified Risks Associated with Cobimetinib

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 10, in Section 5.1.5.3.

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 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 10 in Section 5.1.5.3.

SECTION 5.1.2.2: 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 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~~

Title change only.

Teratogenicity and Development Toxicity

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.

Section 5.1.2.3: 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.~~

Hypersensitivity

Please refer to the cobimetinib IB for additional safety information.

SECTION 5.1.5.3: Management of Specific Toxicities and Dose Modification Guidelines

Table 10: Management of Specific Toxicities and Dose Modification Guidelines

The table has been updated to reflect the latest safety guidance.

SECTION 5.2.3: ~~Non Serious~~ Adverse Events of Special Interest

Adverse events of special interest for this study include the following:

- *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.

SECTION 5.3.5.10: *Adverse Events Associated with an Overdose or Error in Drug Administration*~~Overdoses~~

Title change only.

SECTION 5.3.5.11: Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data*, and safety analyses will not be performed using PRO data*.

SECTION 5.4.3.3: Abortions

Any ~~spontaneous~~ abortion associated with a pregnancy occurring during the study or within 6 months of the last dose of study drug should be classified as a serious adverse event (as the Sponsor considers ~~spontaneous~~ abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB VERSUS VEMURAFENIB PLUS GDC-0973 IN PREVIOUSLY UNTREATED BRAF^{V600}-MUTATION POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA**
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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 return a copy of the form to your local study monitor. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB VERSUS VEMURAFENIB PLUS GDC-0973 IN PREVIOUSLY UNTREATED $BRAF^{V600}$-MUTATION POSITIVE PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC MELANOMA**
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PHASE:	III
INDICATION:	$BRAF^{V600}$-mutation positive patients with unresectable locally advanced or metastatic melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective of Study GO28141 is as follows:

- To evaluate the efficacy of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated $BRAF^{V600}$ mutation–positive patients with unresectable locally advanced or metastatic melanoma, as measured by prolongation of progression-free survival (PFS), as assessed by the study site investigator

The secondary efficacy objective of Study GO28141 is as follows:

- To evaluate the efficacy of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated $BRAF^{V600}$ mutation–positive patients with unresectable locally advanced or metastatic melanoma, as measured by overall survival (OS), objective response rate, duration of response, and PFS as assessed by independent review

Safety Objectives

The safety objective of Study GO28141 is as follows:

- To characterize the toxicity profile in patients receiving vemurafenib and cobimetinib versus vemurafenib and placebo

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective of Study GO28141 is as follows:

- To characterize the pharmacokinetics of cobimetinib and vemurafenib and to compare the pharmacokinetics of vemurafenib when administered with cobimetinib to the pharmacokinetics of vemurafenib when administered with placebo
- To perform exploratory exposure-response analysis, including concentration-QT interval corrected (QTc) analysis

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objective of Study GO28141 is as follows:

- To evaluate health-related quality of life in patients receiving vemurafenib and cobimetinib versus vemurafenib and placebo as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EuroQol 5 dimension (EQ-5D) questionnaire

Exploratory Objectives

The Sponsor 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). Specimens may be used for any of the following:

- To explore the intrinsic and acquired mechanisms of resistance to MEK and BRAF inhibition in tumor samples obtained at baseline, during treatment, and at disease progression
- To study the association of biomarkers with efficacy and/or adverse events associated with medicinal products
- To increase knowledge and understanding of disease biology

Study Design

Description of Study

Study GO28141 is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical study to evaluate the safety and efficacy of vemurafenib in combination with cobimetinib with vemurafenib alone, in previously untreated $BRAF^{V600}$ mutation–positive patients with unresectable locally advanced or metastatic melanoma.

Approximately 500 previously untreated $BRAF^{V600}$ mutation-positive patients with unresectable locally advanced or metastatic melanoma will be randomized in a 1:1 ratio to receive treatment with one of the following regimens:

- Arm A (control arm): vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1–28 and placebo by mouth (PO) once daily (QD) on Days 1–21 of each 28-day treatment cycle
- Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib 60 mg PO QD on Days 1–21 of each 28-day treatment cycle

The stratified, permuted-block randomization scheme will be used for treatment allocation based on the following stratification factors:

- Geographic region (North America, Europe, Australia/New Zealand/others)
- Metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c)

After signing informed consent, patients will undergo screening procedures that include testing for the $BRAF^{V600}$ mutation; laboratory tests (hematology, chemistries, liver function tests); 12-lead ECG; left-ventricular function evaluation (echocardiogram or multigated acquisition [MUGA] scan), contrast-enhanced brain computed tomography (CT) or magnetic resonance imaging (MRI); contrast-enhanced CT or MRI of the chest, abdomen, and pelvis; and ophthalmologic and dermatologic assessments.

All eligible patients will be randomized to treatment in either Arm A (vemurafenib and placebo) or Arm B (vemurafenib and cobimetinib). Vemurafenib will be taken starting on Day 1 to Day 28

of each 28-day treatment cycle. The first dose of vemurafenib should be taken in the morning, and the second dose should be taken in the evening. The cobimetinib or placebo tablet will be taken once daily starting on Day 1 to Day 21 of each 28-day treatment cycle. The cobimetinib or placebo tablet should be taken at approximately the same time each day, preferably in the morning with the vemurafenib dose. Vemurafenib and cobimetinib/placebo can be taken with or without a meal, and should be taken with a glass of water.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the end-of-study treatment visit, and during the follow-up period. Patients will be assessed for adverse events every 2 weeks during the first 2 cycles, then prior to each subsequent cycle, and as necessary throughout the study.

Tumor response will be evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator at 8-week intervals. At the investigator's discretion, CT/MRI scans may be repeated at any time if progressive disease is suspected.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be used to characterize the toxicity profile of the study treatments on all patients. ECG monitoring for patients who receive vemurafenib will be conducted in accordance with the vemurafenib IB. Ongoing ECG monitoring is no longer required for patients who continue to receive only cobimetinib/placebo unless clinically indicated. Dermatologic assessment will be performed at the beginning of Cycle 2 ($\pm$1 week) and per local standard of care thereafter. Ophthalmologic examinations and left ventricular function evaluation (echocardiogram or MUGA) are evaluated throughout the study.

Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest. Patients on the vemurafenib and placebo treatment arm will be eligible to cross over to the vemurafenib and cobimetinib treatment arm prior to disease progression so long as the patient has not discontinued vemurafenib treatment should the investigator feel that the addition of cobimetinib may benefit the patient and the patient provides informed consent and continues to be followed for survival. Patients who have previously discontinued vemurafenib and who are receiving only placebo may not cross over and should discontinue all study treatment.

Number of Patients

This study will enroll approximately 500 patients.

Target Population

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria:

1. Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by the American Joint Committee on Cancer 7th edition. Unresectability of Stage IIIc disease must have confirmation from a surgical oncologist.
2. Patients must be naïve to treatment for locally advanced unresectable or metastatic disease (i.e., NO prior systemic anti-cancer therapy for advanced disease; Stage IIIc and IV). Prior adjuvant therapy (including immunotherapy, e.g., ipilimumab) is allowed.
3. Documentation of BRAF^{V600} mutation–positive status in melanoma tumor tissue (archival or newly obtained tumor samples) using the cobas® 4800 BRAF V600 mutation test
4. Measurable disease per RECIST v1.1
5. Eastern Cooperative Oncology Group Performance Status of 0 or 1
6. Consent to provide archival tissue (either a paraffin-embedded tissue block or up to 20 unstained slides) for biomarker analyses
7. Consent to undergo tumor biopsies of accessible lesions on Cycle 2 Day 15 and at progression for biomarker analyses to explore intrinsic and acquired resistance

General Inclusion Criteria:

8. Male or female patient aged ≥ 18 years
9. 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
10. Life expectancy ≥ 12 weeks
11. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
    - ANC $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 100 \times 10^9$/L
    - Hemoglobin ≥ 9 g/dL
    - Albumin ≥ 2.5 g/dL
    - Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN)
    - AST, ALT, and alkaline phosphatase (ALP) $\leq 3 \times$ ULN, with the following exceptions:
        - Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN
        - Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
    - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance (CrCl) ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockroft-Gault glomerular filtration rate estimation:
      $(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})$
      $72 \times (\text{serum creatinine in mg/dL})$
12. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use 2 effective forms 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 oophorectomy or hysterectomy who have had menses within the last 12 months.
    - Females are not considered to be of childbearing potential if amenorrheic for > 12 months and follicle-stimulating hormone (FSH) level ≥ 40 IU/L.
    - For females who have been amenorrheic for ≥ 2 years, the requirement for FSH measurement at screening will be waived.
    - Effective forms of contraception include surgical sterilization, a reliable barrier method with spermicide, birth control pills, or contraceptive hormone implants. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.
    - Male patients who are surgically sterilized are required to use barrier methods of contraception.
13. Negative serum pregnancy test within 14 days prior to commencement of dosing in women of childbearing potential
14. Absence of any psychological, familial, sociological, or geographical condition that potentially hampers compliance with the study protocol and follow-up after treatment discontinuation schedule; those conditions should be discussed with the patient before trial entry

Patients who meet any of the following criteria will be excluded from study entry:

Cancer-Related Exclusion Criteria:

1. History of prior RAF or MEK pathway inhibitor treatment
2. Palliative radiotherapy within 14 days prior to the first dose of study treatment
3. Major surgery or traumatic injury within 14 days prior to first dose of study treatment

4. Patients with active malignancy (other than BRAF−mutated melanoma) or a previous malignancy within the past 3 years are excluded; except for patients with resected melanoma, resected basal cell carcinoma (BCC), resected cutaneous squamous cell carcinoma (SCC), resected melanoma in-situ, resected carcinoma in-situ of the cervix, and resected carcinoma in-situ of the breast.
5. History of isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer is allowed.

Exclusion Criteria Based on Organ Function
Ocular:

6. History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment / central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration
7. The risk factors for RVO are listed below. Patients will be excluded if they currently have the following conditions:
   a) Uncontrolled glaucoma with intra-ocular pressures ≥ 21 mmHg
   b) Serum cholesterol ≥ Grade 2
   c) Hypertriglyceridemia ≥ Grade 2
   d) Hyperglycemia (fasting) ≥ Grade 2

Cardiac:

8. History of clinically significant cardiac dysfunction, including the following:
   a) Current unstable angina
   b) Symptomatic congestive heart failure of New York Heart Association class 2 or higher (Appendix 7)
   c) History of congenital long QT syndrome or mean (average of triplicate measurements) QTc measured using Fridericia's method ≥ 450 ms at baseline or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus). Please refer to Section 4.5.1.11
   d) Uncontrolled hypertension ≥ Grade 2 (patients with a history hypertension controlled with anti-hypertensives to ≤ Grade 1 are eligible)
   e) Left ventricular ejection fraction (LVEF) below institutional lower limit of normal or below 50%, whichever is lower

Central Nervous System:

9. Patients with active CNS lesions (carcinomatous meningitis) are excluded. However, patients are eligible if:
   a) All known CNS lesions have been treated with stereotactic therapy or surgery, AND
   b) There has been no evidence of clinical and radiographic disease progression in the CNS for ≥ 3 weeks after radiotherapy or surgery
   c) 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:

10. Current severe, uncontrolled systemic disease
11. History of malabsorption or other condition that would interfere with absorption of study drugs
12. Pregnant, lactating, or breast feeding
13. Unwillingness or inability to comply with study and follow-up procedures

14. The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
    a) St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
    b) Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)

Length of Study

The enrollment period is approximately 14 months. The final OS analysis will be performed after the occurrence of approximately 250 deaths (projected to occur at approximately 31 months after the first patient was randomized).

End of Study

The study will end when all patients enrolled have been followed until death, withdrawal of consent, lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

Patients may continue on study treatment until the development of progressive disease, unacceptable toxicity, and/or consent withdrawal. Patients who discontinue study treatment for any reason will be followed for SCC according to the risk management plan, followed for disease progression and followed for survival until death, withdrawal of consent, or they are lost to follow-up. Patients who start subsequent anti-cancer treatment after study treatment discontinuation will still need to be followed for survival and SCC.

Efficacy Outcome Measures

The primary outcome measure for this study is as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever comes first.

The secondary outcome measures are as follows:

- Overall survival, defined as the time from randomization to death from any cause
- Objective response rate for patients with measurable disease at baseline, defined as complete or partial response as assessed by investigator according to RECIST v1.1
- Duration of response for patients with measurable disease at baseline, defined as the time from first occurrence of a documented objective response until the time of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment)
- PFS as assessed by independent review using RECIST v1.1

Safety Outcome Measures

Safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events and serious adverse events, graded according to NCI CTCAE v4.0
- Adverse events of special interest: any RVO; any retinal detachment or central serous chorioretinopathy; Grade ≥ 2 LVEF reduction; Grade ≥ 3 photosensitivity; Grade ≥ 3 elevations of AST, ALT, serum bilirubin OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6; Grade ≥ 3 QT interval prolongation; and any cutaneous primary malignancy, including SCC, keratoacanthoma, BCC, and new primary melanoma.
- Changes in vital signs, ECGs, and clinical laboratory results during the course of study

Pharmacokinetic Outcome Measures

The following PK parameters will be analyzed using a population PK approach and will be reported as applicable.

- Exposure following first dose and steady-state (area under the plasma – concentration time curve through 24 hours [AUC_{0-24}])
- Minimum observed plasma concentration (C_{min}; trough concentration)
- Apparent clearance following oral dosing (CL/F)

Exploratory exposure-response analyses for efficacy and safety endpoints, including QTc, will be performed.

Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- EORTC QLQ-C30
- EuroQol's EQ-5D Questionnaire

Exploratory Outcome Measures

The exploratory biomarker analyses in tumor tissue may investigate potential intrinsic and acquired resistance mechanisms to MEK and BRAF inhibition. Pre-treatment tumor tissue (i.e., archived material or biopsies collected during screening, prior to initiation of study treatment) and tumor biopsies during treatment (Cycle 2 Day 15) and at the end of study treatment (at the time of PD) will be required.

In order to investigate if chromosomal and molecular genetic aberrations are linked to therapeutic outcome and development of severe adverse events in patients treated with vemurafenib and cobimetinib, DNA may be isolated from a single whole blood collected at baseline as well as tumor tissues.

Additional efficacy exploratory analyses will include PFS rates and OS rates at fixed timepoints (e.g., 3, 6, 9, 12 months, etc.).

Investigational Medicinal Products

Test Product

Double-blind study drug will be administered in 28-day cycles.

Cobimetinib or placebo should be taken once daily at approximately the same time each day with the morning vemurafenib dose, and no later than 4 hours after the scheduled time.

Cobimetinib or placebo can be taken with or without a meal. Cobimetinib or placebo tablets should never be chewed, cut, or crushed.

At least 7 days off cobimetinib is required prior to starting a new treatment cycle.

Vemurafenib will be taken orally, at a starting dose of 960 mg (4 tablets) BID. The first dose of vemurafenib should be taken in the morning, and the second dose should be taken in the evening, at least 8 hours after the first dose (the ideal interval between doses is 12 hours).

Vemurafenib can be taken with or without a meal, and should be taken with a glass of water. The vemurafenib tablets should never be chewed, cut, or crushed.

Statistical Methods

Primary Analysis

The primary analysis will be a comparison of PFS between the 2 treatment arms using a stratified log-rank test at an overall 0.05 significance level (2-sided).

The statistical hypothesis of this study is as follows:

H_0: $PFS_{(Arm\ A)} = PFS_{(Arm\ B)}$

H_1: $PFS_{(Arm\ A)} \neq PFS_{(Arm\ B)}$

where $PFS_{(Arm\ A)}$ represents the survival function of PFS in the vemurafenib + placebo arm and $PFS_{(Arm\ B)}$ represents the survival function of PFS in the vemurafenib + cobimetinib arm.

PFS as assessed by Investigator will be the primary endpoint evaluated. PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment using RECIST v1.1. Data from patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data from patients with no post-baseline tumor assessment will be censored at the randomization date.
The hazard ratio for PFS will be estimated using a stratified Cox model. Two-sided 95% CIs for the hazard ratio will be provided. The stratified analyses will incorporate 2 stratification factors: geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c). Results from an unstratified log-rank test and the unstratified hazard ratio will also be presented. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and the Kaplan-Meier curves will be provided.

Determination of Sample Size

Progression-free survival:

The type 1 error (α) for the analysis of the primary endpoint of PFS is 0.05 (2-sided).

Approximately 500 patients will be randomized to treatment. The final analysis of the primary endpoint of PFS will take place when approximately 206 PFS events have occurred. Statistical considerations are based on the following assumptions:

- Stratified log-rank test at 0.05 significance level (2-sided)
- 6 months median PFS for the vemurafenib + placebo arm
- 11 months median PFS for the vemurafenib + cobimetinib arm
- Accrual ramp-up time of 9 months to reach 65 patients per month thereafter for a total enrollment period of approximate 14 months
- 5% dropout rate
- No interim analysis of PFS

A total of 206 PFS events provides > 95% power to detect an improvement in median PFS from 6 months in the vemurafenib + placebo arm to 11 months in the vemurafenib + cobimetinib arm (corresponding to a hazard ratio of 0.55, and the minimal detectable difference is 0.76).

Overall survival:

The type 1 error (α) for the analysis of the secondary endpoint of OS is 0.05 (2-sided).

The final analysis of OS will be performed after the occurrence of approximately 250 deaths. A total of 250 deaths provides approximately 80% power to detect an improvement in median OS from 15 months in the vemurafenib + placebo arm to 21.4 months in the vemurafenib + cobimetinib arm (corresponding to a hazard ratio for death of 0.70) at an overall 2-sided 0.05 significance level.

Interim Analyses

Interim efficacy analysis of primary endpoint:

No interim analyses of the primary endpoint (PFS) will be performed.

Analysis of overall survival:

The OS analyses plan for this study protocol (v5) and the statistical analysis plan (SAP) have been revised. The study will incorporate 2 OS analyses (1 interim and 1 final analysis). The first OS interim analysis was performed at the time of the primary PFS analysis (16 months after the first patient was randomized). The originally planned final analysis for OS at 385 events is anticipated to occur in the second quarter of 2017. The rapid development of other potentially effective therapies for patients with metastatic melanoma provides more treatment options for patients following disease progression, which may potentially confound the OS benefit of vemurafenib + cobimetinib in future OS analyses. Therefore, in order to minimize this potential impact while maintaining a statistically robust evaluation of the OS benefit associated with the combination, the protocol-defined OS analyses have been revised.

The revised plan for OS analyses is to perform the final OS analysis at approximately 250 deaths without further interim analyses. The type 1 error rate would be strictly controlled at the 0.05 level by the continued use of the Lan-DeMets implementation of the O'Brien-Fleming use function as pre-specified in the original protocol and SAP.

The final OS analysis will be performed after the occurrence of approximately 250 deaths (projected to occur at approximately 31 months after the first patient was randomized). The Lan-DeMets implementation of the O'Brien and Fleming use function will be used to control the overall type I error for the OS comparison at a 2-sided, 0.05 significance level.

GLOSSARY OF ABBREVIATIONS

14/14	14 days on/14 days off
21/7	21 days on/7 days off
28/0	28 days on/0 days off
AJCC	American Joint Committee on Cancer
AKI	acute kidney injury
ALP	alkaline phosphatase
AUC	area under the plasma concentration–time curve
AUC_{0-8h}	area under the plasma concentration–time curve from time 0 to 8 hours
AUC_{0-12h}	area under the plasma concentration–time curve from time 0 to 12 hours
AUC_{0-24h}	area under the plasma concentration–time curve from time 0 to 24 hours
BCC	basal cell carcinoma
BID	twice daily
BORR	best overall response rate
BRAFi	BRAF inhibitor
CL/F	apparent clearance following oral dosing
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRO	contract research organization
CSCR	central serous chorioretinopathy
CT	computed tomography
cuSCC	cutaneous squamous cell carcinoma
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response

DRESS	drug reaction with eosinophilia and systemic symptoms
DSMB	Data Safety Monitoring Board
DTIC	dacarbazine
EC	Ethics Committee
ECHO	echocardiograph
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EF	ejection fraction
EORTC	European Organization for Research of Cancer
EQ-5D	EuroQol 5 dimension self-reported questionnaire
ERK	extracellular signal-regulated kinase
FDA	U.S. Food and Drug Administration
FDG-PET	fluorodeoxyglucose–positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FNA	fine needle aspiration
FSH	follicle stimulating hormone
GI	gastrointestinal
GGT	γ glutamyltransferase
HEENT	head, eyes, ears, nose, throat
hERG	human ether-à-go-go
HPV	human papillomavirus
HR	heart rate
HRQL	Health-related quality of life
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IV	intravenous
IxRS	interactive response system

KA	keratoacanthoma
LFT	liver function test
LVEF	left ventricular ejection fraction
MAD	maximal administered dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Affairs
MEK	mitogen-activated protein kinase
MEKi	MEK inhibitor
MBP	microprecipitated bulk powder
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NRAS	neuroblastoma RAS viral oncogene homolog
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
Pap	Papanicolaou
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PO	by mouth
pop PK	population pharmacokinetics
PPI	proton-pump inhibitor
PR	partial response
QD	once daily
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's method
QTcF	QT interval corrected using Fridericia's method
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors

RVO	retinal vein occlusion
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SD	stable disease
$t_{1/2}$	terminal half-life
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
USPI	United States Package Insert

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON MELANOMA

1.1.1 Melanoma

Approximately 160,000 new cases of melanoma are diagnosed globally each year (Ries et al. 2003). According to a World Health Organization report, about 48,000 melanoma-related deaths occur worldwide every year (Lucas 2006). 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 is 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 1 in 14 for men and 1 in 24 for women (SUNSMART 2007, Australian Department of Health and Ageing 2008). According to the National Cancer Institute (NCI), it is estimated that more than 76,000 new melanoma cases will be diagnosed and more than 9000 patients will die from the disease in the United States during 2012 (NCI 2012). Further, incidence rates for melanoma have increased sharply by approximately 6% per year in the United States since the 1970s. There are only a limited number of treatments available for metastatic melanoma.

1.1.2 Role of BRAF Kinase in Melanoma

Recent advances in the understanding of the biology of melanoma have resulted in identification of the role of BRAF kinase in melanoma. Mutated BRAF dimers constitutively activate the RAS-RAF pathway, leading to the generation of transcriptional signaling 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., superficial spreading and nodular melanomas) (Maldonado et al. 2003; Beeram et al. 2005; Curtin et al. 2005; Lang and Mackie 2005). 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 more than 90% of the V600 mutations are V600E (Sanger Institute 2012). 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 V600, result in constitutive activation of the BRAF kinase.

Most of the transforming activity of the $BRAF^{V600}$ is thought to result through the constitutive activation of the mitogen-activated protein kinase (MAPK) pathway (Gray-Schopfer et al. 2007). The therapeutic relevance of BRAF is supported by the demonstration that depletion of messenger RNA for oncogenic BRAF by small interfering

RNA leads to growth inhibition of melanoma cell lines in vitro (Hingorani et al. 2003; Sumimoto et al. 2004). This has led to the development of agents that can inhibit BRAF kinase and tests to identify mutations (Smalley et al. 2007; Ascierto et al. 2010; Flaherty et al. 2010). The cobas® 4800 BRAF V600 mutation test and Sanger Sequencing techniques have been used to identify $BRAF^{V600}$ mutation status in clinical trials.

1.2 BACKGROUND ON BRAF INHIBITOR, VEMURAFENIB

Vemurafenib (RO5185426 or PLX4032) is a low-molecular-weight, orally available inhibitor of the V600-mutant BRAF kinase. 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, Brazil, Mexico, the European Union, Switzerland, Canada, Australia, New Zealand, and Israel.

1.2.1 Clinical Pharmacokinetics of Vemurafenib

Based on dose-limiting toxicities (DLTs) reported at the 1120mg twice daily (BID) dose level, the 960 mg BID dose was considered the maximum tolerated dose (MTD) for vemurafenib. This dose was selected for use in all subsequent clinical trials, including the Phase II (NP22657) and Phase III (NO25026) studies in patients with unresectable Stage IIIc or metastatic melanoma.

Population pharmacokinetic (PK) analysis used pooled data from 458 patients to estimate the median of the steady-state maximum concentration (C_{max}), minimum concentration (C_{min}), and area under the plasma concentration – time curve (AUC) from 0 to 12 hours ($AUC_{0\text{-}12\ h}$). The C_{max}, C_{min}, and $AUC_{0\text{-}12\ h}$ were estimated to be 62 μg/mL, 59 μg/mL, and 734 μg/mL • h, respectively. The pharmacokinetics of vemurafenib are dose proportional between 240 mg BID and 960 mg BID. Population PK analysis also confirmed that the pharmacokinetics of vemurafenib are linear.

Vemurafenib is absorbed with a median time to maximum plasma concentration (t_{max}) of approximately 4 hours. Vemurafenib exhibits marked accumulation after repeat dosing at 960 mg BID with high interpatient variability. The median accumulation ratio estimate for a BID regimen of vemurafenib is 7.36. In the Phase II study, mean vemurafenib plasma concentrations at 4 hours after dose increased from 3.6 μg/mL on Day 1 to 49.0 μg/mL on Day 15 (range: 5.4–118 μg/mL).

At steady state, the mean vemurafenib exposure in plasma is stable (concentrations before and 2–4 hours after the morning dose) as indicated by the mean ratio of 1.13. Similar marked, interpatient variability in plasma exposure was observed at steady state, independent of dose reduction.

Following oral dosing, the absorption rate constant for the population of metastatic melanoma patients is estimated to be 0.19 h^{-1} (with 101% between-patient variability).

The apparent volume of distribution for vemurafenib in metastatic melanoma patients based on population PK analysis is estimated to be 91 L (with 64.8% between-patient variability). Vemurafenib is highly bound to human plasma proteins in vitro (>99%). On average, 95% of the dose was recovered within 18 days, the majority (94%) in feces, with <1% recovered in urine. The parent compound was the predominant component (95%) in plasma.

Additional information can be obtained from the vemurafenib Investigator's Brochure (IB).

1.2.2 Efficacy of Vemurafenib in Patients with BRAFV600 Mutation-Positive Metastatic Melanoma

Phase I, PLX06-02 Study

Among 32 evaluable patients with relapsed/refractory metastatic melanoma who enrolled in the extension cohort of the Phase I, PLX06-02 study, the confirmed best overall response rate (BORR) following vemurafenib treatment was 56.3%: 3 patients (9.4%) achieved a complete response (CR), and 15 patients (46.9%) had a partial response (PR). Ten patients (31.3%) had stable disease (SD), and the remaining 4 patients had progressive disease (PD). The median duration of response (DOR) and progression-free survival (PFS) were 7.6 months and 7.8 months, respectively; the 1-year overall survival (OS) rate was 57% (Flaherty et al. 2010).

Phase II, NP22657 (BRIM 2)

Results of the Phase II, open-label, single-arm study (NP22657) of vemurafenib in 132 patients with progression of metastatic melanoma after first-line treatment showed a confirmed BORR of 53% on the basis of Independent Review Committee assessments. The median DOR and PFS were 6.7 months and 6.8 months, respectively (Sosman et al. 2012).

Phase III, NO25026 (BRIM 3)

Study NO25026 is a Phase III open-label, multicenter, randomized study of vemurafenib in previously untreated patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma. Patients were randomized to treatment with vemurafenib (960 mg BID) or dacarbazine (DTIC; 1000 mg/m^2 every 3 weeks).

A total of 675 patients were randomized to vemurafenib (n=337) or DTIC (n=338). Randomization was stratified according to disease stage, LDH, Eastern Cooperative Oncology Group (ECOG) Performance Status, and geographic region. Baseline characteristics were well balanced between treatment groups. Of patients randomized to vemurafenib, most were male (59%) and white (99%); median age was 56 years (28% were ≥65 years), all patients had ECOG Performance Status of 0 or 1, and the majority of patients had Stage M1c disease. The co-primary efficacy endpoints of the study were OS and PFS.

At the preplanned interim analysis for OS, the Data Safety Monitoring Board (DSMB) recommended a release of the study results because of the compelling efficacy findings. Statistically significant and clinically meaningful improvements were observed in the co-primary endpoints of OS ($p < 0.0001$) and PFS ($p < 0.0001$) (unstratified log-rank test).

The most recent statistical analyses used a clinical cutoff of 1 February 2012 (Chapman et al. 2011). After a median of 12.5 months of follow-up in the vemurafenib arm, the Kaplan-Meier estimate of median survival for patients randomized to vemurafenib was 13.6 months (95% confidence interval [CI]: 12.0–15.2 months). For patients randomized to DTIC, after a median of 8.4 months of follow-up, the Kaplan-Meier estimate of median survival was 9.7 months (95% CI: 7.9–12.8 months). The hazard ratio for death was 0.70 (95% CI: 0.57–0.87) in favor of vemurafenib. Treatment with vemurafenib resulted in clinically meaningful and statistically significant improvements in PFS compared with DTIC treatment (hazard ratio 0.38 [95% CI: 0.32–0.46, $p < 0.001$]). There was a statistically significant improvement in BORR (confirmed) with vemurafenib (57.0%) compared with DTIC (8.6%), as assessed by the investigator.

1.2.3 Safety of Vemurafenib

Vemurafenib clinical safety information 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; micro-precipitated bulk powder (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: 31 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 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 Dose-Limiting Toxicities of Vemurafenib

The Phase I study PLX06-02 demonstrated that vemurafenib has generally been well tolerated in patients in the dose-escalation and melanoma-extension cohorts 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 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.

1.2.3.2 Clinical Safety in Phase II Study NP22657 (BRIM-2)

Study NP22657 (BRIM-2), was 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. Treatment-related adverse events occurred in 130 (98%) patients. The majority of adverse events were mild or moderate in intensity. The most commonly reported adverse events (occurring 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%).

Seventy-three percent of patients in Study NP22657 (BRIM-2) had at least 1 Grade 3 or higher adverse event. Sixty-one percent of patients had at least 1 treatment-related Grade 3 or higher adverse event. The most commonly reported treatment-related Grade 3 or higher adverse events (incidence ≥5%) were: squamous cell carcinoma (SCC) of skin (23%), serum γ glutamyltransferase (GGT) increase (9%), basal cell carcinoma (BCC; 7%), rash (7%), maculo-papular rash (6%), and arthralgia (6%).

Study NP22657 (BRIM-2) incorporated a QT/QT interval corrected (QTc) analysis with triplicate digital 12-lead ECGs obtained at 10 study visits throughout the study (see Section 1.2.5.4).

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

Ninety-nine percent of patients in the vemurafenib group and 91% of patients in the DTIC group experienced at least 1 adverse event. The majority of adverse events were mild or moderate in intensity. The most commonly reported adverse events (occurring in ≥30% of patients) in the vemurafenib group were in the skin-related adverse events body system (vemurafenib 93% vs. DTIC 23%); the most common skin-related adverse events were alopecia, rash, and photosensitivity.

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

Grade ≥ 3 Adverse Events

Fifty-nine percent of patients in the vemurafenib arm and 33% of patients in the DTIC arm experienced at least 1 adverse event that was Grade 3 or higher in intensity. The percentage of vemurafenib-treated patients with cuSCC and keratoacanthoma (KA) were 16% and 9%, respectively, compared with < 1% and 0% for DTIC-treated patients (all cases of cuSCC and KA were considered to be treatment-related, Grade 3 in intensity, and serious). Other common Grade 3 or higher adverse events in the vemurafenib group included photosensitivity reaction (9%), rash (8%), maculo-papular rash (8%), and arthralgia (4%); the corresponding frequencies of these adverse events in the DTIC group were 0%, 0%, 0%, and < 1%.

1.2.4 Deaths and Serious Adverse Events among Patients Receiving Vemurafenib

Across all studies, the majority of reported deaths were attributed to PD. In the pivotal Phase III Study NO25026 (BRIM-3), 19% of patients in the vemurafenib group and 34% of patients in the DTIC group died.

Across the NO25026 (BRIM-3), NP22657 (BRIM-2), and NP25163 studies, the most commonly reported vemurafenib-related serious adverse event was cuSCC.
In Study NO25026 (BRIM-3), 42% of patients in the vemurafenib group and 18% of patients in the DTIC group experienced at least 1 serious adverse event. Thirty-one percent of patients in the vemurafenib group and 5% of patients in the DTIC group experienced at least 1 treatment-related serious adverse event. The most common treatment-related serious adverse events in the vemurafenib group were cuSCC (17%) and KA (9%). No other treatment-related serious adverse event occurred in > 1% of patients in either treatment group.

1.2.5 Adverse Events of Special Interest for Vemurafenib

1.2.5.1 Cutaneous Squamous Cell Carcinoma

In Studies NO25026, NP22657, and NP25163, 79 (23.5%), 34 (25.8%), and 10 (19.2%) patients treated with vemurafenib developed cuSCC/KA, respectively.

Suspicious lesions were surgically excised if possible and submitted to a central dermatopathology laboratory designated by the Sponsor for classification based on histologic characteristics (independent of the site's local pathologic diagnosis). As of 12 May 2011, a total of 268 biopsies from 76 patients from Studies NO25026, NP22657, and NP25163 had been reviewed by the central dermatopathology laboratory.

Approximately half of all lesions were diagnosed as "SCC"; the other half were diagnosed as "other." The majority of SCC lesions (132 of 138 lesions, 96%) were classified as KA type (well-differentiated neoplasms with very low potential for invasive or metastatic disease). Lesions diagnosed as "other" included verruca vulgaris, actinic

keratosis, early KA, wart, benign keratosis, scar, no neoplasm, BCC, no diagnosis, and seborrheic keratosis.

Although events of cuSCC are serious, cuSCC can be monitored and treated. The metastatic potential of cuSCC is $<5\%$ in 5 years, especially for the KA type (Alam and Ratner 2001). A careful follow-up or risk mitigation plan with regular dermatological examinations has been established to monitor and treat cuSCC in patients receiving vemurafenib and during follow-up (see Section 5.1.4.1).

1.2.5.2 Second Primary Melanomas

Eight skin lesions were reported as new primary melanomas in 7 patients in the Phase III, NO25026 study. These lesions were managed with excision and without sequelae, and patients continued vemurafenib treatment for their underlying metastatic melanoma without dose adjustment.

1.2.5.3 Other Neoplasms

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 tonsillar SCC after receiving vemurafenib for >200 days. The patient had a [redacted] pack-year history of [redacted] use. The patient's biopsy tested strongly positive for p16 by immunohistochemistry, but no evidence of a RAS mutation or epidermal growth factor receptor amplification or mutation was present.

A second case occurred in study NP25163 (a PK/pharmacodynamic study). This patient had an invasive SCC of the tongue. [redacted] was previously treated for metastatic melanoma with ipilimumab, therapeutic vaccine (type not specified), and high dose interleukin-2, before enrollment on study 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 papillomavirus (HPV) genome.

A careful follow-up or risk mitigation plan, including head and neck examinations, anal examinations, pelvic examinations, and chest computed tomography (CT) scans, has been established to monitor and treat SCC in patients who receive vemurafenib (see Section 5.1.4.1).

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.

Progression of Cancers Associated with RAS Mutations

Based on mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations.

One case of progression of NRAS-mutated chronic myelomonocytic leukemia (CMML) occurred in a male patient with metastatic melanoma who had been treated with vemurafenib for < 2 weeks (Callahan et al. 2012). After the first dose of vemurafenib, laboratory results showed a marked leukocytosis and monocytosis, and vemurafenib treatment was subsequently stopped. In subsequent cycles, there was a temporal relationship between vemurafenib treatment and increase in WBC and absolute monocyte counts through multiple cycles of dechallenge and rechallenge. In vitro studies demonstrated proliferation of the leukemic cell population upon stimulation with vemurafenib, an effect that was reversed upon addition of a MEKi. Further, the cells exhibited dose-dependent and reversible activation of ERK in the NRAS-mutated leukemic clone. A second case of progression of a pre-existing RAS-mutated malignancy (pancreatic adenocarcinoma with KRAS mutation) was reported with vemurafenib in 2014 (Grey et al. 2014). On the basis of its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. Vemurafenib should be used with caution in patients with a prior concurrent cancer associated with RAS mutation. Full details are provided in the current vemurafenib IB.

1.2.5.4 ECG Analysis

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 (960 mg BID) did not appear to have a clinically meaningful effect on heart rate (HR) 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 QTc prolongation values > 500 ms (Grade 3), while 49 (37.1%) and 6 (4.5%) patients exhibited QTc prolongation values > 450 ms and > 480 ms, respectively. No patients had treatment-emergent QT (uncorrected) values > 500 ms. Maximal treatment-emergent individual QTc prolongation changes from baseline of > 30 ms were observed in 58 (43.9%) patients, but only 1 (0.8%) patient exhibited a QTc prolongation change from baseline of > 60 ms. 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% CI 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 15.1 ms (upper boundary of the 2-sided 90% CI of 17.7 ms) was detected at a pre-dose timepoint. There were no cases of torsade des pointes in any vemurafenib-treated patient in metastatic melanoma studies.

For a detailed summary of QTc prolongation among patients who received vemurafenib, see the vemurafenib IB or the USPi.

1.2.5.5 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 (Aithal et al. 2011). 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 outcome of one case of severe liver injury was reported as completely resolved with vemurafenib discontinuation, while information on the outcome of the second case of severe liver injury is not available at this time. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to alkaline phosphatase (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.

1.2.6 Other Adverse Events of Clinical Significance

1.2.6.1 Severe Dermatologic Reactions

Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis in the pivotal clinical trial.

As of 31 March 2013, 12 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been observed with vemurafenib treatment, but no case was reported to result in death. The time to onset was 7 to 25 days. In the majority of patients (7), vemurafenib was discontinued. Some patients (5) were treated with systemic steroids with corresponding improvement or resolution of symptoms. In addition, 2 patients with Grade 3 rash, who were treated with vemurafenib after ipilimumab, had biopsies that showed pathology consistent with drug hypersensitivity reaction (Harding et al. 2012). Full details are available in the current vemurafenib IB.

1.2.6.2 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.

1.2.6.3 Panniculitis

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

1.2.6.4 Pancreatitis

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 re-challenge/de-challenge information. The clinical presentation, including mild to moderate severity, was consistent with the clinical picture of drug-induced pancreatitis (Lankisch and Gottesleben 1995).

1.2.6.5 Potentiation of Radiation Toxicity

Potentiation of radiation treatment toxicity is an adverse drug reaction for vemurafenib. As of the fourth quarter of 2014, an adverse 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 cases). 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 current vemurafenib IB.

1.2.6.6 Acute Kidney Injury

An adverse drug reaction of acute kidney injury (AKI), 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 cases were biopsy–proven interstitial nephritis, and approximately 3% of cases were acute tubular injury/necrosis. No fatal cases were related to AKI.

Renal function should be monitored in patients 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.

1.2.7 Safety of Vemurafenib in Combination with Ipilimumab

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) (Ribas et al. 2012). All liver laboratory abnormalities were asymptomatic and reversible with permanent discontinuation of the study drugs or, in some cases, administration of corticosteroids. On the basis of these data, concurrent administration of ipilimumab and

vemurafenib is not recommended outside of a clinical trial. Full details are available in the current vemurafenib IB.

1.3 BACKGROUND ON MEK INHIBITOR COBIMETINIB

1.3.1 Role of MEK in Melanoma

The best characterized substrate of BRAF is MEK. Phosphorylation of MEK by BRAF results in increased MEK catalytic activity. Cancer cells transformed by $BRAF^{V600}$ are exceptionally sensitive to MEK inhibition in vitro. Allosteric MEK inhibitors (MEKi) can result in G1 phase growth arrest in melanoma cells (Smalley et al. 2006; Solit et al. 2006; Haass et al. 2008). In vitro, MEKi reduce cell proliferation, soft agar colony formation, and matrigel invasion of $BRAF^{V600}$-mutant melanoma cells, and are also effective against $BRAF^{V600}$ melanoma xenografts, suggesting a potentially important role for MEKi in melanoma and other tumors harboring the $BRAF^{V600}$ mutation (Solit et al. 2006).

1.3.2 Cobimetinib / XL518 (MEK Inhibitor)

Cobimetinib (GDC-0973/RO5514041/XL518) is a potent and highly selective inhibitor of MEK1 and MEK2, central components of the RAS/RAF pathway.

1.3.3 Nonclinical Studies with Cobimetinib

Cobimetinib inhibits proliferation of a variety of human tumor cell lines by inhibiting MEK1 and MEK2. In addition, cobimetinib inhibits 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.

1.3.4 Phase I Clinical Study of Cobimetinib

Study MEK4592g is a multicenter, Phase I, non-randomized, open-label, dose-escalation study. The primary objectives of this study are to evaluate the safety, tolerability, and MTD of cobimetinib administered orally as repeated doses in patients with solid tumors.

As of the data cutoff date of 11 June 2013, 115 patients had been treated in Study MEK4592g.

In Stage I, 36 patients with advanced solid malignancies were enrolled in successive cohorts and received cobimetinib on a 21-day on, 7-day off (21/7) dosing schedule at the following dose levels: 0.05 mg/kg, 0.10 mg/kg, and 0.20 mg/kg in liquid dosage

formulation and 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg in capsule formulation (Cohorts 1 – 8, respectively). The maximal administered dose (MAD) during Stage I was 80 mg; the MTD is 60 mg when cobimetinib is administered on a 21/7 dosing schedule.

In Stage IA, 20 patients were treated with cobimetinib on a 14-day on, 14-day off (14/14) dosing schedule in successive cohorts at the following dose levels: 60 mg, 80 mg, 100 mg, and 125 mg in capsule formulation (Cohorts 1A–4A, respectively). The MAD of Stage IA was 125 mg, and the MTD is 100 mg when cobimetinib is administered on a 14/14 dosing schedule.

Stages II and IIA are expansion stages that further evaluate the safety, potential efficacy, and pharmacodynamic effects of cobimetinib at the MTDs determined in Stage I and Stage IA in patients with RAS– or RAF-mutant tumors.

In Stage II, 20 patients were enrolled and received 60 mg cobimetinib on a 21/7 dosing schedule. In Stage IIA, 21 patients were been enrolled and received 100 mg cobimetinib on a 14/14 dosing schedule.

In Stage III, 18 advanced solid tumor patients were enrolled and received 60 mg cobimetinib on a 21/7 dosing schedule in a drug-drug interaction study to evaluate the possible effect of cobimetinib on the pharmacokinetics of dextromethorphan and midazolam.

1.3.5 Clinical Pharmacokinetics of Cobimetinib

PK data are available from cancer patients treated with cobimetinib in the Phase I study (MEK4592g). The PK parameters were reasonably consistent between both dosing schedules (14/14 and 21/7) at a given dose.

Cobimetinib is rapidly absorbed, with t_{max} ranging from 1 hour to 6 hours across all doses. C_{max} and AUC were dose proportional in the range from 0.05 mg/kg to 80 mg. Exposures at the 125-mg dose on a 14/14 schedule increased slightly more than dose-proportionally compared with exposures at 100 mg.

On the basis of the mean terminal half-life ($t_{1/2}$) of approximately 48.8 hours, a 2-fold to 3-fold accumulation is expected with daily oral dosing, and steady-state exposures should be achieved in 8–10 days. Cobimetinib has minimal renal elimination and is mainly eliminated by metabolism in the liver. EXEL-0382, a putative metabolite of Cobimetinib, was found at very low levels in plasma and, therefore, not monitored.

Cobimetinib has also been administered to healthy subjects in the following clinical pharmacology studies:

- MEK4952g: Phase I absolute bioavailability study comparing oral and intravenous (IV) administration of cobimetinib (n = 13)

- MEK4953g: Phase I relative bioavailability and food-effect study of cobimetinib (n = 20)
- MEK4954g: Phase I study evaluating the effect of rabeprazole, a proton-pump inhibitor (PPI), on the relative bioavailability of cobimetinib (n = 20)

The results from these 3 completed clinical pharmacology studies in healthy volunteers indicate that the pharmacokinetics of cobimetinib do not appear to be altered by food or co-administration with PPIs and that the absolute bioavailability of cobimetinib was 45.9% (90% CI: 39.74%–53.06%).

For more information, please refer to the cobimetinib IB.

1.3.6 Safety in Phase I Clinical Study of Cobimetinib (MEK4592g)

1.3.6.1 Dose-Limiting Toxicities

As of 8 October 2012, 4 DLTs had been 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, 2 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.

1.3.7 Adverse Events in Phase I Clinical Study of Cobimetinib (MEK4592g)

1.3.7.1 Adverse Events Related to Cobimetinib

In Study MEK4592g, as of 29 May 2012, 48 of 56 patients (85.7%) in the 21/7 dosing group experienced an adverse event that was reported as related to cobimetinib (Table 1). The most frequent adverse events attributed by the investigator to cobimetinib were diarrhea (48.2%); rash, including dermatitis acneiform and rash erythematous (51.8%); edema, including periorbital, peripheral, facial, and generalized edema 34.0%); and fatigue (30.4%).

Table 1 All Adverse Event Related to Cobimetinib Occurring in ≥10% of Patients in Study MEK4592g—21/7 Dosing Regimen Safety Evaluable (Clinical Cutoff 29 May 2012)

MedDRA System Organ Class Preferred Term	0.05 mg/kg (n=4)	0.10 mg/kg (n=3)	0.20 mg/kg (n=3)	10 mg (n=3)	20 mg (n=3)	40 mg (n=6)	60 mg (n=27)	80 mg (n=7)	All Patients (n=56)
Any adverse events, n (%)	3 (75.0)	3 (100.0)	2 (66.7)	3 (100.0)	2 (66.7)	5 (83.3)	23 (85.2)	7 (100.0)	48 (85.7)
Gastrointestinal disorders	3 (75.0)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	2 (33.3)	18 (66.7)	6 (85.7)	34 (60.7)
Diarrhea	1 (25.0)	1 (33.3)	1 (33.3)	1 (33.3)	2 (66.7)	1 (16.7)	15 (55.6)	5 (71.4)	27 (48.2)
Nausea	1 (25.0)	(0.0)	(0.0)	1 (33.3)	(0.0)	(0.0)	6 (22.2)	2 (28.6)	10 (17.9)
Stomatitis	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	1 (16.7)	3 (11.1)	2 (28.6)	6 (10.7)
Vomiting	(0.0)	(0.0)	(0.0)	(0.0)	1 (33.3)	1 (16.7)	3 (11.1)	(0.0)	5 (8.9)
General disorders and administration site conditions	2 (50.0)	3 (100.0)	(0.0)	1 (33.3)	(0.0)	1 (16.7)	15 (55.6)	4 (57.1)	26 (46.4)
Fatigue	2 (50.0)	2 (66.7)	(0.0)	1 (33.3)	(0.0)	(0.0)	9 (33.3)	3 (42.9)	17 (30.4)
Edema peripheral	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	1 (16.7)	7 (25.9)	3 (42.9)	11 (19.6)
Skin and subcutaneous tissue disorders	1 (25.0)	(0.0)	1 (33.3)	1 (33.3)	1 (33.3)	3 (50.0)	19 (70.4)	6 (85.7)	32 (57.1)
Rash	1 (25.0)	(0.0)	(0.0)	(0.0)	(0.0)	3 (50.0)	16 (59.3)	5 (71.4)	25 (44.6)
Dry skin	(0.0)	(0.0)	(0.0)	1 (33.3)	(0.0)	1 (16.7)	2 (7.4)	3 (42.9)	7 (12.5)

As of 29 May 2012, 39 of 41 patients (95.1%) in the 14/14 dosing group had experienced at least 1 adverse event that was reported as related to cobimetinib (Table 2). The most frequent adverse events attributed by the investigator to cobimetinib were diarrhea (78.0%); rash (63.4%, including dermatitis acneiform, rash generalized, and rash maculo-papular); fatigue (48.8%); vomiting (41.5%); edema, including peripheral, facial (swelling of face), and periorbital (34.1%); nausea (36.6%); eye disorders, including blurred vision, macular degeneration, subretinal fluid, and vitreous floaters (29.3%); and abdominal pain (26.8%).

Table 2 All Adverse Events Related to Cobimetinib Occurring in ≥10% of Patients in Study MEK4592g—14/14 Dosing Regimen Safety Evaluable (Clinical Cutoff 29 May 2012)

MedDRA System Organ Class Preferred Term	60 mg (n=3)	80 mg (n=3)	100 mg (n=29)	125 mg (n=6)	All Patients (n=41)
Any adverse events, n (%)	3 (100.0)	3 (100.0)	27 (93.1)	6 (100.0)	39 (95.1)
Eye disorders[a]	(0.0)	1 (33.3)	9 (31.0)	4 (66.7)	14 (34.1)
Visual impairment	(0.0)	(0.0)	3 (10.3)	2 (33.3)	5 (12.2)
Gastrointestinal disorders	2 (66.7)	2 (66.7)	26 (89.7)	6 (100.0)	36 (87.8)
Diarrhea	1 (33.3)	2 (66.7)	23 (79.3)	6 (100.0)	32 (78.0)
Vomiting	(0.0)	2 (66.7)	14 (48.3)	1 (16.7)	17 (41.5)
Nausea	(0.0)	2 (66.7)	12 (41.4)	1 (16.7)	15 (36.6)
Abdominal pain	(0.0)	(0.0)	9 (31.0)	1 (16.7)	10 (24.4)
Stomatitis	(0.0)	1 (33.3)	3 (10.3)	1 (16.7)	5 (12.2)
General disorders and administration site conditions	1 (33.3)	1 (33.3)	20 (69.0)	1 (16.7)	23 (56.1)
Fatigue	(0.0)	(0.0)	19 (65.5)	1 (16.7)	20 (48.8)
Edema peripheral	(0.0)	(0.0)	6 (20.7)	1 (16.7)	7 (17.1)
Edema	1 (33.3)	(0.0)	4 (13.8)	(0.0)	5 (12.2)
Metabolism and nutrition disorders	(0.0)	1 (33.3)	13 (44.8)	1 (16.7)	15 (36.6)
Decreased appetite	(0.0)	1 (33.3)	6 (20.7)	(0.0)	7 (17.1)
Skin and subcutaneous tissue disorders	3 (100.0)	2 (66.7)	19 (65.5)	3 (50.0)	27 (65.9)
Rash	2 (66.7)	2 (66.7)	15 (51.7)	2 (33.3)	21 (51.2)
Dermatitis acneiform	(0.0)	(0.0)	3 (10.3)	2 (33.3)	5 (12.2)

[a] Verbatim terms of serous macular detachment and serous retinal macular detachment were auto-encoded in error as the preferred term of macular detachment. All events reported as macular degeneration were neurosensory detachment, a reversible accumulation of fluid between the layers of the retina.

1.3.7.2 Grade ≥3 Adverse Events Related to Cobimetinib

For patients in the 21/7 dosing group, no Grade 3 or greater adverse events reported as treatment-related were reported at the following dose levels: 0.05 mg/kg, 0.10 mg/kg, 0.20 mg/kg, 10 mg, or 20 mg. Ten (17.9%) of 56 patients experienced a total of 14 Grade 3 or higher adverse events reported as treatment-related at dose levels ≥40 mg. At the 40-mg dose level, 1 patient had Grade 3 elevated ammonia levels and

Grade 4 hepatic encephalopathy. At the 60-mg dose level, 1 patient experienced Grade 3 atrial fibrillation and Grade 3 acneiform dermatitis; 3 patients experienced Grade 3 fatigue; 1 patient experienced Grade 3 nausea; and 1 patient experienced Grade 5 respiratory distress, for which other possible contributing etiological factors included the disease under study (metastatic melanoma). At the 80-mg dose level, 2 patients experienced Grade 3 diarrhea. One patient experienced Grade 4 leukopenia, Grade 3 dysphagia, Grade 3 syncope, and Grade 3 rash.

Among patients in the 14/14 dose group, 17 (41.5%) of 41 patients experienced Grade 3 or higher adverse events reported as treatment related. No treatment-related Grade 3 or higher adverse events were observed at the 60-mg dose level. At the 80-mg dose level, 1 patient experienced Grade 3 diarrhea. At the 100-mg dose level, 1 patient experienced Grade 3 lymphopenia; 1 patient experienced Grade 3 anemia; 1 patient experienced Grade 3 elevated AST, Grade 3 elevated CPK-MM, and Grade 3 hypertension; 1 patient experienced Grade 3 abdominal pain; 4 patients experienced Grade 3 diarrhea; 2 patients experienced Grade 3 fatigue; 1 patient experienced Grade 3 hypokalemia; and 3 patients experienced Grade 3 rash. At the 125-mg dose level, 1 patient experienced Grade 3 blurred vision associated with neurosensory detachment of the retina; 1 patient experienced Grade 3 rash; 1 patient experienced Grade 3 urticaria; and 1 patient experienced Grade 5 cardio-respiratory arrest.

1.3.7.3 Deaths and Serious Adverse Events of Cobimetinib

Deaths in Study MEK4592g

As of 8 October 2012, 97 patients were evaluable for safety. There were 26 deaths in Study MEK4592g, 14 of which occurred within 30 days of the last administration of study drug. Of the 14 deaths, all but 2 were reported as due to disease progression. One patient died from cardiopulmonary arrest secondary to disease progression, and the other died from worsening ovarian cancer. Refer to “Serious Adverse Events in Study MEK4592g” below for details on these 2 patients.

Please refer to the cobimetinib IB for further details on deaths reported on Study MEK4592g.

Serious Adverse Events in Study MEK4592g

As of 8 October 2012, 41 patients had experienced at least 1 serious adverse event in Study MEK4592g. Of those, 11 patients experienced at least 1 serious adverse event reported as related to cobimetinib.

Two Grade 5 adverse events were attributed to cobimetinib by the investigator. For one patient who experienced Grade 5 cardio-respiratory arrest (125 mg), the other suspected causes of the event included the disease under study (metastatic breast cancer) and other unspecified concurrent conditions. For the other patient who experienced Grade 5 fatal respiratory distress (60 mg), the other possible contributing etiological factor

included the disease under study (metastatic melanoma). Please refer to the cobimetinib IB for additional details on other serious adverse events.

1.3.7.4 Adverse Events of Special Interest for Cobimetinib

Ocular Toxicity in Study MEK4592g and Study MEK4752g

In Study MEK4592g, visual disturbances associated with reversible accumulation of fluid between the layers of the retina were reported as related to cobimetinib in 12 patients: 4 at 125 mg (14/14), 5 at 100 mg (14/14), and 3 at 60 mg (21/7). Of the 12 patients affected, 2 had subretinal fluid observed incidentally on an ophthalmologic examination without visual symptoms (1 patient each at 100 mg and 60 mg); 8 patients resumed cobimetinib at the same (2 at 60 mg and 3 at 100 mg) or a reduced dose (2 at 125 mg and 1 at 100 mg); and 1 had symptom recurrence after a dose reduction from 125 mg to 100 mg cobimetinib. One DLT of Grade 3 blurred vision was reported at 125 mg; all other visual disturbances (including blurred vision and seeing flashing lights) were Grade 1–2. All events resolved within 1 week of stopping cobimetinib. These visual disturbances associated with reversible accumulation of fluid between the layers of the retina occurred only with doses at or above the MTD.

In Study MEK4752g, 8 (7%) of 123 patients experienced Grade 1 eye disorders, including photophobia, blurred vision, and visual impairment attributed to cobimetinib and/or GDC-0941, which resolved without study drug interruption.

In Study NO25395, 1 patient, who had a history of uveitis, developed Grade 2 uveitis, which was effectively treated with steroid eye drops. The episode of uveitis occurred at Cycle 1 Day 22 coincident with development of a Grade 3 rash. Vemurafenib was interrupted for the Grade 3 rash, which improved by Cycle 1 Day 27 with systemic steroid therapy. Ophthalmologic examination at the time of the uveitis flare did not reveal any retinal abnormalities, such as neurosensory retinal detachment or retinal vein occlusion, and the patient continued on steroid eye drops as previously prescribed.

One patient developed Grade 2 iritis in [redacted] left eye during Cycle 9 of study treatment. Ophthalmologic examination did not identify central serous chorioretinopathy (CSCR) or retinal vein occlusion. Vemurafenib was temporarily interrupted without minimal improvement in [redacted] symptoms. Cessation of cobimetinib during the scheduled 14-days off did improve the patient's symptoms. The patient continued on the study combination and [redacted] symptoms were controlled with steroid eye drops.

One patient who experienced Grade 2 blurred vision started having visual symptoms at Cycle 1 Day 2. The patient noted '[redacted]," and the patient [redacted]. However, the patient was still able to drive to [redacted] clinic appointment on Cycle 1 Day 8. The patient was asked to stop cobimetinib, and an ophthalmology evaluation demonstrated serous retinopathy. No surgical intervention was required, and, at Cycle 1 Day 14, the patient noticed improvement in [redacted] vision and restarted vemurafenib (the cobimetinib schedule was on 14 days on / 14 days off).

In subsequent cycles, the patient continued on combination therapy at vemurafenib 960 mg BID and cobimetinib 40-mg once daily (QD) 14/14 without recurrence of serious retinopathy or visual symptoms.

CPK Elevation in Study MEK4592g and Study MEK4752

In Study MEK4592g, there is limited information as to the frequency of CPK elevation in patients receiving cobimetinib monotherapy, because CPK testing has not been a part of the routine safety laboratory assessments. One patient who received cobimetinib at 100 mg/day on a 14/14 schedule in Study MEK4592g had Grade 2–3 CK-MM elevations. The patient was asymptomatic and without clinical or laboratory evidence for myocardial injury or rhabdomyolysis.

In Study MEK4752, 22 (17.9%) of 123 patients have experienced CPK elevations attributed to study drugs by the investigator. Four (3.2%) of 123 patients experienced Grade 3 or higher CPK-MM elevations. In Cohort 5 (40 mg cobimetinib + 130 mg GDC-0941, 21/7) 1 patient had a DLT and serious adverse event of Grade 4 CPK elevation. In Cohort E (125 mg cobimetinib + 245 mg GDC-0941, intermittent MEK), 1 patient experienced a Grade 4 CPK-MM elevation on Cycle 1 Day 15, with Grade 1 CK-MB elevation. In Cohort C (125 mg cobimetinib + 130 mg GDC-0941, intermittent MEK), 1 patient experienced a Grade 3 CPK-MM elevation on Cycle 1 Day 18. In the pancreatic expansion cohort (125 mg cobimetinib + 180 mg GDC-0941, intermittent MEK) 1 patient experienced Grade 3 CPK elevation with elevated troponin in Cycle 1 Day 8; study drugs were discontinued. The CPK elevation resolved to Grade 2 within 2 days, and on Cycle 1 Day 9 an serious adverse event of Grade 4 anaphylaxis was treated with corticosteroids and resolved within 24 hours. The majority of CPK elevations reported were asymptomatic and resolved with or without study interruption. In Study NO25395, 14 (20%) patients have experience elevated CPK. All CPK elevations were asymptomatic and were not associated with cardiac injury or rhabdomyolysis, and no interventions were required to specifically address this laboratory abnormality.

1.3.8 Clinical Efficacy in Study MEK4592g

Preliminary analyses of efficacy (anti-tumor activity) of cobimetinib have been performed with data from ongoing Study MEK4592g. Although not a primary objective of the study, clinical efficacy was measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, which classifies a favorable tumor response as a CR, a PR, or SD.

As 29 May 2012, data from Study MEK4592g indicate that there was 1 unconfirmed complete response and 6 partial responses (5 confirmed and 1 unconfirmed). Of these 7 responders, 6 were patients with $BRAF^{V600E}$ mutation-positive melanoma and 1 was a patient with unknown mutation status. These responses were durable with a median time on cobimetinib study drug treatment of 280 days (range 42–721+ days) (Table 3).

In addition, there were 5 patients in Study MEK4592g with prolonged stable disease of ≥5 months in the following tumor types: carcinoid (47+months), non–small cell lung cancer (13 months), adenoid cystic carcinoma (7 months), esophageal cancer (6 months), and sarcoma (5 months).

Table 3 MEK4592g: Cobimetinib Single Agent Responses in Melanoma Patients Treated at Maximum-Tolerated Dose (Clinical Cutoff Date 29 May 2012)

Subject	Cancer Type/Genotype	Cobimetinib Dose	Schedule	Best RECIST Response	Days on Study (as of 29May2012)
[redacted]	$BRAF^{V600K}$ melanoma	100	14/14	SD	67[a]
	$BRAF^{V600E}$ melanoma	60	21/7	NA	31
	$BRAF^{V600K}$ melanoma	60	21/7	cPR	334
	RAS/BRAF wt melanoma	100	14/14	PD	48
	Melanoma	100	14/14	cPR	721
	$BRAF^{V600E}$ $PIK3CA^{E545K/D}$ melanoma	60	21/7	cPR	158
	$BRAF^{V600E}$ melanoma	60	21/7	cPR	280
	$BRAF^{V600E}$ melanoma	100	14/14	uPR	42[c]
	NRAS Q61L melanoma	100	14/14	NA	14[b]
	$BRAF^{V600E}$ melanoma	100	14/14	uCR	464+
	$BRAF^{V600E}$ melanoma	100	14/14	cPR	239
	Ocular melanoma	60	21/7	PD	14[b]

cPR=confirmed partial response; NA=not applicable; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; uPR=unconfirmed partial response.

[a] Discontinued due to serious adverse event.

[b] Discontinued due to clinical PD.

[c] Withdrew consent.

1.4 BACKGROUND ON COMBINED BRAF AND MEK INHIBITION

1.4.1 Rationale for Combined BRAF and MEK Inhibition

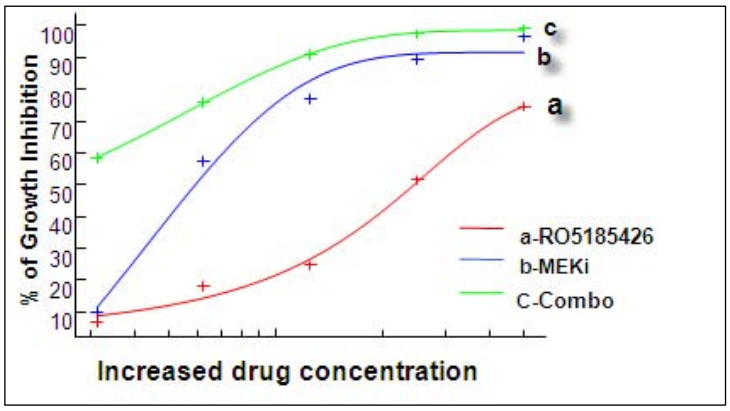
Despite vemurafenib having significant clinical activity in patients with advanced $BRAF^{V600}$ mutation-positive melanoma, the duration of disease control is brief at approximately 6 months. Several mechanisms of acquired resistance to vemurafenib therapy have been described. These result in reactivation of the RAS/RAF pathway (Johannessen et al. 2010; Nazarian et al. 2010; Villanueva et al. 2010; Poulikakos et al. 2011; Su et al. 2012; Wagle et al. 2011; Shi et al. 2012). The addition of a MEKi to vemurafenib abrogates vemurafenib resistance (Nazarian et al. 2010; Villanueva et al. 2010; Atefi et al. 2011; Poulikakos et al. 2011; Shi et al. 2012;

Su et al. 2012). These findings, together with preclinical evidence that combined inhibition of BRAF and MEK prevents the emergence of resistance (Paraiso et al. 2010), support the clinical evaluation of combination therapy strategies incorporating MEK inhibition with BRAF inhibitors (BRAFi) in order to combat emerging resistance.

1.4.2 Preclinical Data of Combined BRAF and MEK 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 MEKi), or to RO5068760. The combination of BRAF inhibition by vemurafenib and MEK inhibition by RO5068760 (see Figure 1) abrogated the constitutive up-regulation of ERK phosphorylation, inhibited cell cycle progression, and induced apoptosis in the resistant cells to a greater extent than either agent alone.

Figure 1 Combination of Vemurafenib with a MEK Inhibitor (RO5068760) Demonstrates a Synergistic Anti-Proliferation Effect in the Acquired-Resistance Melanoma Cell Model

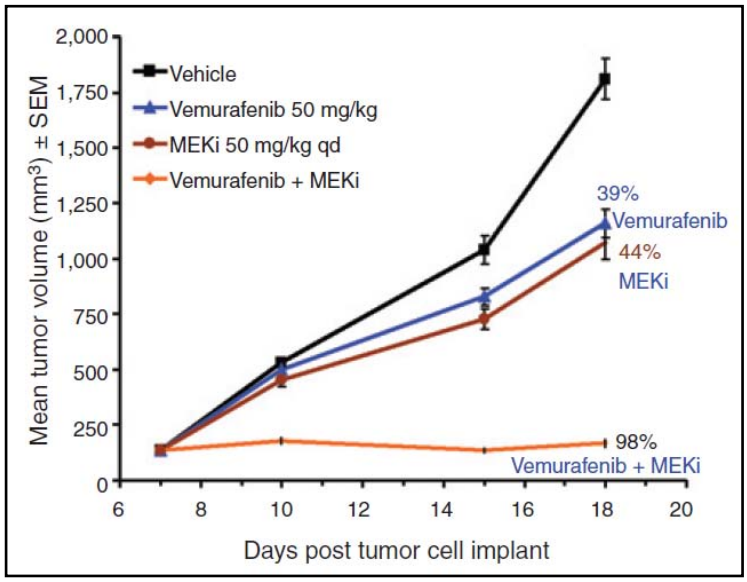


MEKi = MEK inhibitor; RO5185426 = vemurafenib.

An in vivo efficacy study in nude mice bearing $BRAF^{V600}$-positive A375 melanoma xenograft tumors with acquired resistance to vemurafenib demonstrated synergistic anti-tumor activity when vemurafenib was combined with the MEKi RO5068760 (see Figure 2) (Su et al. 2012). Similar results have also been seen in the same model with cobimetinib in combination with vemurafenib (see the cobimetinib IB).

These in vivo and in vitro studies suggest that combined RAF/MEK pharmacologic inhibition of the BRAF pathway is more effective than suppressing either alone. Combined inhibition may suppress the emergence of the pathway-specific resistance in tumors harboring the $BRAF^{V600}$ mutation. This supports the use of combined BRAF and MEK inhibition in previously untreated $BRAF^{V600}$ mutation-positive patients with locally advanced unresectable or metastatic melanoma.

Figure 2 In Vivo Combination of Vemurafenib and MEKi in the Vemurafenib-Resistant A375 Melanoma Xenograft Model Overcomes Acquired Resistance



MEKi = MEK inhibitor; SEM = standard error of the mean.

1.4.3 Study NO25395 – Phase Ib Cobimetinib in Combination with Vemurafenib

Study NO25395 (BRIM-7) is a Phase Ib study designed to assess the safety, tolerability, and pharmacokinetics of combined MEK inhibition with cobimetinib and BRAF inhibition with vemurafenib. This multicenter study has 2 stages: a dose-escalation stage and a cohort-expansion stage.

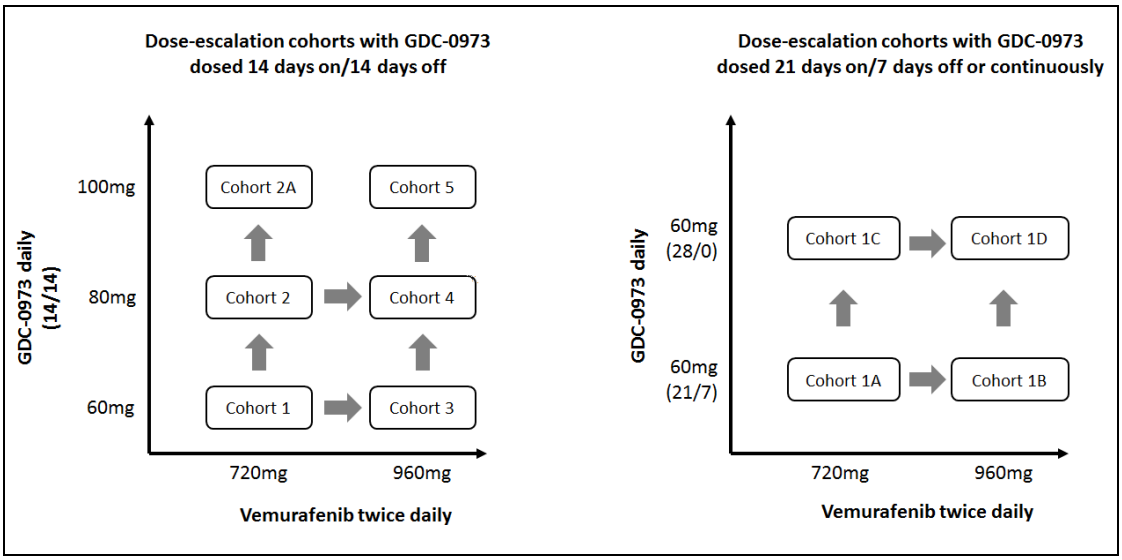
This study is being conducted in patients with $BRAF^{V600}$ mutation-positive, unresectable locally advanced or metastatic melanoma who are either vemurafenib naive or have progressed on vemurafenib treatment. Key inclusion criteria include the presence of the V600 mutation in melanoma tumor tissue using the cobas® 4800 BRAF V600 mutation test, measurable disease per RECIST v1.1, ECOG Performance Status of ≤ 1, and adequate hematologic and end organ function as assessed through key laboratory measures.

All patients in the dose-escalation stage receive twice daily vemurafenib in combination with cobimetinib administered daily according to one of the following 28-day schedules: 14 consecutive days of study drug followed by a 14-day drug holiday (14/14), 21 consecutive days of study drug followed by a 7-day drug holiday (21/7), or as a continuous daily dose (28/0). Each treatment cycle is 28 days.

There are 10 dose-escalation cohorts of 3–6 patients per cohort (see Figure 3). Patients in Cohort 1 received vemurafenib at a dose of 720 mg BID continually and cobimetinib

60 mg QD for 14 consecutive days of each 28-day cycle of combination dosing (14/14). Dose-escalation used the standard 3+3 design and proceeded in increments, taking into account the safety and tolerability of the combination.

Figure 3 Dose-Escalation Plan for the Combination of Vemurafenib and Cobimetinib Administered on a 14/14, 21/7, and 28/0 (Continual) Schedule in BRIM-7 (Study NO25395)



1.4.3.1 Safety in Study NO25395 (BRIM-7)

As of the clinical cutoff date of 6 July 2012, a total of 70 patients had received combination treatment with vemurafenib and cobimetinib (see Table 4).

Table 4 Cohort Summary of Patients Treated with Vemurafenib and Cobimetinib in Study NO25395 (Clinical Cutoff 6 July 2012)

Cohort	n
Cohort 1: vemurafenib 720 mg BID + cobimetinib 60 mg QD 14/14	5
Cohort 1A and Expansion Cohort 1A: vemurafenib 720 mg BID + cobimetinib 60 mg QD 21/7	28
Cohort 1B and Expansion Cohort 1B: vemurafenib 960 mg BID + cobimetinib 60 mg QD 21/7	19
Cohort 1C: vemurafenib 720 mg BID + cobimetinib 60 mg QD 28/0	3
Cohort 2: vemurafenib 720 mg BID + cobimetinib 80 mg QD 14/14	4
Cohort 2A: vemurafenib 720 mg BID + cobimetinib 100 mg QD 14/14	3
Cohort 3: vemurafenib 960 mg BID + cobimetinib 60 mg QD 14/14	3
Cohort 4: vemurafenib 960 mg BID + cobimetinib 80 mg QD 14/14	5

BID = twice daily; QD = once daily.

Dose-Limiting Toxicities

As of the clinical cutoff date of 6 July 2012, the following dose-levels have been deemed safe and tolerable:

- Vemurafenib 720 mg BID + cobimetinib 60 mg QD 14/14 (Cohort 1)
- Vemurafenib 720 mg BID + cobimetinib 80 mg QD 14/14 (Cohort 2)
- Vemurafenib 960 mg BID + cobimetinib 60 mg QD 14/14 (Cohort 3)
- Vemurafenib 720 mg BID + cobimetinib 60 mg QD 21/7 (Cohort 1A)
- Vemurafenib 960 mg BID + cobimetinib 60 mg QD 21/7 (Cohort 1B)
- Vemurafenib 720 mg BID + cobimetinib 60 mg QD 28/0 (Cohort 1C)

There has been only one DLT observed, as of the clinical cutoff date of 6 July 2012. The DLT was Grade 3 QTc prolongation and this occurred in 1 of the first 3 patients in Cohort 1B (vemurafenib 960 mg BID + cobimetinib 60 mg QD 21/7). The patient was a [redacted]-year-old [redacted] with a history of [redacted]. The patient had a QTc interval of 458 ms approximately 4 months prior to starting vemurafenib; [redacted] QT interval corrected using Bazett's method (QTcB) was 470 ms just prior to starting vemurafenib. After 2 months of vemurafenib monotherapy at 960 mg BID, the patient's QTcB interval was 503 ms; however, [redacted] remained on vemurafenib without dose modification. After approximately 4 months on vemurafenib monotherapy, [redacted] experienced disease progression and was enrolled in Study NO25395. [redacted] screening ECG (while still receiving vemurafenib 960 mg BID) showed a QTc interval of 449 ms (QTcB, 461 ms; QT interval corrected using Fridericia's method [QTcF], 450 ms). [redacted] triplicate QTc intervals obtained just prior to starting combination therapy with vemurafenib and cobimetinib were 444, 446, and 473 ms (QTcB, 485, 497, and 513 ms; QTcF, 453, 459, and 484 ms). At Cycle 1 Day 14, the patient's QTc interval reached a peak of 527 ms (QTcB, 533 ms; QTcF, 528 ms), corresponding with a Grade 3 abnormality. Vemurafenib was discontinued, and the patient remained on cobimetinib. The patient did not have any electrolyte abnormalities at the time of the Grade 3 QTc interval prolongation. The patient's subsequent QTc intervals while receiving cobimetinib monotherapy varied from 420 to 430 ms. The patient subsequently discontinued from the study after experiencing progressive disease on cobimetinib monotherapy.

As a result of the occurrence of one DLT among the first 3 patients at the vemurafenib 960 mg BID + cobimetinib 60 mg QD 21/7 dosing schedule, an additional 3 patients were enrolled in this cohort. No other patients treated at this dose level experienced a DLT. The dose-level was declared safe and tolerable with only 1 out of 6 patients having experienced a DLT. Additional accrual to this dose level in the expansion stage is ongoing.

Adverse Events in Study NO25395

As of the clinical cutoff date of 6 July 2012, out of the 70 patients treated with combination vemurafenib/cobimetinib, 68 patients (97.1%) had experienced at least 1 treatment-emergent adverse event. Mild to moderate adverse events (Grade 1 or 2) were observed in 41 patients (58.6%), and 26 patients (37.1%) experienced Grade 3 (severe) or Grade 4 (life-threatening) adverse events. There was one Grade 5 adverse event: a cerebrovascular accident.

The most common treatment-emergent adverse events observed in Study NO25395 are shown in Table 5.

Diarrhea (54.3%), non-acneiform rash (54.3%), fatigue (38.6%), nausea (35.7%), and photosensitivity (31.4%) were the most common adverse events observed. Most of these adverse events were mild or moderate in intensity.

There were 21 patients with Grade 3 adverse events. The most common Grade 3 adverse events were non–acneiform rash (5 patients [7.1%]), diarrhea (4 patients [7%]), and ALP elevation (3 patients [4. 3%]). There were 5 patients with Grade 4 adverse events (GGT elevation [2 patients–2.9%], tonsil SCC [1.4%], CPK elevation [1.4%], and GI hemorrhage [1.4%]).

Liver function test (LFT) elevations were observed in 18 (25.7%) patients. The most common abnormality noted was elevations in serum ALP. Most elevations in LFTs were Grade 1 or 2 in intensity.

Fourteen (20.0%) patients experienced CPK elevation: 1 patient with a Grade 4 event, 2 patients with Grade 3 events, and 9 patients with Grade 2 events. These events were all attributed to either cobimetinib or the combination of cobimetinib and vemurafenib. No reports of CPK elevation were associated with any symptoms or evidence of cardiac injury or rhabdomyolysis. No interventions were required to specifically address this laboratory abnormality; all CPK elevations resolved spontaneously while the patient continued treatment with cobimetinib or during the treatment holiday period.

The adverse event profile of vemurafenib in combination with cobimetinib observed in this current update (clinical cutoff date 6 July 2012) is consistent with that previously observed at the earlier clinical cutoffs.

Table 5 Treatment-Emergent Adverse Events of Any Grade Occurring among ≥10% of Patients in Study NO25395 (Clinical Cutoff 6 July 2012)

	Grade 1 or 2		Grade 3 or 4		Total	
	n	%	n	%	n	%
Non-acneiform rash[a]	33	47.1	5	7.1	38	54.3
Diarrhea	34	48.6	4	5.7	38	54. 3
Nausea	24	34.3	1	1.4	25	35.7
Sunburn / photosensitivity	22	31.4	0	0	22	31.4
Liver function test elevation[b]	14	20.0	4	5.7	18	25.7
Decreased appetite	15	21.4	0	0	15	21.4
Pyrexia	15	21.4	0	0	15	21.4
Creatine phosphokinase elevation	11	15.7	3	4.3	14	20.0
Vomiting	12	17.1	0	0	12	17.1
Arthralgia	10	14.3	1	1.4	11	15.7
Acneiform rash[c]	9	12.9	1	1.4	10	14.3
Constipation	10	14.3	0	0	10	14.3
Edema peripheral	10	14.3	0	0	10	14.3
Chills	9	12.9	0	0	9	12.9
Myalgia	9	12.9	0	0	9	12.9
Pruritis	8	11.4	0	0	8	11.4
Anemia	6	8.6	1	1.4	7	10.0
Hypertension	6	8.6	1	1.4	7	10.0
Alopecia	7	10.0	0	0	7	10.0

Table 5 Treatment-Emergent Adverse Events of Any Grade Occurring among ≥10% of Patients in Study NO25395 (Clinical Cutoff 6 July 2012) (cont.)

	Grade 1 or 2		Grade 3 or 4		Total	
	n	%	n	%	n	%
Creatinine elevation	7	10.0	0	0	7	10.0
Dyspnea	7	10.0	0	0	7	10.0

LFT = liver function test.

a Non-acneiform rash includes MedDRA terms rash, rash generalised, rash maculo-papular, rash macular, rash papular, rash erythematous, erythema, rash pruritic, skin exfoliation, lividity (livedoid-like rash)

b LFT elevation includes MedDRA terms liver function test abnormal, hepatic enzyme increased, ALP increased, bilirubin increased, hyperbilirubinaemia, AST and ALT increased, transaminases increased, and γ-glutamyltransferase increased

c Acneiform rash includes MedDRA terms dermatitis acneiform, acne, rash pustular

Adverse Events Related to Study Treatment in Study NO25395

The most common adverse events in Study NO25395 that were reported as related to vemurafenib and/or cobimetinib by the study investigator are described in Table 6. Treatment–emergent adverse events that were assessed as related to either study drug occurred in 67 patients (95.7%) out of 70 patients who were treated with the combination.

Non-acneiform rash, diarrhea, photosensitivity / sunburn, fatigue, and nausea were the most common adverse events reported as related to either vemurafenib, cobimetinib, or both study drugs, occurring in 52.9%, 51.4%, 31.4%, 30.0% and 28.6% of patients, respectively. Most of these adverse events were mild or moderate in severity (Grades 1 or 2).

the adverse events related to study treatment observed in this current update (clinical cutoff date 6 July 2012) were consistent with those previously observed in earlier clinical cutoffs.

Table 6 Treatment-Emergent Related Adverse Events of Any Grade Attributed to Vemurafenib and/or Cobimetinib in Study NO25395 (Clinical Cutoff 6 July 2012)

	Grade 1 or 2		Grade 3 or 4		Total	
	n	%	n	%	n	%
Non-acneiform rash[a]	32	47.1	5	7.1	37	52.9
Diarrhea	32	45.7	4	5.7	36	51.4
Photosensitivity / sunburn	22	31.4	0	0	22	31.4
Fatigue	20	28.6	1	1.4	21	30.0
Nausea	19	27.1	1	1.4	20	28.6
Liver function test elevation[b]	11	15.7	3	4.3	14	20.0
CPK elevation	11	15.7	3	4.3	14	20.0
Pyrexia	10	14.3	0	0	10	14.3
Acneiform rash[c]	8	11.4	1	1.4	9	12.9
Decreased appetite	9	12.9	0	0	9	12.9
Myalgia	9	12.9	0	0	9	12.9
Vomiting	9	12.9	0	0	9	12.9
Anemia	5	7.1	1	1.4	6	8.6
Headache	5	7.1	0	0	5	7.1
Edema peripheral	5	7.1	0	0	5	7.1
Chills	3	4.3	0	0	3	4.3
QT prolongation	2	2.9	1	1.4	3	4.3
Constipation	1	1.4	0	0	1	1.4

LFT = liver function test.

[a] Non-acneiform rash includes MedDRA terms rash, rash generalised, rash maculo-papular, rash macular, rash papular, rash erythematous, erythema, rash pruritic, skin exfoliation, lividity (livedoid-like rash)

[b] LFT elevation includes MedDRA terms liver function test abnormal, hepatic enzyme increased, ALP increased, bilirubin increased, hyperbilirubinaemia, AST and ALT increased, transaminases increased, and γ-glutamyltransferase increased

[c] Acneiform rash includes MedDRA terms dermatitis acneiform, acne, rash pustular

Grade ≥3 Adverse Events in Study NO25395

As of the clinical cutoff date of 6 July 2012, 27 patients (38.6%) had experienced Grade 3 or higher adverse events (see Table 7).

In this current update (clinical cutoff date of 6 July 2012), 1 Grade 5 adverse event was reported (cerebrovascular accident). Five patients had Grade 4 adverse events (GGT

elevation [2 patients], tonsil SCC, CPK elevation, GI hemorrhage) and 21 patients had Grade 3 adverse events. The cases of cerebrovascular accident, tonsil SCC, and GI hemorrhage are discussed in the following section on serious adverse event.

Grade 3 non-acneiform rash was observed in 5 patients (7.1%). Grade 3 or 4 CPK elevations were observed in 3 patients (4.3%); all CPK elevations were asymptomatic and were not associated with cardiac injury or rhabdomyolysis; no interventions were required to specifically address this laboratory abnormality.

Four patients (5.7%) experienced Grade 3 diarrhea. One patient in Cohort 2A (vemurafenib 720 mg BID and cobimetinib 100 mg QD on a 14/14 schedule) developed Grade 3 syncope, Grade 3 diarrhea, Grade 3 rash, and Grade 3 VIIth cranial nerve paralysis. This patient initially developed a Grade 3 rash on Cycle 1 Day 20. The rash resolved after vemurafenib treatment was interrupted for 1 week. On Cycle 2 Day 13, the patient developed Grade 3 diarrhea. The patient had a Grade 3 syncopal episode on Cycle 2 Day 14. ECG evaluation showed no ECG abnormalities, including no QT interval abnormalities. Vemurafenib was stopped (and cobimetinib was on treatment holiday) on Cycle 2 Day 14. Vemurafenib 720 mg BID was restarted on Cycle 2 Day 22. At Cycle 2 Day 27, this patient developed VIIth cranial nerve paralysis, which interfered with activities of daily living. Cranio-spinal imaging did not identify any pathology. Both vemurafenib and cobimetinib were permanently discontinued after the patient decided to withdraw from the study. After discontinuation of study drugs, there was gradual improvement of the VIIth cranial nerve paralysis with corticosteroid therapy over 6 weeks. The investigators reported the VIIth nerve paralysis as related to vemurafenib and/or cobimetinib treatment.

Grade 3 and higher LFT elevations occurred in 4 patients (5.7%). The Grade 3 and higher LFT abnormalities observed were:

- One patient – Grade 3 ALP elevation and Grade 3 transaminase elevation
- One patient – Grade 3 ALP elevation and Grade 4 GGT elevation
- One patient – Grade 4 GGT elevation
- One patient – Grade 3 ALP elevation

One patient developed Grade 3 hypotension and Grade 3 dehydration after being diagnosed with Grade 1 pneumonia.

One patient with extensive bone metastasis developed a Grade 3 subtrochanteric fracture on Cycle 1 Day 25 of study therapy. The patient subsequently underwent surgery for the femur fracture. Post-operatively, the patient's hemoglobin was 9.6 g/dL but approximately 4 weeks later, the patient's hemoglobin decreased to 7.4 g/dL corresponding to Grade 3 anemia. The investigator attributed the anemia to be related to combination therapy but recognized that other factors such as surgery and extensive bone metastases may have contributed to the anemia.

In addition, 1 patient developed Grade 3 pneumonia associated with Grade 3 mental status change and Grade 3 hypophosphatemia. Another patient developed Grade 3 malignant pleural effusion associated with Grade 3 hypoxia and Grade 3 lymphopenia.

Table 7 All Grade ≥3 Adverse Events in Study NO25395 (Clinical Cutoff 6 July 2012)

Adverse Events Grade ≥3, n=70	Grade 3		Grade 4		Grade 5		Total	
	n	%	n	%	n	%	n	%
Cerebrovascular accident [1]	0	0	0	0	1	1.4	1	1.4
GGT elevation [2, 3]	0	0	2	2.9	0	0	2	2.9
CPK elevation [4]	2	2.9	1	1.4	0	0	3	4.3
Gastrointestinal hemorrhage	0	0	1	1.4	0	0	1	1.4
Tonsil SCC	0	0	1	1.4	0	0	1	1.4
Non-acneiform rash* [1, 2, 5]	5	7.1	0	0	0	0	5	7.1
Diarrhea [5, 6, 7]	4	5.7	0	0	0	0	4	5.7
ALP elevation [2, 8, 9]	3	4.3	0	0	0	0	3	4.3
Hypophosphataemia [4]	2	2.9	0	0	0	0	2	2.9
Convulsion [3]	1	1.4	0	0	0	0	1	1.4
Cutaneous SCC [4]	1	1.4	0	0	0	0	1	1.4
VIIth nerve paralysis [5]	1	1.4	0	0	0	0	1	1.4
Syncope [5]	1	1.4	0	0	0	0	1	1.4
Nausea [6]	1	1.4	0	0	0	0	1	1.4
Acneiform rash [7]	1	1.4	0	0	0	0	1	1.4
Fatigue [7]	1	1.4	0	0	0	0	1	1.4
Presyncope [8]	1	1.4	0	0	0	0	1	1.4
Transaminases elevation [8]	1	1.4	0	0	0	0	1	1.4
QT prolongation [9]	1	1.4	0	0	0	0	1	1.4
Dehydration [10]	1	1.4	0	0	0	0	1	1.4
Hypotension [10]	1	1.4	0	0	0	0	1	1.4
Hypoxia [11]	1	1.4	0	0	0	0	1	1.4
Pleural effusion [11]	1	1.4	0	0	0	0	1	1.4
Lymphopenia [11]	1	1.4	0	0	0	0	1	1.4
Pneumonia [12]	1	1.4	0	0	0	0	1	1.4
Mental status change [12]	1	1.4	0	0	0	0	1	1.4
Anemia [13]	1	1.4	0	0	0	0	1	1.4
Femur fracture [13]	1	1.4	0	0	0	0	1	1.4
Hypertension	1	1.4	0	0	0	0	1	1.4
Abdominal distension	1	1.4	0	0	0	0	1	1.4

Table 7 All Grade ≥3 Adverse Events in Study NO25395 (Clinical Cutoff 6 July 2012) (cont.)

Adverse Events Grade ≥3, n=70	Grade 3		Grade 4		Grade 5		Total	
	n	%	n	%	n	%	n	%
Wound infection	1	1.4	0	0	0	0	1	1.4
Hyponatremia	1	1.4	0	0	0	0	1	1.4
Arthralgia	1	1.4	0	0	0	0	1	1.4
Back pain	1	1.4	0	0	0	0	1	1.4
Hyperkeratosis	1	1.4	0	0	0	0	1	1.4

CPK=creatine phosphokinase; GGT=γ glutamyltransferase; SCC=squamous cell carcinoma.

* Non-acneiform rash includes MedDRA terms rash maculo-papular and rash generalize

[1-13] Patients who experienced more than one Grade ≥3 adverse event are each indicated with a different superscript Arabic numeral after the name of each adverse event they experienced.

Serious Adverse Events in Study NO25395

As of the clinical cutoff date of 6 July 2012, 15 patients (21.4%) had experienced serious adverse events in Study NO25395. The serious adverse events are listed in Table 8.

One patient experienced a Grade 5 serious adverse event in Study NO25395, a [redacted]. This patient was a [redacted]-year-old [redacted] with metastatic melanoma with a known history of [redacted]. The patient started on Cycle 1 Day 1 of Study NO25395 on [redacted] with vemurafenib at 720 mg BID and cobimetinib at 60 mg on a 21/7 schedule. [redacted] attained partial response as [redacted] best overall tumor response. On [redacted], [redacted] developed [redacted] and was hospitalized. Brain magnetic resonance imaging (MRI) identified new brain metastasis, and [redacted]. On [redacted], while still recovering in hospital, [redacted] had an acute stroke and died on [redacted].

Non-cutaneous SCC (Grade 4 tonsillar SCC) was observed in 1 patient in Study NO25395. This patient is a [redacted]-year-old [redacted] diagnosed with metastatic melanoma in [redacted]. The patient received first-line treatment with vemurafenib 960 mg BID in Study NO25026 (BRIM-3) for approximately 13 months from [redacted]. At the time of disease progression, abnormal metabolic activity in the patient's left tonsil was noted on positron emission tomography (PET) scan. Otolaryngology evaluation at that time noted tonsillar enlargement, but no additional diagnostic or therapeutic intervention was undertaken at that time. The patient was subsequently enrolled in Study NO25395 (BRIM-7) and started combination therapy in Cohort 3 (vemurafenib 960 mg BID+cobimetinib 60 mg on a 14/14 schedule) in [redacted]. The patient developed melanoma disease progression after 4 cycles of treatment and discontinued the study in [redacted]. The patient's left tonsil was re-assessed in early [redacted]

and at that time was noted to be larger. Clinical staging around that time (including CT scan) showed left tonsillar mass and regional lymph node enlargement. A biopsy of the left tonsillar mass was performed shortly thereafter, which corroborated the diagnosis of SCC but, due to crush artifact, it was difficult to assign pathologic stage. The biopsy stained strongly for p16, which is suggestive of HPV-mediated oncogenesis. That patient had an additional risk factor for SCC of the head and neck, a [redacted] pack−year [redacted] history. The patient subsequently underwent [redacted] in [redacted], which identified muscle invasion (T4), then subsequently received radiotherapy. Biomarker assessments on the [redacted] tissue confirmed the presence of HPV genome (serotype 16) in tumor tissue. There was no evidence of epidermal growth factor receptor amplification of mutation and no evidence of NRAS mutation.

One patient was hospitalized on two separate occasions, for Grade 1 syncope and Grade 4 GI hemorrhage. The Grade 1 syncope occurred on Cycle 1 Day 19 while at church. There were no ECG abnormalities or cardiac enzyme elevation. Tilt-table testing was abnormal, suggesting a neurocardiogenic cause. The patient was subsequently discharged and continued on study therapy without any dose modifications. At Cycle 2 Day 22, the patient developed GI hemorrhage requiring hospitalization and blood transfusion. The bleeding source was found to be a pre-existing left mesenteric lesion. The patient subsequently underwent [redacted] and continued on study therapy.

One patient was hospitalized for Grade 3 convulsions in Cycle 3. This patient had a known history of [redacted] that was controlled on [redacted]. Brain MRI performed after the onset of [redacted] did not identify any brain metastasis. [redacted] was added to improve [redacted] control and the patient continued of study therapy attaining a partial response.

One patient developed well differentiated cuSCC, keratoacanthoma-type, while on study in Cohort 1B (vemurafenib 960 mg BID + cobimetinib 60 mg QD 21/7). The cuSCC was identified on the skin of the patient's left lower leg during Cycle 3 of study therapy. The patient underwent complete resection of the cuSCC and continued on study therapy.

One patient developed Grade 2 facial edema and Grade 2 maculo-papular rash at Cycle 1 Day 10. The patient required hospitalization to receive IV corticosteroid therapy for the facial edema, which resolved rapidly; the patient was able to restart study therapy 1 day later without dose modification. This patient subsequently was placed on a tapering course of oral corticosteroids without recurrent symptoms. This patient also developed Grade 3 LFT elevation at Cycle 2 Day 22 that was managed with interruption of vemurafenib.

One other patient was hospitalized for Grade 3 maculo-papular rash. This treatment-naïve patient was treated with vemurafenib 960 mg BID + cobimetinib 80 mg QD on a 14/14 schedule. The patient developed a Grade 3 generalized maculo-papular

rash with Grade 1 fever, chills, and CPK elevation, leading to interruption both study drugs on Cycle 1 Day 10. The patient was hospitalized. No infectious etiology was identified. The rash resolved at Cycle 1 Day 16 and the patient resumed vemurafenib at 720 mg BID (cobimetinib was not given because of 14 day off period).

One patient was hospitalized for Grade 3 nausea. This treatment-naïve patient had Grade 3 diarrhea at Cycle 1 Day 8, which was managed with supportive care and study drug interruption without dose reduction. At Cycle 2 Day 14 the patient was hospitalized for Grade 3 nausea. Brain MRI did not show evidence of brain metastasis. Esophagogastroduodenoscopy identified esophageal ulcers and gastric antrum erythema. Biopsy results showed acute and chronic esophagitis and ulceration. The patient was subsequently discharged on a PPI. The patient continued on study therapy and attained a partial response.

One patient with pre-existing bone metastasis developed a femur fracture on Cycle 1 Day 25. The patient underwent [redacted] and was off study therapy for 1 day.

One patient with known bone metastases was admitted to hospital for palliation of Grade 3 back pain from Cycle 1 Day 11 to Cycle 1 Day 15. Spinal cord compression was not identified during the evaluation. The patient's pain medication was optimized and the patient was subsequently discharged. The patient continued to receive study therapy during the hospitalization.

One patient was admitted for Grade 3 wound infection. This patient developed new brain metastasis and was taken off Study NO25395 as a result of disease progression. Eight days after stopping study therapy, [redacted]. The wound was sutured in the emergency room, but 6 days later the patient complained of discharge from [redacted] wound, which was diagnosed as a Grade 3 wound infection. The patient was admitted and administered IV antibiotics and discharged 2 days later on oral antibiotics.

One patient developed hyperthyroidism during Cycle 2 Day 8 of treatment with vemurafenib and cobimetinib. This patient had previously received ipilimumab approximately 7 months prior to starting in Study NO25395. During the visit on Cycle 2 Day 8 of study therapy, the patient developed Grade 1 fatigue, Grade 1 anorexia, and Grade 2 diarrhea. An endocrinologic evaluation showed that the patient had a thyroid-stimulating hormone level 0.011 mIU/L (institution's normal 0.4–4.0 mIU/L) and free thyroxine level over 6 ng/mL (institution's normal 0.89–1.76 ng/ml). The patient was started on proplythiouracil and continued on study therapy. However, the patient's fatigue and anorexia remained at Grade 1 and diarrhea resolved to Grade 1 with loperamide and diphenoxylate.

In addition, 1 patient was hospitalized for Grade 3 dehydration and hypotension, 1 patient was hospitalized for Grade 3 mental status change coincident with Grade 3 pneumonia, and 1 patient was hospitalized for a Grade 3 malignant pleural effusion.

The following serious adverse event occurred after the 6 July 2012 cutoff but is included due to the seriousness of the event:

On [redacted], (Cycle 6 Day 5), 1 patient was admitted to an outside hospital for dyspnea and diagnosed with systolic heart failure. Both study drugs were held. A transthoracic-echocardiogram ([redacted]) showed a mildly dilated left ventricle, normal left ventricle thickness, left ventricular ejection fraction (LVEF) approximately 25%, and moderate mitral regurgitation. A Regadenoson stress test ([redacted]) was negative for ischemia or infarction. The LVEF was estimated at 27%. The patient was managed for heart failure with metoprolol, lisinopril, furosemide, and spironolactone. Upon discharge, the patient was seen at the clinic on [redacted]. However, [redacted] QTc was elevated (457 ms [average]). The patient resumed vemurafenib, and cobimetinib was permanently discontinued.

Table 8 Serious Adverse Events in Study NO25395 (Clinical Cutoff 6 July 2012)

Patient ID Cohort and Study Drug Doses	Serious Adverse Events[a]
[redacted] Cohort–1A - V 720 mg BID + G 60 mg QD 21/7	Grade 5 cerebrovascular accident Grade 2 convulsions
[redacted] Cohort–3 - V 960 mg BID + G 60 mg QD 14/14	Grade 4 tonsil SCC
[redacted] Cohort–1C - V 720 mg BID + G 60 mg QD 28/0	Grade 1 syncope Grade 4 gastrointestinal hemorrhage
[redacted] Cohort–1 - V 720 mg BID + G 60 mg QD 14/14	Grade 3 dehydration Grade 3 hypotension
[redacted] Cohort–1A - V 720 mg BID + G 60 mg QD 21/7	Grade 3 pneumonia Grade 3 mental status change
[redacted] Cohort–2A - V 720 mg BID + G 100 mg QD 14/14	Grade 3 pleural effusion
[redacted] Cohort–1A - V 720 mg BID + G 60 mg QD 21/7	Grade 3 convulsions
[redacted] Cohort–1B - V 960 mg BID + G 60 mg QD 21/7	Grade 3 well differentiated cuSCC, keratoacanthoma type
[redacted] Cohort–1A - V 720 mg BID + G 60 mg QD 21/7	Grade 2 facial edema Grade 2 maculo-papular rash
[redacted] Cohort–4 - V 960 mg BID + G 80 mg QD 14/14	Grade 3 maculo-papular rash
[redacted] Cohort–1A - V 720 mg BID + G 60 mg QD 21/7	Grade 3 nausea
[redacted] Cohort–1C - V 720 mg BID + G 60 mg QD 28/0	Grade 3 femur fracture
[redacted] Cohort–1A - V 720 mg BID + G 60 mg QD 21/7	Grade 3 back pain

Table 8 Serious Adverse Events in Study NO25395 (Clinical Cutoff 6 July 2012) (cont.)

Patient ID Cohort and Study Drug Doses	Serious Adverse Events*
[redacted] Cohort–2 - V 720 mg BID + G 80 mg QD 14/14	Grade 3 wound infection
[redacted] Cohort–1C - V 720 mg BID + G 60 mg QD 28/0	Grade 2 hyperthyroidism

BID = twice daily; cuSCC = cutaneous squamous cell carcinoma; G = cobimetinib; QD = once daily; SCC = squamous cell carcinoma; V = vemurafenib.

[a] In addition, 1 patient (discussed above) experienced the serious adverse event of cardiac failure after the 6 July 2012 clinical cutoff date. This patient is not included in this table.

Deaths in Study NO25395

As of the clinical cutoff date of 6 July 2012, 15 patients (21.4%) who had received combination therapy in Study NO25395 had died; 10 patients died within 30 days of the last administration of study drug. All but one death was attributable to disease progression (previously discussed in the serious adverse events portion of Section 1.4.3.1).

1.4.4 Primary and Final Analysis of Study GO28141

Primary analysis of study GO28141 was conducted with a data cutoff of 9 May 2014 (Larkin et al. 2014). At the time, median PFS for the 247 patients enrolled in the vemurafenib + cobimetinib arm was 9.9 months versus 6.2 months for the 248 patients enrolled in the vemurafenib + placebo arm (hazard ratio: 0.51; 95% CI: 0.39, 0.68). Similarly objective response rate (ORR) was 68% versus 45% ($p < 0.0001$) for vemurafenib + cobimetinib versus vemurafenib + placebo. Final analysis of OS occurred with a data cutoff of 28 August 2015. At the time, median OS was 22.3 months for patients treated with vemurafenib + cobimetinib versus 17.4 months for patients treated with vemurafenib + placebo (hazard ratio: 0.70; 95% CI: 0.55, 0.90). Overall, safety was consistent with a positive benefit-risk profile for the combination.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The clinical activity of vemurafenib in $BRAF^{V600}$ mutation-positive advanced melanoma patients has been substantiated by the pivotal Phase III study of vemurafenib versus DTIC (NO25026 [BRIM-3]). Despite prolongation of PFS and OS, disease progression occurs after a median of approximately 6–7 months for vemurafenib-treated patients.

Several mechanisms of acquired resistance to vemurafenib therapy have been described that result in reactivation of the RAS/RAF pathway (Johannessen et al. 2010; Nazarian et al. 2010; Villanueva et al. 2010; Poulikakos et al. 2011; Wagle et al. 2011; Shi et al. 2012; Su et al. 2012). Addition of a MEKi to vemurafenib abrogates

vemurafenib resistance (Nazarian et al. 2010; Villanueva et al. 2010; Atefi et al. 2011; Poulikakos et al. 2011; Shi et al. 2012; Su et al. 2012). These findings, together with nonclinical evidence that combined inhibition of BRAF and MEK prevents the emergence of resistance (Paraiso et al. 2010), support the clinical evaluation of combination therapy strategies incorporating MEKi with BRAFi to combat emerging resistance.

Data from the ongoing Phase Ib Study NO25395 (BRIM-7) has identified the proposed investigational dose (vemurafenib 960 mg BID on Days 1–28 and cobimetinib 60 mg QD Days 1–21, in 28-day treatment cycles) as safe and well tolerated. Further characterization of the safety profile of the combination of vemurafenib and cobimetinib at their respective single-agent MTD is ongoing in the expansion stage of the Phase Ib study.

The risks associated with this combination therapy are further reduced through a safety plan that incorporates into the eligibility criteria to exclude patients at unacceptable risk, enhanced monitoring of all patients, specific risk mitigation plans, and dose modification guidelines. An independent DSMB reviewed unblinded safety data from the study every 3 months up to the final efficacy analysis. Following study unblinding and rigorous review of the safety data it was decided to discontinue quarterly DSMB review of unblinded safety data.

Taking into account the efficacy and safety data of single-agent vemurafenib and cobimetinib observed to date, and the favorable adverse effect profile of the combination observed in the Phase Ib study, the potential benefits of combination therapy and the extent of safety monitoring proposed, the potential benefit for patients with unresectable locally advanced or metastatic melanoma who participate in Study GO28141 outweigh the potential risks.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective of Study GO28141 is as follows:

- To evaluate the efficacy of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated $BRAF^{V600}$ mutation–positive patients with unresectable locally advanced or metastatic melanoma, as measured by prolongation of PFS, as assessed by the study site investigator

The secondary efficacy objective of Study GO28141 is as follows:

- To evaluate the efficacy of vemurafenib in combination with cobimetinib, compared with vemurafenib and placebo, in previously untreated $BRAF^{V600}$ mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by OS, ORR, DOR, and PFS as assessed by independent review

2.2 SAFETY OBJECTIVE

The safety objective of Study GO28141 is as follows:

- To characterize the toxicity profile in patients receiving vemurafenib and cobimetinib versus vemurafenib and placebo

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective of Study GO28141 is as follows:

- To characterize the pharmacokinetics of cobimetinib and vemurafenib and to compare the pharmacokinetics of vemurafenib when administered with cobimetinib to the pharmacokinetics of vemurafenib when administered with placebo
- To perform exploratory exposure-response analysis, including concentration-QTc analysis

2.4 PATIENT-REPORTED OUTCOME OBJECTIVE

The patient-reported outcome (PRO) objective of Study GO28141 is as follows:

- To evaluate health-related quality of life (HRQL) in patients receiving vemurafenib and cobimetinib versus vemurafenib and placebo as measured by the European Organization for Research and Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EuroQol 5 dimension (EQ-5D) questionnaire

2.5 EXPLORATORY OBJECTIVES

The Sponsor 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). Specimens may be used for any of the following:

- To explore the intrinsic and acquired mechanisms of resistance to MEK and BRAF inhibition in tumor samples obtained at baseline, during treatment, and at disease progression
- To study the association of biomarkers with efficacy and/or adverse events associated with medicinal products
- To increase knowledge and understanding of disease biology

3. GO28141 STUDY DESIGN

3.1 DESCRIPTION OF GO28141 STUDY DESIGN

GO28141 is a multicenter, randomized, double-blind, placebo-controlled Phase III clinical study to evaluate the safety and efficacy of vemurafenib in combination with cobimetinib with vemurafenib alone, in previously untreated $BRAF^{V600}$ mutation-positive patients with unresectable locally advanced or metastatic melanoma.

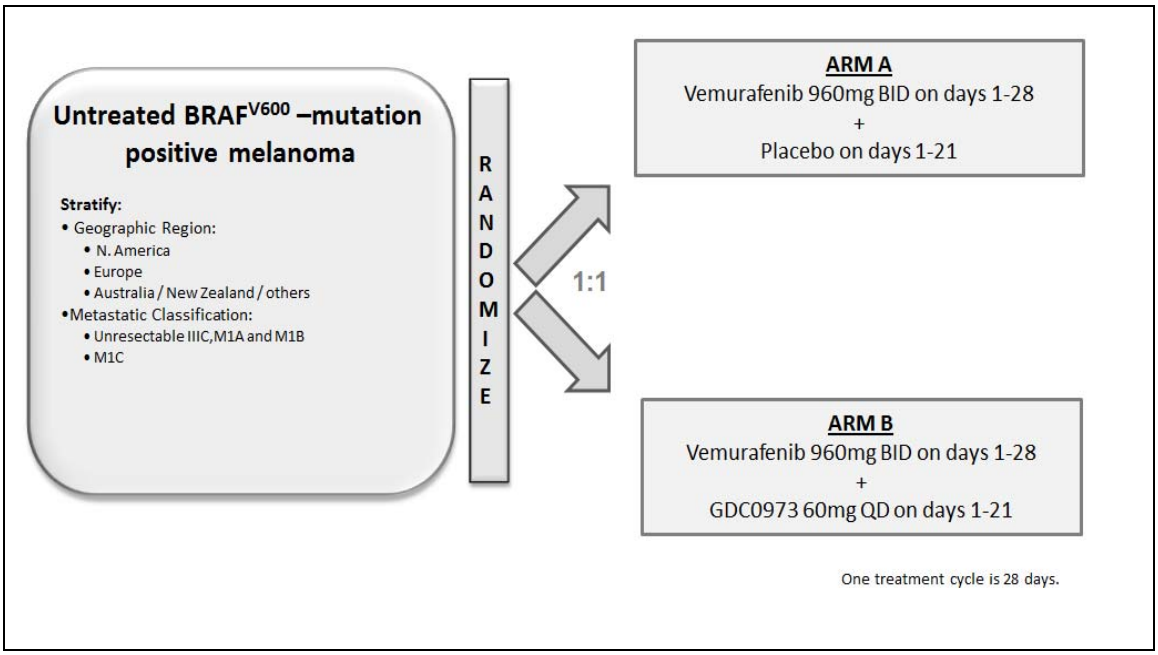
Approximately 500 previously untreated BRAF^{V600} mutation-positive patients with unresectable locally advanced or metastatic melanoma will be randomized in a 1:1 ratio to receive treatment with one of the following regimens:

- Arm A (control arm): vemurafenib 960 mg by mouth (PO) BID on Days 1–28 and placebo PO QD on Days 1–21 of each 28-day treatment cycle
- Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib 60 mg PO QD on Days 1–21 of each 28-day treatment cycle

The stratified, permuted-block randomization scheme will be used for treatment allocation based on the following stratification factors (Figure 4):

- Geographic region (North America, Europe, Australia/New Zealand/others)
- Metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c)

Figure 4 Study GO28141 Randomization Scheme



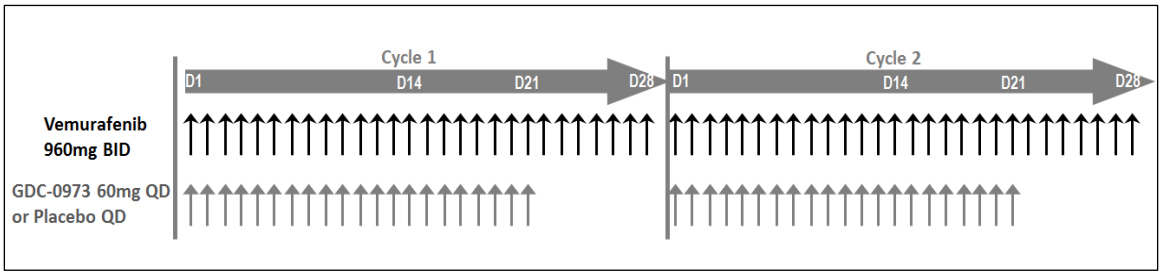
BID = twice daily; QD = once daily.

The schedule of study assessments and procedures are detailed in Appendix 1. After signing informed consent, patients will undergo screening procedures that include testing for the BRAF^{V600} mutation; laboratory tests (hematology, chemistries, LFTs); 12-lead ECG; left-ventricular function evaluation (echocardiogram or MUGA), contrast-enhanced brain CT or MRI; contrast-enhanced CT or MRI of the chest, abdomen, and pelvis; and ophthalmologic and dermatologic assessments. For a detailed list of screening assessments, please refer to Appendix 1.

All eligible patients will be randomized to treatment in either Arm A (vemurafenib and placebo) or Arm B (vemurafenib and cobimetinib). Vemurafenib will be taken starting on Day 1 to Day 28 of each 28-day treatment cycle. The first dose of vemurafenib should be taken in the morning, and the second dose should be taken in the evening. The cobimetinib or placebo tablet will be taken once daily starting on Day 1 to Day 21 of each 28-day treatment cycle. The cobimetinib or placebo tablet should be taken at approximately the same time each day, preferably in the morning with the vemurafenib dose. Vemurafenib and cobimetinib/placebo can be taken with or without a meal, and should be taken with a glass of water.

Figure 5 shows the dosing scheme for vemurafenib and cobimetinib/placebo in the proposed study.

Figure 5 Study GO28141 Dosing Scheme



BID = twice daily; D = day; QD = once daily.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the end-of-study treatment visit, and during the follow-up period. Patients will be assessed for adverse events every 2 weeks during the first 2 cycles, then prior to each subsequent cycle, and as necessary throughout the study.

Tumor response will be evaluated according to RECIST v1.1. Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator at 8-week intervals. At the investigator's discretion, CT/MRI scans may be repeated at any time if PD is suspected.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be used to characterize the toxicity profile of the study treatments on all patients. ECG monitoring for patients who receive vemurafenib will be conducted in accordance with the vemurafenib IB. Ongoing ECG monitoring is no longer required for patients who continue to receive only cobimetinib/placebo unless clinically indicated. Dermatologic assessment will be performed at the beginning of Cycle 2 (±1 week) and per local

standard of care thereafter. Ophthalmologic examinations and left ventricular function evaluation (echocardiogram or MUGA) are evaluated throughout the study.

Treatment will continue until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest. Patients on the vemurafenib and placebo treatment arm will be eligible to cross over to the vemurafenib and cobimetinib treatment arm prior to disease progression so long as the patient has not discontinued vemurafenib treatment should the investigator feel that the addition of cobimetinib may benefit the patient and the patient provides informed consent and continues to be followed for survival. Patients who have previously discontinued vemurafenib and who are receiving only placebo may not cross over and should discontinue all study treatment.

3.2 END OF STUDY

The study will end when all patients enrolled have been followed until death, withdrawal of consent, loss to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

Patients may continue on study treatment until the development of progressive disease, unacceptable toxicity, and/or consent withdrawal. Patients who discontinue study treatment for any reason will be followed for SCC according to the risk management plan (see Section 5.1.3), followed for disease progression and followed for survival until death, withdrawal of consent, or they are lost to follow-up. Patients who start subsequent anti-cancer treatment after study treatment discontinuation will still need to be followed for survival and SCC.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Test Product Dosage/Regimen

The vemurafenib dose selected was based on clinical efficacy and safety initially observed in Study PLX06-02 (Phase I) at the MTD of 960 mg BID. This was further characterized in Studies NP22657 (Phase II) and NO25026 (Phase III) of vemurafenib in locally advanced unresectable or metastatic melanoma. This dose is the recommended starting dose of vemurafenib.

Study MEK4592g (Phase I) identified the MTD of single-agent cobimetinib to be 60 mg QD on a 21-day on, 7-day off (21/7) schedule and at 100 mg QD on a 14-day on, 14-day off (14/14) schedule. The 21/7 dosing schedule for cobimetinib offers a longer duration of drug exposure and consequently, a more prolonged suppression of MEK compared to the 14/14 schedule. The lower dose of cobimetinib in the 21/7 schedule is also associated with a lower rate of adverse events (including Grade $\geq$3 adverse events).

In Study NO25395 (Phase Ib), the combination of vemurafenib and cobimetinib 21/7 was delivered at their respective single-agent MTDs. This dose has cleared the DLT criteria and shown to be tolerable.

Continuous dosing of cobimetinib was not explored in the monotherapy Phase I study (MEK4592g). In Study NO25395, two dose cohorts have been designated to explore continuous dosing cobimetinib with vemurafenib. This dose level may potentially result in poor tolerability at doses that exceed the single–agent MTD of cobimetinib, and result in significant dose reductions that may not adequately suppress the activity of MEK in the tumor cells.

3.3.2 Rationale for Patient Population

The proposed study will enroll treatment-naïve patients with unresectable locally advanced Stage IIIc or metastatic melanoma as defined by the American Joint Committee on Cancer (AJCC) classification v.7. This study will be conducted only in patients whose melanoma harbors the BRAF V600 mutation. This represents the population for which vemurafenib is indicated. The cobas® 4800 BRAF V600 mutation test is the approved companion diagnostic test for vemurafenib and will be used to determine the presence of the BRAF V600 mutation.

Several exclusion criteria were put in place to ensure patient safety going into the study. Patients who are pregnant are not allowed on the study as the effect of vemurafenib and cobimetinib on the developing fetus is not known. Similarly, patients and their partners are required to use of effective contraception.

Given that vemurafenib results in mild QTc prolongation, patients will be required to have a baseline screening ECG and those whose QTc interval is $>$450 ms or who have congenital long QT syndrome will be excluded.

To mitigate the risk of ophthalmologic adverse events associated with MEKi as a class effect, patients are required to undergo ophthalmologic examination to evaluate risk factor for or findings indicative of neurosensory retinal detachment, CSCR or retinal vein occlusion (RVO) prior to starting study treatment. Patients with such conditions will be excluded.

3.3.3 Rationale for Control Group

Patients on the control arm will receive vemurafenib and placebo. Vemurafenib is the current standard of care for patients with advanced $BRAF^{V600}$ mutation-positive melanoma, and therefore, would be the standard in which future therapies should be compared against in this patient population.

This will be a placebo-controlled, double-blind study. Use of a placebo control will help to minimize bias in reporting of key assessments of safety, efficacy, and quality of life. After key assessments of these parameters have been assessed, placebo plus vemurafenib patients will be allowed to cross over to active therapy (vemurafenib plus cobimetinib) so long as the patient has not discontinued vemurafenib and provided that the treating physician believes that there will be additional benefit given that the

combination has demonstrated a positive benefit-risk profile over single-agent vemurafenib.

3.3.4 Rationale for Pharmacokinetic Assessments

A sparse sampling strategy will be applied in this study. Samples for PK characterization of cobimetinib and vemurafenib will be collected as outlined in Appendix 2. Samples will be collected on Day 1 and Day 15 of Cycle 1 and Day 15 of Cycle 2. The sampling schedule is designed to enable characterization of vemurafenib and cobimetinib using population PK methodology (pop PK) for characterization following first dose (Day 1) and steady-state (Day 15). In addition, the vemurafenib PK data from Arm A and Arm B will allow evaluation of whether cobimetinib alters vemurafenib pharmacokinetics. The cobimetinib PK data from Arm B will allow comparison to single-agent cobimetinib data to evaluate whether exposures are altered when administered in combination with vemurafenib.

3.3.5 Rationale for Collection of DNA for Exploratory Analyses of Pharmacogenetic Polymorphisms

Genetic variants of drug-metabolizing enzymes and transporters can alter the pharmacokinetics of drugs, affecting their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at higher risk for adverse events associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Results from in vitro metabolism studies suggest that cobimetinib is metabolized by cytochrome P450 enzymes CYP3A. A blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics of vemurafenib and cobimetinib. The decision to analyze the samples will be based on a review of the PK data. For example, if a patient in a given cohort has substantially higher cobimetinib plasma levels than other patients in that cohort, he or she may carry a defective allele of a gene important in the metabolism or transport of cobimetinib. The genotyping efforts would be guided by results from in vitro metabolism studies and by results from ongoing clinical studies with cobimetinib and vemurafenib.

The pharmacogenetic analysis, if needed, will be performed on identifiable DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis may be restricted to the evaluation of genes that may be involved in the pharmacokinetics of cobimetinib and vemurafenib (e.g., drug metabolism, disposition, or elimination genes). Samples may be stored and analyzed up to 5 years after completion of the study, at which time all DNA samples collected for this analysis will be destroyed.

3.3.6 Rationale for Biomarker Assessments

The Sponsor 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. The rationale for the planned biomarker analyses is explained below. However, because the body of knowledge of potential new biomarkers is evolving, the definitive list of analyses may be modified on the basis of new information.

Investigation of Response and Resistance Biomarkers

This study may explore biomarkers associated with treatment response and resistance, including intrinsic and acquired resistance to BRAF/MEK inhibition in tumor tissues at baseline and at the time of disease progression.

Given the genetic heterogeneity of melanoma tumors, the magnitude of response to combined BRAF/MEK inhibition may be different in certain tumors. To identify mechanisms of resistance, molecular analyses may include assessment of genetic and activation status of the targeted MAPK pathway, potential escape mechanisms such as receptor tyrosine kinases and PI3K/PTEN pathways, and components of the tumor stroma (e.g., tumor infiltrating lymphocytes). These analyses may be conducted at the DNA, RNA, protein, and cell levels. In addition, expression of melanoma prognostic markers and alternative drug targets may be explored. These analyses are essential to identify patients who will benefit the most from the combination therapies and potential cause for resistance, which could help in considering future treatments.

Investigation of biomarkers in plasma samples

$BRAF^{V600}$ mutation may be evaluated both in tumor biopsies and in plasma collected during this study. It has been shown that tumor-specific mutations can be identified in plasma of patients. Analysis and correlation of BRAF mutations in plasma and biopsy will help to further evaluate the option of using plasma for the detection of tumor specific mutations.

3.3.7 Rationale for Health-related Quality of Life Assessment and Health Economic Assessment

The HRQL EORTC QLQ-C30 is included to characterize the impact of treatment on patients while receiving and following vemurafenib and cobimetinib exposure. These data should allow for quantification of the health economic impact of these treatments, given the externally validated data generated from the EQ-5D self-reported questionnaire. The collection of this type of data will provide greater insights for both the medical and patient communities to understand patient-reported value and quality of life when exposed to the combination of vemurafenib and cobimetinib treatments.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measure

The primary outcome measure for this study is as follows:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1 (Appendix 3), or death from any cause, whichever comes first.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary outcome measures are as follows:

- Overall survival, defined as the time from randomization to death from any cause
- Objective response rate for patients with measurable disease at baseline, defined as complete or partial response as assessed by investigator according to RECIST v1.1
- Duration of response for patients with measurable disease at baseline, defined as the time from first occurrence of a documented objective response until the time of disease progression, as determined by investigator review of tumor assessments using RECIST v1.1, or death from any cause during the study (i.e., within 30 days after the last dose of study treatment)
- PFS as assessed by independent review using RECIST v1.1

3.4.2 Safety Outcome Measures

Safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events and serious adverse events, graded according to NCI CTCAE v4.0
- Adverse events of special interest: any RVO; any retinal detachment or CSCR; Grade $\geq$3 photosensitivity; Grade $\geq$ 2 LVEF reduction; Grade $\geq$3 elevations of AST, ALT, serum bilirubin OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6; Grade $\geq$3 QT interval prolongation; and any cutaneous and non-cutaneous primary malignancy, including SCC, KA, BCC, and new primary melanoma.
- Changes in vital signs, ECGs, and clinical laboratory results during the course of study

3.4.3 Pharmacokinetic Outcome Measures

The following PK parameters will be analyzed using a pop PK approach and will be reported as applicable. Please see Section 6.6 for further details.

- Exposure following first dose and steady-state (AUC_{0-24})
- Minimum observed plasma concentration (C_{min}; trough concentration)
- Apparent clearance following oral dosing (CL/F)

Exploratory exposure-response analyses for efficacy and safety endpoints, including QTc, will be performed

3.4.4 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- EORTC QLQ-C30
- EuroQol's EQ-5D Questionnaire

The PRO questionnaires (EORTC QLQ-C30 and EQ-5D) were supplied in the local language(s) of each participating country.

3.4.5 Exploratory Outcome Measures

The exploratory biomarker analyses in tumor tissue may investigate potential intrinsic and acquired resistance mechanisms to MEK and BRAF inhibition. Pre-treatment tumor tissue (i.e., archived material or biopsies collected during screening, prior to initiation of study treatment) and tumor biopsies during treatment (Cycle 2 Day 15) and at the end of study treatment (at the time of PD) will be required.

In order to investigate if chromosomal and molecular genetic aberrations are linked to therapeutic outcome and development of severe adverse events in patients treated with vemurafenib and cobimetinib, DNA may be isolated from a single whole blood collected at baseline as well as tumor tissues.

Additional efficacy exploratory analyses will include PFS rates and OS rates at fixed timepoints (e.g., 3, 6, 9, 12 months, etc.).

3.5 MINIMIZATION OF BIAS

Patients will be randomly assigned to receive vemurafenib and placebo or vemurafenib and cobimetinib through use of an interactive response system (IxRS). Placebo tablets for cobimetinib and packaging configurations will have physical characteristics that will not permit their identification as distinct from those of cobimetinib.

Following the final efficacy analysis and extensive evaluation of safety data, quarterly DSMB review of unblinded safety data will no longer occur. Sponsor personnel will not have access to by-arm efficacy and safety summaries or listings prior to the formal reporting of the primary efficacy results.

Only when knowledge of the investigational product is essential for the safety of the patient, the investigator may unblind a patient's treatment assignment. In such cases, the IxRS system will be used to allow disclosure of an individual patient's treatment assignment to the treating investigator. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly (see Section 4.2).

4. METHODS AND MATERIALS

4.1 PATIENTS

To be eligible for Study GO28141, patients must be previously untreated with unresectable locally advanced or metastatic melanoma. Patients must have the $BRAF^{V600}$ mutation confirmed on their melanoma tumor tissue using the cobas® 4800 BRAF V600 mutation test (see Section 4.5.1.1 and Appendix 10). All patients must meet all of the inclusion and none of the exclusion criteria detailed in Sections 4.1.1 and 4.1.2, respectively.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria:

1. Patients with histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined by AJCC 7th edition (Appendix 8). Unresectability of Stage IIIc disease must have confirmation from a surgical oncologist.
2. Patients must be naïve to treatment for locally advanced unresectable or metastatic disease (i.e., NO prior systemic anti-cancer therapy for advanced disease; Stage IIIc and IV). Prior adjuvant therapy (including immunotherapy, e.g., ipilimumab) is allowed.
3. Documentation of $BRAF^{V600}$ mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor samples) using the cobas® 4800 BRAF V600 mutation test.
4. Measurable disease per RECIST v1.1 (Appendix 3).
5. ECOG Performance Status of 0 or 1 (Appendix 4).
6. Consent to provide archival tissue (either a paraffin-embedded tissue block or up to 20 unstained slides) for biomarker analyses.
7. Consent to undergo tumor biopsies of accessible lesions on Cycle 2 Day 15 and at progression for biomarker analyses to explore intrinsic and acquired resistance.

General Inclusion Criteria:

8. Male or female patient aged ≥ 18 years.
9. 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.
10. Life expectancy ≥ 12 weeks.
11. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:
    - ANC $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 100 \times 10^9$/L

- Hemoglobin ≥ 9 g/dL
- Albumin ≥ 2.5 g/dL
- Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN)
- AST, ALT, and ALP $\leq 3 \times$ ULN, with the following exceptions:
  - Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN
  - Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
- Serum creatinine $\leq 1.5 \times$ ULN or CrCl ≥ 40 mL/min on the basis of measured CrCl from a 24-hour urine collection or Cockroft-Gault glomerular filtration rate estimation:
  $\frac{(140\text{-age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$

12. Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use 2 effective forms 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 oophorectomy or hysterectomy who have had menses within the last 12 months.
    - Females are not considered to be of childbearing potential if amenorrheic for >12 months and follicle-stimulating hormone (FSH) level ≥ 40 IU/L.
    - For females who have been amenorrheic for ≥ 2 years, the requirement for FSH measurement at screening will be waived.
    - Effective forms of contraception includes surgical sterilization, a reliable barrier method with spermicide, birth control pills, or contraceptive hormone implants. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.
    - Male patients who are surgically sterilized are required to use barrier methods of contraception.
13. Negative serum pregnancy test within 14 days prior to commencement of dosing in women of childbearing potential.
14. Absence of any psychological, familial, sociological, or geographical condition that potentially hampers compliance with the study protocol and follow-up after treatment discontinuation schedule; those conditions should be discussed with the patient before trial entry.

4.1.2 Exclusion Criteria

Cancer-Related Exclusion Criteria:

1. History of prior RAF or MEK pathway inhibitor treatment.
2. Palliative radiotherapy within 14 days prior to the first dose of study treatment.

3. Major surgery or traumatic injury within 14 days prior to first dose of study treatment.
4. Patients with active malignancy (other than BRAF−mutated melanoma) or a previous malignancy within the past 3 years are excluded; except for patients with resected melanoma, resected BCC, resected cutaneous SCC, resected melanoma in-situ, resected carcinoma in-situ of the cervix, and resected carcinoma in-situ of the breast.
5. History of isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer is allowed.

Exclusion Criteria Based on Organ Function

Ocular:

6. History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment / CSCR, RVO, or neovascular macular degeneration.
7. The risk factors for RVO are listed below. Patients will be excluded if they currently have the following conditions:
    a) Uncontrolled glaucoma with intra-ocular pressures $>$21 mmHg
    b) Serum cholesterol $\geq$Grade 2
    c) Hypertriglyceridemia $\geq$Grade 2
    d) Hyperglycemia (fasting) $\geq$Grade 2

Cardiac:

8. Clinically significant cardiac dysfunction, including the following:
    a) Current unstable angina
    b) Current symptomatic congestive heart failure of New York Heart Association class 2 or higher (Appendix 7)
    c) History of congenital long QT syndrome or mean (average of triplicate measurements) QTcF $>$450 ms at baseline or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus). Please refer to Section 4.5.1.11.
    d) Current uncontrolled hypertension $\geq$Grade 2 (patients with a history hypertension controlled with anti-hypertensives to $\leq$Grade 1 are eligible).
    e) LVEF below institutional lower limit of normal or below 50%, whichever is lower

Central Nervous System:

9. Patients with active CNS lesions (including carcinomatous meningitis) are excluded. However, patients are eligible if:
    a) All known CNS lesions have been treated with stereotactic therapy or surgery, AND

b) There has been no evidence of clinical and radiographic disease progression in the CNS for ≥ 3 weeks after radiotherapy or surgery.

c) 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:

10. Current severe, uncontrolled systemic disease.
11. History of malabsorption or other condition that would interfere with absorption of study drugs.
12. Pregnant, lactating, or breast feeding.
13. Unwillingness or inability to comply with study and follow-up procedures
14. The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
    a) St. John's wort or hyperforin (potent cytochrome P450 CYP3A4 enzyme inducer)
    b) Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)

4.2 METHOD OF TREATMENT ASSIGNMENT, BLINDING, AND UNBLINDING

After written informed consent has been obtained and eligibility has been established, each patient will be assigned an identification number and be randomized to 1 of the 2 treatment arms through use of an IxRS.

Randomization will be stratified by metastatic stage (unresectable Stage IIIc, M1a, and M1b; M1c) and region (North America, Europe, Australia/New Zealand/others).
A stratified, permuted, block randomization scheme will be used to obtain approximately a 1:1 ratio between the 2 treatment groups. There is no pre-specified gender or ethnicity distribution in this study. It is expected that enrollment into this study will be representative of the gender and ethnicity distribution found in patients with unresectable or metastatic melanoma in the participating countries.

The investigator, patient, and Sponsor will be blinded to treatment assignment until completion of the final efficacy analysis of OS.

Prior to unblinding at the final overall survival efficacy analysis:

Treatment codes should not be broken except in emergency situations. In such cases, the IxRS system will be used to allow disclosure of an individual patient's treatment assignment to the treating investigator. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any

premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

Per health authority reporting requirements, the treatment code will be available through IxRS to the Roche Drug Safety Group for all unexpected serious adverse events that are considered by the Investigator to be related to study drug (see Section 5.7).

The investigator may request unblinding of a patient's treatment assignment only when knowledge of the investigational product is essential for the safety of the patient. In such cases, the IxRS system will be used to allow disclosure of an individual patient's treatment assignment to the treating investigator. Any site requests for unblinding, for any reason apart from emergency situations, require consultation with the Roche Medical Monitor.

Upon completion of the final overall survival efficacy analysis:

Upon completion of the final OS analysis and approval by the investigator's local IRB/EC, investigators will receive a list of active patients at their site with their treatment assignments. Unblinded patients in the placebo arm who remain on vemurafenib and who choose not to cross over will no longer receive placebo and will continue to receive vemurafenib only.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Vemurafenib, cobimetinib, and placebo 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.

Vemurafenib, cobimetinib, and placebo will be stored at the clinical site under the required storage conditions as indicated on the study drug labels. Patients will be asked to store study drugs at the required storage conditions noted on the label, out of the reach of children or other co-inhabitants.

4.3.1.1 Cobimetinib/Placebo

The 20 mg cobimetinib drug product is a film-coated, immediate release tablet. The white tablet is round with the engraving "ROCHE" on one side. Cobimetinib placebo tablets have been manufactured to match the size, shape, and color of the cobimetinib

active tablets and consist of the same inactive ingredients used in the corresponding active drug product. Cobimetinib and placebo will be packaged in blister packs.

The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol-part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc.

Cobimetinib and placebo should not be stored above 25°C (77°F).

If study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the monitor.

The Sponsor may switch to the commercial supply of cobimetinib in the future. At such time, the commercial drug product will be 20 mg, round, white, film-coated tablets with "COB" debossed on one side. Cobimetinib tablets will be packaged in blister packs for clinical use.

4.3.1.2 Vemurafenib

The 240 mg vemurafenib drug product is a tablet light pink in color, oval shaped, with the engraving "ROCHE." Vemurafenib will be packaged in bottles.

The inactive ingredients in vemurafenib tablets are as follows: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, hydroxypropyl cellulose (tablet core), polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red (tablet coating).

Vemurafenib will need to be stored at room temperature 20°C–25°C (68°F–77°F); excursions will be permitted between 15°C and 30°C (59°F and 86°F).

If study drug is stored outside of the permitted temperature ranges, quarantine the affected supply and contact the monitor.

4.3.2 Dosage, Administration, and Compliance

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

If a dose of study drug is missed (i.e., 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.

At least 7 days off cobimetinib is required prior to starting a new treatment cycle.

Each study cycle is defined by the 28-day dosing cycle of cobimetinib (21 days on, 7 days off). In the event that cobimetinib dosing is interrupted beyond the 28-day dosing cycle, the next cycle will start when cobimetinib dosing resumes. If cobimetinib is discontinued permanently, a cycle is then defined by a 28-day dosing cycle of vemurafenib.

Guidelines for interruption, dose modification, and permanent discontinuation of study drugs are provided in Section 5.1.

4.3.2.1 Cobimetinib/Placebo

Cobimetinib or placebo should be taken once daily at approximately the same time each day with the morning vemurafenib dose, and no later than 4 hours after the scheduled time.

Cobimetinib or placebo can be taken with or without a meal. Cobimetinib or placebo tablets should never be chewed, cut, or crushed.

Upon completion of the final OS analysis, patients in the placebo arm who are unblinded and choose not to cross over to cobimetinib will no longer need to receive placebo and will continue to receive vemurafenib only, unless they had previously discontinued vemurafenib, in which case they will discontinue all study treatment.

4.3.2.2 Vemurafenib

Vemurafenib will be taken orally, at a starting dose of 960 mg (4 tablets) BID. The first dose of vemurafenib should be taken in the morning, and the second dose should be taken in the evening, at least 8 hours after the first dose (the ideal interval between doses is 12 hours).

Vemurafenib can be taken with or without a meal, and should be taken with a glass of water. The vemurafenib tablets should never be chewed, cut, or crushed.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (vemurafenib, cobimetinib, and placebo) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Study Access to Vemurafenib and Cobimetinib

The Sponsor will evaluate the appropriateness of continuing to provide vemurafenib and cobimetinib to study patients after evaluating the primary efficacy outcome measure and safety data gathered in the study; these analyses may be conducted prior to completion of the study. If these data are medically and statistically significant, the Sponsor may amend the protocol to continue to provide vemurafenib and cobimetinib in an open-label extension study to patients in that treatment arm who have shown a demonstrable benefit from vemurafenib and cobimetinib treatment during this study (as measured by improvement in investigator-assessed PFS).

4.4 CONCOMITANT TREATMENT

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to Cycle 1 Day 1 through the end-of study treatment visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or maintenance therapy should continue their use as outlined in the eligibility criteria. Please note that potential interactions between vemurafenib and hormonal contraceptives may decrease the effectiveness of hormonal contraceptives.

Pain medications may be administered according to local standard practice guidelines while the patient is in the study.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. 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 drugs.

Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the course of the study.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study and for at least 14 days prior to initiation of study treatment, unless otherwise specified below:

- Any prior or concomitant therapy intended for the treatment of advanced melanoma, either approved by health authorities or experimental, including chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy, or investigational agents is prohibited. Patients who received prior adjuvant immunotherapy are allowed on the study.

- Palliative radiotherapy or major surgery within 14 days prior to first dose of study treatment is prohibited.

4.4.3 Prohibited Foods and Supplements

Use of the following foods is prohibited during the study and for at least 7 days prior to initiation of study treatment, unless otherwise specified below:

- St. John's wort or hyperforin (potent CYP3A4 enzyme inducer)
- Grapefruit juice (potent CYP3A4 enzyme inhibitor)

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 4 weeks after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever comes first. These patients will also continue to be followed for survival.

4.4.4 Medication Precautions in Case of Drug–Drug Interactions

Vemurafenib

Results from an in vivo drug – drug interaction study in patients with cancer demonstrated that vemurafenib is a moderate cytochrome 1A2 inhibitor, a weak CYP2D6 inhibitor, and a CYP3A4 inducer. Concomitant use of vemurafenib and agents with narrow therapeutic indices that are metabolized by CYP1A2, CYP2D6, and CYP3A4 is not recommended as vemurafenib may alter their concentrations.
If co-administration cannot be avoided, exercise caution and consider a dose reduction of the concomitant CYP1A2 and CYP2D6 substrate drug.

Based on in vitro data, vemurafenib is a substrate of CYP3A4, and therefore, concomitant administration of strong CYP3A4 inhibitors or inducers may alter vemurafenib concentrations. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) and inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) should be used with caution when co-administered with vemurafenib. Mild induction of CYP2B6 by vemurafenib was noted in vitro at a vemurafenib concentration of 10 µM. It is currently unknown whether vemurafenib at a plasma level of 100 µM observed in patients at steady state (approximately 50 µg/mL) may decrease plasma concentrations of concomitantly administered CYP2B6 substrates, such as bupropion.

Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate) and as such, co-administration of vemurafenib and warfarin warrants caution. While the in vitro 50% inhibitory concentration (IC_{50}) value of vemurafenib was 11.9 µM for CYP2C8, therefore, a potential risk for clinical inhibitory effect on CYP2C8 cannot be excluded although a large effect appears unlikely.

Cobimetinib

Based on in vitro data, cobimetinib is a substrate of CYP3A4 and UGT2B7. It has also been shown to be an inhibitor of CYP3A4 and CYP2D6. A study in cancer patients was conducted to determine if there is any clinically significant inhibition of a probe substrate of CYP3A (midazolam) or CYP2D6 (dextromethorphan). Preliminary results from the study indicate no effect on either CYP3A or CYP2D6. In the presence of steady-state cobimetinib, midazolam exposure was unchanged relative to midazolam alone, with a geometric mean ratio of 1.06 (95% CI: 0.84, 1.32) for midazolam $AUC_{0-\infty}$. When dextromethorphan was administered with steady-state cobimetinib, dextromethorphan exposure was unchanged as compared to dextromethorphan alone, with geometric mean ratio of 1.04 (95% CI: 0.87, 1.23) for dextromethorphan $AUC_{0-\infty}$. Given that cobimetinib is a substrate of CYP3A, potent inhibitors and inducers of CYP3A4 (listed below) may affect cobimetinib exposures and hence should be avoided. If use of one 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, troleandomycin, and voriconazole.
- Strong CYP3A4/5 inducers such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, and phenobarbital.

The study protocol includes a non-exhaustive list of typical examples of CYP1A2, CYP2C9, CYP2D6, and CYP3A narrow therapeutic substrates that require caution for administering with vemurafenib. CYP3A4, and CYP2C9 substrates and CYP3A4 inducers and inhibitors. The website http://medicine.iupui.edu/clinpharm/ddis/ provides information on drugs that are substrates, inhibitors and inducers of the various human cytochrome P450 enzymes (Appendix 11).

4.4.5 Medications Affecting the QT Interval

Certain medications could affect the results of QT intervals on ECG measurements required in this study. Caution should be exercised when the study drugs are co-administered with drugs that cause QTc prolongation or cardiac arrhythmia, and when patients have a pre-existing cardiac disease or ECG abnormality that may predispose them to cardiac dysrhythmia. Investigators should closely monitor patients who are on medications and/or supplements that may affect the QT 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 9. Please refer to http://www.azcert.org/ for additional information and references.

Vemurafenib

The effect of vemurafenib 960 mg administered BID on QTc intervals was evaluated in a multicenter, open-label, single-arm study in 132 previously treated patients with

$BRAF^{V600}$ mutation-positive metastatic melanoma (Study NP22657). No large changes in mean QTc interval from baseline (i.e., >20 ms) were detected in the trial. However, vemurafenib is associated with concentration-dependent QTc prolongation. In the first month of treatment, the largest mean change from baseline of 12.8 ms (upper boundary of the 2-sided 90% CI-14.9 ms) was observed at 2 hours post-dose on Day 15. In the first 6 months of treatment, the largest mean change from baseline of 15.1 ms (upper boundary of the 2-sided 90% CI-17.7 ms) was observed at a pre-dose timepoint.

Cobimetinib

Cobimetinib was shown to inhibit the human ether-à-go-go (hERG) channel activity with a concentration required to achieve 50% inhibition of 1 µM using single cellular electrophysiological recordings. The in vitro hERG mean IC_{50} value of 1 µM (531 ng/mL, unbound), is approximately 8-fold higher than peak exposures up to 64 ng/mL (free-fraction corrected) at the maximal dose evaluated in Phase I (125 mg) and 27-fold higher than peak exposures at the proposed Phase III dose (60 mg, free C_{max} = 19 ng/mL). Moreover, no effects on ECG or hemodynamic parameters were observed in a dedicated cardiovascular safety pharmacology study in telemetry-instrumented dogs, at up to 5.2 ng/mL (free-fraction corrected C_{max}).

Triplicate ECG data were collected in all patients in MEK4592g (Phase Ia single-agent study) and were analyzed for concentration-QTc relationship using matching cobimetinib concentration data. ECG data were available from doses of 0.05 mg/kg to 125 mg QD. A preliminary analysis of concentration-QTc shows no relationship between cobimetinib plasma concentration and QTcF or QTcF change from baseline. The probability of observing QTc outlying values >500 ms is very unlikely in the plasma concentration range up to 1140 ng/mL. At 60 mg QD (the planned dose for combination with vemurafenib), the mean C_{max} was 306 ng/mL and hence unlikely to be associated with any QTc prolongation based on this analysis.

In this study (GO28141), no additive clinical effect on QT interval prolongation was observed when patients were treated with cobimetinib in combination with vemurafenib.

4.5 STUDY ASSESSMENTS

The schedule of study assessments and procedures are detailed in Appendix 1.

4.5.1 Description of Study Assessments

4.5.1.1 $BRAF^{V600}$ Mutation Testing

$BRAF^{V600}$ mutation testing must be performed with the cobas 4800 BRAF V600 mutation test (Appendix 10). Only patients whose melanoma tumors test positive for the $BRAF^{V600}$ mutation on the cobas® 4800 BRAF V600 mutation test will be eligible for enrollment in the clinical study if other eligibility criteria are met. Tumor samples may be obtained from the primary melanoma tumor or any metastatic site, as long as the requirements below are met. $BRAF^{V600}$ mutation testing must be performed prior to

additional screening tests and requirements. Standard-of-care tests or examinations may be performed concurrently with the $BRAF^{V600}$ mutation testing. The 28-day window (Day -28 to Day -1) for performing screening assessments opens at the time the first additional screening assessment is performed after the cobas® 4800 BRAF V600 mutation test result is available.

The cobas® 4800 BRAF V600 mutation may be tested at a Roche-designated Central Reference Laboratory or at a non-Roche-designated laboratory. If a non–Roche-designated laboratory is used for $BRAF^{V600}$ mutation testing, documentation of the test procedures and results must be included as source documentation.

Archival or newly obtained formalin-fixed paraffin-embedded (FFPE) tumor specimens may be utilized for the cobas® 4800 BRAF V600 mutation test. Tissues obtained from fine needle aspirations (FNA) are not permitted. FFPE tumor block or 5 serially cut, unstained tumor tissue slides from each block will be collected at screening for the cobas test.

For patients eligible for the study, additional testing will be performed at Roche or in a centralized specialty laboratory. These additional investigations will be done retrospectively and not influence patient's eligibility for this study.

For patients whose tumor samples undergo cobas® 4800 BRAF V600 mutation testing at a Roche-designated central testing facility, tumor blocks from the patients who are not eligible for the study will be returned after mutation testing has been completed.

4.5.1.2 Medical History and Demographic Data

Medical history includes clinically significant diseases within the previous 3 years, major surgeries, cancer history (including prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to Cycle 1 Day 1. Demographic data will include age, sex, and self-reported race/ethnicity (where applicable/permissible).

4.5.1.3 Vital Signs

The following vital signs will be recorded for all patients:

- Temperature (°C)
- HR
- Respiratory rate
- Systolic and diastolic blood pressure
    - Blood pressure and HR measurements will be recorded with the patient in the seated position after a 5-minute rest period.

4.5.1.4 Physical Examinations

Patients will be asked specifically about skin and vision changes as part of each physical examination in addition to interval medical history. Note: If vital signs and physical examination are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

A complete physical examination should include measurement of height and weight, and head, eye, ear, nose, and throat (HEENT), neck, cardiovascular, dermatological, musculoskeletal, respiratory, GI, and neurological system exams. Examination of the HEENT must include visual inspection and/or palpation of the oral cavity and oropharynx, and palpation of the draining lymph nodes of the neck. Visual evaluation of the anus and digital evaluation of the anal canal is required as part of the physical examination at screening and thereafter per local standard of care for vemurafenib-treated patients. Endoscopic examination (colonoscopy or sigmoidoscopy) is not required for examination of the anus or anal canal.

All female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Papanicolaou (Pap) smear at screening and thereafter per local standard of care. Pelvic examinations, including Pap smear, which were conducted up to 12 months prior to screening and found to be normal need not be repeated at screening.

HEENT, anal, and gynecological examinations are part of the surveillance measures for identifying non-cuSCC (see Section 5.1.4.2). Any non-cuSCC should be staged and managed per the local standard of care.

Changes from baseline should be noted at each subsequent physical examination. New or worsened physical exam abnormalities should be recorded as adverse events, if appropriate. An interval medical history should be obtained coincident with each follow-up physical exam, which documents changes from baseline in new or concomitant diseases, medications, and allergies.

4.5.1.5 Tumor and Response Evaluations

Following formal institutional approval of protocol v5, patients on study should be evaluated for disease progression according to the local standard of care with the same radiographic method employed during the conduct of the study. The frequency of tumor assessments may be according to the local standard of care and treating physician's usual practice.

The Independent Review Committee will discontinue the review of tumor assessment data following the final PFS analysis.

For patients who discontinue study treatment for reasons other than investigator–determined disease progression, tumor assessments should continue to be performed according to the local standard of care and treating physician's usual practice.

For patients with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated.

4.5.1.6 Dermatologic Examination

A complete history of prior dermatologic interventions and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, and phototherapy for psoriasis) must be collected at baseline.

Complete evaluation of the skin by a dermatologist, or qualified equivalent medical specialist, will be conducted at baseline (up to 28 days prior to Cycle 1, Day 1), Cycle 2, Day 1 (±1 week), and thereafter per local standard of care thereafter while receiving study treatment, and at the end of study treatment.

Any suspicious lesions identified must be biopsied or resected and sent for pathologic examination. The available specimen block/sections should be sent to the Roche-designated central pathology laboratory for confirmation of diagnosis. Instruction manuals and supply kits will be provided for all central laboratory assessments. Actinic keratosis, KA, or other skin conditions identified by the dermatologist or qualified equivalent medical specialist should be treated per local standards of care.

4.5.1.7 Ophthalmology Examination

All patients will undergo ophthalmologic examination at the following timepoints:

- Screening
- Cycle 2, Day 1 ±1 week
- On Day 1 of Cycles 5, 8 and 11 (every 3 treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every 6 treatment cycles) ±2 weeks
- End-of-study-treatment visit

All patients will need to undergo baseline ophthalmologic examination to evaluate for evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO or neovascular macular degeneration. Ophthalmologic examination must be performed by a qualified ophthalmologist. Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Patients with such conditions will be excluded from the study as detailed in the inclusion/exclusion criteria.

Baseline ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (OCT; spectral domain OCT, if not available, may be substituted with time-domain OCT).

Serial surveillance ophthalmologic examination will comprise all examinations performed at the baseline ophthalmologic examination. Ophthalmologic examination does not need to be performed at end-of-study-treatment visit if one has been performed within the last 12 weeks and there were no clinically significant findings and/or changes from prior exam.

For patients who cross over from placebo to cobimetinib treatment, the ophthalmologic examination schedule should begin again, with exams at the following timepoints:

- Within 28 days of, but not after the first day of cross over
- Start of second cycle after cross over, Day 1 $\pm$1 week
- On Day 1 of Cycles 5, 8 and 11 after cross over (every three treatment cycles) $\pm$2 weeks
- On Day 1 of Cycles 15, 19, 23 after cross over (every four treatment cycles) $\pm$2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 after cross over, etc. (every six treatment cycles) $\pm$2 weeks
- End-of-study-treatment visit

4.5.1.8 Laboratory Assessments

All screening laboratory assessments should be obtained within 14 days prior to initiation of study drug on Cycle 1, Day 1. Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.

Laboratory assessments required on the study are as follows:

Hematology:	Hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocyte, monocyte, eosinophil and basophil counts, and other cells), and platelet count.
Chemistry:	BUN, creatinine, sodium, potassium, chloride, bicarbonate, phosphorus, magnesium, total calcium, albumin, LDH, CPK, fasting blood glucose, and fasting lipid panel.
Liver function tests:	ALT, AST, total bilirubin, ALP, and GGT.
Pregnancy test and FSH:	All women of childbearing potential (as defined in inclusion criteria) will have a serum pregnancy test at screening. Women who have had amenorrhea for $>$12 months but $<$2 years should have a screening FSH.

These laboratory assessments will be analyzed at the study site's local laboratory.

Blood and tumor tissue samples for biomarker, pharmacogenomics sample, and PK samples will be sent to one or several Roche-designated central laboratories or to the

Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

4.5.1.9 Patient Reported Outcomes

Following approval of v5 of the protocol, PRO data will no longer be collected.

4.5.1.10 Pharmacokinetic Assessments

Plasma concentrations of vemurafenib and cobimetinib will be measured in a central laboratory using validated assays. Venous blood samples will be collected according to the schedule of PK assessments (see Section 4.5.2.2 and Appendix 2) at the following timepoints:

- 1 – 4 hours after the first dose on Cycle 1, Day 1
- Pre-dose on Cycle 1, Day 15 ± 3 days
- 2 – 4 hours post-dose on Cycle 1, Day 15 ± 3 days
- Pre-dose on Cycle 2, Day 15 ± 3 days

On the days of PK sample procurement, patients are not required to fast; however, the time of the last meal must be recorded in the eCRF.

The procedures for the collection, handling, and shipping of PK samples can be found in the laboratory manual. PK samples for analysis of vemurafenib concentration will be collected in sodium heparin tubes and will require 2 mL of venous blood at each timepoint. PK samples for analysis of cobimetinib concentration will be collected in K2-EDTA tubes and will require 3 mL of venous blood at each timepoint.

The total volume of blood collected for PK assessments will be approximately 16–20 mL during the entire study. Unscheduled PK samples are not considered in this calculation (see Section 4.5.2.2).

4.5.1.11 Cardiac Evaluation – ECGs and Evaluation of Left Ventricular Function

ECG

Vemurafenib is associated with concentration-dependent QTc prolongation (see Section 4.4.5). Cobimetinib, as either monotherapy or in combination with vemurafenib, is not associated with QTc prolongation (see cobimetinib IB). All patients who continue to receive vemurafenib will undergo ECG monitoring in accordance with the vemurafenib IB (e.g., at Day 15, monthly during the first 3 months and then every 3 months thereafter or more frequently if clinically indicated). ECGs should be conducted per local standard of care. Central ECG reading will no longer be conducted.

For patients who have discontinued vemurafenib but are continuing treatment with cobimetinib or placebo, ECG monitoring is not required unless clinically indicated.

Evaluation of Left Ventricular Function

There is a potential for MEKi, including cobimetinib, to result in reductions in LVEF (Flaherty et al. 2012).

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%). See Section 1.3.7.4 and the cobimetinib IB for further details.

All patients will undergo evaluation of LVEF, either by echocardiography (ECHO) or multiple gated ejection acquisition scan (MUGA) at the following timepoints:

- Screening
- Cycle 2, Day 1 ±1 week
- On Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, and 23 (every 4 treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every 6 treatment cycles) ±2 weeks
- End-of-study-treatment visit

Evaluation of LVEF does not need to be performed at end-of-study treatment visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment as clinically indicated until resolution.

Evaluation of LVEF must be performed by the same method for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO for each individual patient.

Investigators must be aware of local institution regulations regarding repeat MUGA scans. The repeat administration of radioisotopes is limited in some nuclear medicine laboratories and some patients in this study could require monitoring on 4 occasions or more.

For patients who cross over from placebo to cobimetinib treatment, the ECHO/MUGA schedule must begin again, with exams at the following timepoints:

- Within 28 days of, but not after the first day of cross over
- Start of second cycle after cross over, Day 1 ±1 week
- On Day 1 of Cycles 5, 8, and 11 after cross over (every three treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, and 23 after cross over (every four treatment cycles) ±2 weeks

- On Day 1 of Cycles 29, 35, 41, 47 after cross over, etc. (every six treatment cycles) ±2 weeks
- End-of-study-treatment visit

4.5.1.12 Exploratory Biomarker Assessments

Patient specimens for dynamic (non-inherited) and genetic (inherited) biomarker discovery and validation will be collected from all patients participating in the trial. These specimens will be used for research purposes to identify biomarkers that correlate with response/resistance or severity of adverse effects to combined BRAF and MEK inhibition. This will help researchers to better understand the pathogenesis, course, and outcome of cutaneous melanoma and related diseases. The biomarker analyses are listed below each objective. Additional markers might be evaluated if further scientific evidence provides justification. The details of the biomarker analysis will be specified in a separate Biomarker Analysis Plan.

- Identify biomarkers of response and resistance in clinical specimens collected at pretreatment (archival and/or baseline), during treatment (Cycle 2 Day 15), and at the end-of-study treatment (disease progression). Biomarker analysis may include:
    - Mutation and copy number changes in RAF/RAS/MEK, other oncogenes, and tumor suppressor genes by DNA sequencing
    - Levels of pErk, pS6, PTEN and RTKs, such as MET by immunohistochemistry
    - Infiltration of immune-cells, such as CD3/CD4/CD8 positive T-cells, in tumor environment by immunofluorescence staining
    - Expression of BRAF, PDGFR, IGF1R, and other components of melanoma signaling pathways by Fluigidm Melanoma Panel
- Identify potential biomarkers in blood to monitor for melanoma progression. Biomarker analysis may include:
    - Circulating DNA that harbors the V600 mutation of BRAF
- Characterization of SCC (cutaneous and non-cutaneous), or other non-cuSCC new primary neoplasms and normal skin. Analysis may include:
    - HRAS/KRAS/NRAS, BRAF, TP53 mutations as well as other tumor specific mutations
    - ERK phosphorylation and proliferation
    - Additional markers dependent on the type of lesion or if new scientific evidence warrants

Biopsies of accessible melanoma lesions are mandatory upon patient's consent to participate in the trial. Tumor biopsies will be obtained at three timepoints:

- Baseline sample: within 28 days of Cycle 1, Day 1; either FFPE or fresh-frozen tumor biopsy (or both) may be provided
    - Baseline sample biopsies should be completed at least 48 hours before the initiation of study drug therapy on Cycle 1 Day 1. Archival tissue may be submitted in place of newly obtained tumor tissue for the baseline sample biopsy.
      Note: 10–20 unstained FFPE slides will be accepted only if the tumor block cannot be provided.
- On treatment cycle: on Cycle 2, Day 15 (±1 week); either FFPE or fresh-frozen tumor biopsy (or both) may be provided.
- Disease progression sample: at time of PD; either FFPE or fresh-frozen tumor biopsy (or both) may be provided.
    - The lesion must be a progressing lesion while the patient is still receiving study drugs or within 3 days after last study treatment.

Excisional biopsies, punch biopsies, 14-gauge core needle biopsies are acceptable. FNA biopsies are not acceptable.

- Plasma
    - Blood samples for biomarker analysis will be obtained on Day 1 of Cycles 1, 3 and 5 and at the time of disease progression. The following blood sample will be required at each timepoint: one 6-mL blood sample anticoagulated in EDTA (Schedule of Assessments, Appendix 1)

The total blood loss for plasma biomarker assessments will be approximately 6 mL per study visit.

- Whole blood
    - A mandatory blood sample (one 6-mL blood sample anticoagulated in EDTA) for genotyping analysis will be collected on Cycle 1 Day 1 (Schedule of Assessments, Appendix 1).
    - If consent is obtained, an optional blood sample (one 6-mL blood sample anticoagulated in EDTA) for RCR will be collected on Cycle 1 Day 1 (Schedule of Assessments, Appendix 1).

- Presumed or suspected SCC (cutaneous and non-cutaneous), new primary melanoma, other suspicious lesions, and normal skin
    - FFPE tissue or 10–20 unstained FFPE slides from a presumed or suspected SCC (cutaneous and non-cutaneous), new primary melanoma, or other suspicious lesion. Blocks will be returned after analyses are complete.
    - A FFPE specimen containing normal skin (sun exposed if possible) from patients who develop cuSCC or new primary melanoma (only 1 specimen of normal skin is required from patients who develop multiple cuSCCs during study treatment). Note: normal skin biopsies should be collected at the time the cuSCC lesion, new primary melanoma, or other suspicious lesion is excised in an area of skin with hair follicles present to the level of subcutaneous tissue. These samples may be obtained by using a 3-mm to 4-mm punch biopsy device, which should not require suturing.
    - Biopsies of suspicious malignant lesions not thought to represent SCC or new primary melanoma (e.g., BCC) may be submitted at the discretion of the investigator.

Sampling procedures, storage conditions, and shipment instructions for all biomarker samples (including normal skin) will be detailed in a separate laboratory manual.

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4.

Storage of patient specimens:

Exploratory biomarker samples (with the exception of the original archival tissue block) will be stored for up to 5 years after completion of the study. Archival tissue blocks will be returned at the latest within 3–6 months. Patients will have the option to consent to the storage of samples remaining after protocol-defined analyses for up to 15 years in the Roche Clinical Repository (RCR) (see Section 4.5.1.14). If no consent has been given for long-term storage, all samples will be destroyed no later than 5 years after the final close of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.

4.5.1.13 Unscheduled Assessments

A clinic visit should be scheduled any time there is a safety issue or any unscheduled assessments need to be performed.

4.5.1.14 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for exploratory biomarker analyses from patients who give specific consent to participate in this optional research will be stored in the RCR. These specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or other effects associated with medicinal products
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics for these assays

Approval by the Institutional Review Board or Ethics Committee

Storage of samples in the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

For all patients, date of consent should be recorded on the associated page of the eCRF. RCR specimens will be stored until completely depleted for up to 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Optional Samples for RCR

The following samples will be used for identification of dynamic (non-inherited) biomarkers:

- Remaining blood and plasma samples
- Remaining FFPE or FF tissue (with the exception of archival FFPE blocks, which will be returned to the sites) for tumor protein expression or somatic tumor-related RNA/DNA analyses.

The following sample will be used for identification of genetic (inherited) biomarkers:

- One 6-mL whole blood sample (anticoagulated in K3-EDTA) at Cycle 1, Day 1

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens. Upon receipt by the RCR, each

specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. 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 data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the 15 year storage period. A separate, specific signature will be required to document a patient's agreement to provide RCR specimens. Patients who decline to participate will check a “no” box in the appropriate section and will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent to long term storage of exploratory biomarker specimens for further research in the RCR have the right to withdraw their consent to long term storage of his or her specimens at any time for any reason. If a patient wishes to withdraw consent to the long term storage of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO28141 does not, by itself, constitute withdrawal of specimens from long term storage in the RCR. Likewise, a patient's withdrawal from long term storage in the RCR does not constitute withdrawal from Study GO28141.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

In addition to an internal review body, an independent Science and Ethics Advisory Group, consisting of experts in the fields of biology, ethics, sociology, and law, will advise Roche regarding the use of RCR specimens and on the scientific and ethical aspects of handling genetic information.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. All signed Informed Consent Forms will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the patient is randomized to study treatment. Unless otherwise specified, screening and pretreatment tests and evaluations will be performed within 28 days of randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used, and such tests do not need to be repeated for screening.

Requirement for the cobas® 4800 BRAF V600 mutation test is detailed in Section 4.5.1.1. The 28-day window (Day -28 to Day -1) for performing screening assessments opens at

the time the first additional screening assessment is performed after the cobas® 4800 BRAF V600 mutation test result is available.

For a complete description of study assessments, refer to Section 4.5.1 and Appendix 1.

The following assessments will be performed at screening:

- Informed consent
- $BRAF^{V600}$ mutation status of the primary tumor or metastatic site confirmed using the cobas® 4800 BRAF V600 mutation test.
- Medical history and demographics
- Concomitant medications
- Complete physical examination, ECOG Performance Status, height, weight, and vital signs.
- Visual and digital evaluation of the anus and anal canal.
- All female patients will undergo pelvic examination including visual inspection of the uterine cervix and Pap smear at to monitor for cervical carcinoma.
- Baseline dermatologic examination for cuSCC surveillance by a dermatologist or qualified equivalent medical specialist
- Hematology, serum chemistries, including fasting blood glucose and lipid panel, LFTs
- Serum pregnancy test, FSH, if applicable
- Stage of melanoma according to the AJCC (v. 7.0) classification (Appendix 8), based on physical examination, imaging studies (contrast-enhanced CT or MRI of the chest, abdomen, and pelvis as well as the site of the primary tumor; contrast-enhanced MRI of the brain [or CT if MRI is not generally available)].
- ECG and evaluation of left ventricular function with either ECHO or MUGA
- Baseline complete ophthalmologic evaluation that includes visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (spectral domain OCT, if not available, may be substituted with time domain OCT).
- Melanoma tumor tissue (archival or newly obtained tumor tissue) for exploratory biomarker assessments.
- Cutaneous SCC tumor tissue for suspicious neoplasms

The following assessments are required on Cycle 1, Day 1 (prior to administration of study treatment*):

- Randomization with the IxRS (can be done up to 72 hours prior to Cycle 1 Day 1)
- ECGs in accordance with the vemurafenib IB and conducted per local standard of care for patients receiving vemurafenib. See Section 4.5.1.4.

- Vital signs, weight, physical examination
  Note: If vital signs and physical examination are assessed within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
- Hematology, serum chemistries, and LFTs
  Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
- Blood for biomarker analysis
- Blood for pharmacogenetic analysis
- RCR DNA sample, an optional whole blood sample (6 mL in EDTA) for exploratory biomarker assessments.
- Dispense diary for drug accountability

*In addition, a blood sample for PK assessment will be taken at 1–4 hours after dose of study treatment.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Study

Assessments scheduled on the day of study drug administration should be performed prior to study drug dosing, unless otherwise specified. Unless otherwise specified, assessments that are done every 2 weeks should be performed within a ±2 days window. Assessments that are performed monthly should be performed within a window of ±3 days.

For a complete description of study assessments, refer to Section 4.5.1 and Appendix 1.

The following assessments will be performed during the study: as indicated in the schedule of assessments (Appendix 1):

- Interval medical history including documentation of new or worsening adverse events and concomitant medications.
- ECOG Performance Status
- Vital signs. As part of the physical examination, a thorough head and neck evaluation to monitor for non-cutaneous SCC, consisting of visual inspection and palpation of the oral cavity, oropharynx and neck lymph node palpation, must be performed by the site investigator.
- ECGs in accordance with the vemurafenib IB and conducted per local standard of care for patients receiving vemurafenib. See Section 4.5.1.4.
- Hematology.
- Serum chemistries and LFTs.
- Evaluation of left ventricular function with either ECHO or MUGA.
- Ophthalmologic evaluation. See Section 4.5.1.7.

- Tumor assessments as clinically indicated
- Dermatologic examination performed by a dermatologist, or qualified equivalent medical specialist, for surveillance of cuSCC, new primary melanoma, or other cutaneous neoplasms per local standard of care.
- Biopsy of suspected SCC (cutaneous and non-cutaneous), or other new primary neoplasms (FFPE tissue blocks or 10–20 unstained tissue slides).
- Melanoma tumor tissue biopsy, if clinically accessible.
- PK assessments for vemurafenib and cobimetinib.
- Blood samples for biomarker analysis.
- Drug accountability.

Please see Appendix 1 for the Schedule of Assessments performed during the treatment period.

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

4.5.2.3 End-of-Study-Treatment Visit

Patients may remain on study treatment until disease progression as assessed by the investigator, unacceptable toxicity, or study termination by the Sponsor. The following are required as part of the end-of-study treatment visit:

- Interval medical history including documentation of new or worsening adverse events.
- Concomitant medications
- Physical examination (including HEENT) and vital signs.
- Dermatologic examination for surveillance of cuSCC, new primary melanoma, or other cutaneous neoplasms, if one was not performed within the last 12 weeks.
- Ophthalmologic evaluation, if one was not performed within the last 12 weeks.
- Evaluation of left ventricular function if one was not performed within the last 12 weeks.
- Melanoma tumor tissue biopsy at time of melanoma progression, if clinically accessible.
- Blood samples for biomarker
- Drug accountability.

4.5.2.4 Post-Study Treatment and Survival Follow-Up Assessments

Please see Appendix 1 for the Schedule of Assessments performed during follow-up. Upon study treatment discontinuation or withdrawal from study treatment, patients are required to continue the following assessments as indicated in the Schedule of Assessments:

- Physical examination and vital signs.
- Dermatologic examination performed by a dermatologist, or qualified equivalent medical specialist, for surveillance of cuSCC, new primary melanoma, or other cutaneous neoplasms per local standard of care.
- Anal examination (all patients) and gynecological examination (female patients only), including visual inspection of the uterine cervix and Pap smear per local standard of care.
- CT/MRI of the chest to monitor for the occurrence of SCC per local standard of care.
- Survival follow-up, including subsequent anti-cancer therapy information will be collected via telephone calls and/or clinic visits every 12 weeks until death.

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.

4.5.2.5 Adverse Event Follow Up

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

After completion of study treatment, adverse events should be followed as outlined in Sections 5.5 and 5.6.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study

- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study and/or study procedures (e.g., dosing instructions, study visits)

4.6.1.1 Discontinuation from Study Treatment

Patients must discontinue study treatment if they experience any of the following:

- Disease progression per investigator assessment
- Intolerance of study treatment despite undergoing protocol defined dose reduction
- Pregnancy
- Withdrawal of consent

Patients who discontinue study drug for any reason will be asked to return to the clinic for end-of-study-treatment visit and undergo follow-up assessments (see Sections 4.5.2.3 and 4.5.2.4, respectively). The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug will not be replaced.

4.6.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

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 and survival status. These steps for contacting patients will be recorded in the source document.

If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF. The patient should be followed until the adverse event has resolved, if possible.

4.6.1.3 Withdrawal of Patients from the Roche Clinical Repository

Please refer to Section 4.5.1.14.

4.6.2 Study and Site 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:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- All enrolled patients have discontinued study treatment.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Cobimetinib for use with vemurafenib is approved in the United States*, Canada, members of the* European Union*, and* other countries. The safety plan for patients in this study is based on clinical experience with cobimetinib in completed and ongoing studies. The anticipated important safety risks for cobimetinib are outlined below. Please refer to the cobimetinib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients who participate in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification, and treatment interruption or discontinuation, are provided below. There are management guidelines for specific toxicities of cobimetinib in Section 5.1.4.

5.1.1 Risks Associated with Vemurafenib

The toxicity profile for vemurafenib has been documented from safety data derived from seven studies of over 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., γ glutamyltransferase, alkaline phosphatase, ALT, AST, and bilirubin).

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 cutaneous squamous cell carcinomas (mainly keratoacanthoma type). The majority of

these were observed within the first 16 weeks of vemurafenib exposure and were not treatment limiting. The risk for cutaneous squamous cell carcinoma will be mitigated through the use of a Risk Management Plan as outlined in Section 5.1.3. 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 squamous cell carcinoma 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, two 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 (Lankisch and Gottesleben 1995).

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., computed tomography 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 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.

5.1.2 Risks Associated with Cobimetinib

Information related to risks attributed to cobimetinib is based on safety data from this Phase III Study GO28141 (cobimetinib plus vemurafenib), Phase Ib Study NO25395 (cobimetinib plus vemurafenib), and Phase I Study MEK4592g (cobimetinib

monotherapy). For further information regarding clinical safety, please refer to the current cobimetinib Investigator's Brochure.

5.1.2.1 *Important* Identified Risks Associated with Cobimetinib

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 10*, in Section 5.1.5.3.*

Serous Retinopathy

Serous retinopathy (fluid accumulation within the layers of the retina) has been observed in patients treated with MEK-inhibitors, including cobimetinib (Flaherty et al. 2012). 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 the events were asymptomatic Grade 1 events. Few patients treated with cobimetinib plus vemurafenib experienced Grade $\geq$ 3 ocular 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 Appendix 1). Details regarding baseline and subsequent ophthalmologic examinations are provided in Section 4.5.1.7.

Guidelines for management of patients who develop Grade ≥ 2 visual disorders or retinopathy are provided in Table 10 in Section 5.1.5.3.

Left Ventricular Dysfunction

Decrease in left ventricular ejection fraction from baseline has been reported in patients receiving cobimetinib. Left ventricular dysfunction may occur with signs and symptoms of cardiac failure, or reduction in left ventricular ejection fraction events may be asymptomatic.

Left ventricular dysfunction has been characterized in the Phase III Study GO28141. The study incorporated prospective serial left ventricular ejection fraction evaluation in all patients. With active surveillance, measured reductions in left ventricular ejection fraction 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 left ventricular ejection fraction and the remaining patients were asymptomatic. Most left ventricular ejection fraction reduction events in patients on cobimetinib plus vemurafenib (62%) improved or resolved with management according to the dose-modification guidelines (see Table 10 in Section 5.1.5.3).

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 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 10 in Section 5.1.5.3.

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 Table 10 in Section 5.1.5.3 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 events were reported in 2 patients (0.8%) treated with cobimetinib plus vemurafenib.

5.1.2.2 Potential Risks Associated with Cobimetinib

Liver Laboratory Abnormalities and Severe Hepatotoxicity

Liver laboratory test abnormalities, including increases in ALT, AST, and alkaline phosphatase, 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 Development Toxicity

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.

5.1.2.3 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%; 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.

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.

5.1.3 General Safety Mitigation Plan

5.1.3.1 Eligibility Criteria

Eligibility criteria promulgated for this study will guard the safety of patients in this trial. The exclusion criteria for safety will include (but are not limited to) the following: major surgical procedure or significant traumatic injury within 2 weeks prior to first dose of study drug treatment; pregnancy or breastfeeding; clinically significant cardiovascular disease; history of congenital long QT syndrome or QTc interval $>$450 ms at baseline; inadequate bone marrow, hepatic, or renal function; and other clinically significant comorbid conditions.

5.1.3.2 Monitoring

Safety will be evaluated in this study through the monitoring of all adverse events and targeted laboratory assessments according to NCI CTCAE v4.0. Patients will be monitored every 2 weeks during the first 2 cycles, then prior to each subsequent cycle, and as necessary throughout the study. All treatment-emergent adverse events and serious adverse events, whether or not deemed treatment related, will be followed until they resolve or become stabilized, the patient is lost to follow up or withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event or serious adverse event.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries, liver function tests, and blood counts. All serious adverse events and protocol-defined adverse events of special interest will be reported in an expedited fashion.

5.1.4 Monitoring and Management of Specific Toxicities and Conditions that May Arise with Vemurafenib and/or Cobimetinib Treatment

5.1.4.1 Primary Cutaneous Squamous Cell Carcinoma and Other New Cutaneous Malignancies

Complete evaluation of the skin by a dermatologist, or qualified equivalent medical specialist, will be conducted at baseline (up to 28 days prior to Cycle 1, Day 1), Cycle 2, Day 1 ($\pm$1 week) of study treatment, every 3 treatment cycles (12 weeks $\pm$2 weeks) thereafter while receiving study treatment and at the end-of-study-treatment visit. Dermatologic examination does not need to be performed at end-of-study-treatment visit if the evaluation has been performed within the last 12 weeks.

An unscheduled dermatology examination may be performed during treatment for investigation of any new skin lesions that are suspected of being cuSCC or new primary cutaneous neoplasm.

The dermatologic evaluation will include:

- Complete history of prior dermatologic medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior cuSCC, use of tanning beds, precursor lesions and phototherapy for psoriasis)
- Skin examination for cuSCC, BCC, actinic keratosis, KA, and/or second primary melanoma.
- Appropriately map any suspicious lesions that may represent cuSCC, BCC, actinic keratosis, KA, and/or second primary melanoma.
- Biopsy and/or excision of any suspicious lesions identified at baseline and while on study.
- Treatment of identified skin neoplasms or conditions per local standards of care.
- Available specimen block/sections should be sent to a Roche-designated central pathology laboratory for confirmation of diagnosis and further molecular characterization.

If a patient develops cuSCC either during or after withdrawal from the study, this information must be collected and reported as an adverse event of special interest to the Sponsor, whether it is deemed related or unrelated to study drug.

If a patient develops a new primary cutaneous neoplasm either during or 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.

5.1.4.2 New Non-Cutaneous Primary Malignancies

All new primary malignancies will be reported until 12 months after discontinuation of vemurafenib. If a patient develops a new non-cutaneous, primary malignancy during or up to 12 months after discontinuation of vemurafenib, this event must be reported as a

serious adverse event to the Sponsor, whether it is deemed related or unrelated to study drug. Thereafter, only new primary malignancies thought to be related to study treatment will be reported as serious adverse events.

Any suspicious lesion identified must be biopsied/excised and a specimen (tissue block/sections) sent to a Roche-designated central pathology laboratory for pathological examination and further molecular characterization.

Head and Neck Examination

The complete physical examination performed at the beginning of every cycle should include examination of HEENT and neck (including lymph nodes) by the investigator to monitor for the occurrence of SCC in the upper aerodigestive tract.

Lung Examination

Patients will undergo CT/MRI of the chest to monitor for the occurrence of SCC while on study treatment and per local standard of care. The chest CT/MRI scan performed as clinically indicated as part of the tumor assessment may be used for lung SCC surveillance while on study treatment.

Anal Examination

Visual inspection and digital examination of the anus and anal canal will be performed at screening, thereafter per local standard of care, and at other times as clinically indicated to monitor for anal SCC. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated.

Gynecological Examination

All female patients will undergo pelvic examination including visual inspection of the uterine cervix and Pap smear at screening, thereafter per local standard of care, and at other times as clinically indicated to monitor for the occurrence of cervical carcinoma.

5.1.4.3 Skin Toxicities Other than Neoplastic/Premalignant Lesions

The skin toxicities other than neoplastic/premalignant lesions observed in patients treated with vemurafenib and/or include rash, pruritus, palmar-plantar erythrodysesthesia, dry skin, and exfoliation. Of these, the most common has been rash (maculo-papular or acneiform), which has generally been manageable with supportive care. Skin toxicities other than neoplastic/premalignant lesions, will be managed with supportive care according to institutional guidelines as well as by dose interruption/modification.

Mild to severe photosensitivity has been reported in patients who received vemurafenib in clinical studies. For managing photosensitivity, patients are advised to:

- Avoid prolonged sun exposure while taking study treatment and for at least 5 days after discontinuation.

- Use broad-spectrum (UVA and UVB) sunscreen and lip balm (at least SPF >30) to help protect against sunburn.

5.1.4.4 Ocular Toxicity

All patients will undergo ophthalmologic examination at the following timepoints:

- Screening
- Cycle 2 Day 1 ±1 week
- On Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, and 23 (every 4 treatment cycles) ±2 weeks
- On Day 1 of Cycles 19, 35, 41, 47, etc. (every 6 treatment cycles) ±2 weeks

For patients who cross over from placebo to cobimetinib treatment, the ophthalmologic examination schedule should begin again, with exams at the following timepoints:

- Within 28 days of, but not after the first day of cross over
- Start of second cycle after cross over, Day 1 ±1 week
- On Day 1 of Cycles 5, 8 and 11 after cross over (every three treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, 23 after cross over (every four treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 after cross over, etc. (every six treatment cycles) ±2 weeks
- End-of-study-treatment visit

Baseline and serial surveillance ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain OCT (spectral domain OCT, if not available, may be substituted with time-domain OCT).

See Section 4.5.1.7.

5.1.4.5 Cardiac Toxicity

ECG

The following measures will be implemented to minimize the risk of ventricular arrhythmia in patients with metastatic melanoma treated in this study:

- Patients with a baseline QTc >450 ms or a history of congenital long QT syndrome are not eligible to participate in this study.
- Concomitant medications known to prolong QTc interval should be avoided if possible.
- ECG monitoring for patients who receive vemurafenib will be conducted in accordance with the vemurafenib IB. Ongoing ECG monitoring is no longer required for patients who continue to receive only cobimetinib/placebo unless clinically indicated.

- Guidelines for interruption of treatment and dose reduction in the setting of QTc prolongation are described in Table 10.
- Vemurafenib treatment should be permanently discontinued if the QTc interval increases to > 500 ms AND the increment from baseline exceeds 60 ms.

Evaluation of Left Ventricular Function

All patients will undergo evaluation of LVEF, either by ECHO or MUGA at the following timepoints:

- Screening
- Cycle 2, Day 1 ±1 week
- On Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, and 23 (every 4 treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every 6 treatment cycles) ±2 weeks
- End-of-study-treatment visit

For patients who cross over from placebo to cobimetinib treatment, the ECHO/MUGA schedule must begin again, with exams at the following timepoints:

- Within 28 days of, but not after the first day of cross over
- Start of second cycle after cross over, Day 1 ±1 week
- On Day 1 of Cycles 5, 8, and 11 after cross over (every three treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, and 23 after cross over (every four treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 after cross over, etc. (every six treatment cycles) ±2 weeks
- End-of-study-treatment visit

See Section 4.5.1.11.

Guidelines for interruption/dose modification in the setting of decreased LVEF are provided in Table 10.

5.1.4.6 Hepatic Toxicity

Grade 4 elevations of serum γ glutamyltransferase and other less severe liver function abnormalities have been reported in patients treated with vemurafenib and cobimetinib. These have generally been managed with interruption of treatment and dose reduction. All patients will undergo liver function testing (AST, ALT, total bilirubin, ALP, and γ glutamyltransferase) at periodic intervals while on study treatment (see Appendix 1). Guidelines for interruption/dose modification in the setting of liver function abnormality are provided in Table 10.

5.1.5 Management of Specific Adverse Events

Dose levels for dose reductions are listed in Table 9.

Table 9 Dose Level Reductions

Dose reduction	Vemurafenib	Cobimetinib
1 dose level	720 mg BID	40 mg QD
2 dose levels	480 mg BID	20 mg QD

BID = twice daily; QD = once daily.

Dose modifications, interruptions, and delays of vemurafenib and/or cobimetinib study treatment should be made on the basis of the guidelines provided in Table 10. The dose modification guidelines are not intended to replace clinical judgment or dictate care of individual patients. Dose reduction of each study drug is independent of the other study drug. Dose re-escalation is not allowed.

5.1.5.1 Rash Management

The appearance of rash must be differentiated as acneiform, non-acneiform or drug–induced photosensitive rash / sunburn.

Prior to starting study treatment, patients must be advised to:

- Avoid unnecessary or prolonged sun exposure while taking study treatment and for at least 5 days after discontinuation.
- Use broad-spectrum (UVA and UVB) sunscreen and lip balm (at least SPF $>$30) to help protect against sunburn.
- Use thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) on dry areas of the body.

For Grade 1 to 2 rash, the following supportive measures may be considered:

- For non-acneiform rash, mild strength topical steroid (e.g. hydrocortisone 1% cream).
- For acneiform rash, doxycycline 100 mg BID or minocycline 100 mg BID for 1–2 weeks.
- For pruritic lesions, the cool compresses and oral/topical antihistamine agents
- For photosensitive lesions / sunburn, use cool compresses and avoid further sun exposure.
- For desquamation, thick emollients and mild soap are recommended.

For Grade$\geq$3 rash, see Table 10: management of specific toxicities and dose modification guidelines.

5.1.5.2 Diarrhea Management

Rule out other or concomitant causes, including medications (e.g., stool softeners, laxatives, antacids), infection by *Clostridium difficile*, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber.

For Grade 1 to 2 diarrhea:

- Dietary modifications:
    - Stop all lactose-containing products and eat small meals.
    - The BRAT (banana, rice, apples, toast) diet may be helpful.
    - Encourage adequate hydration.
- Loperamide:
    - Suggested initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool; up to a maximum of 16 mg/day.
    - Continue loperamide is suggested until diarrhea-free for 12 hours.
    - If Grade $\leq$ 2 diarrhea persists after 48 hours total treatment with loperamide, consider second-line agents (otreotide, budesonide, or tincture of opium).

For Grade $\geq$ 3 diarrhea, see Table 10: Management of Specific Toxicities and Dose Modification Guidelines.

5.1.5.3 Management of Specific Toxicities and Dose Modification Guidelines

Table 10 Management of Specific Toxicities and Dose Modification Guidelines

Adverse Event	Action
A) Rash Grade ≥ 3	The appearance of rash must be characterized as acneiform or non-acneiform. No change in vemurafenib and cobimetinib dosing will be implemented for Grade ≤ 2 rash; patients should receive maximal supportive care per institutional guidelines. <u>Acneiform rash</u> Hold cobimetinib dosing until Grade ≤ 2. Vemurafenib dosing may continue when cobimetinib is interrupted. Reduce cobimetinib by 1 dose level. If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3, further reduce cobimetinib by another dose level. Permanently discontinue cobimetinib if restarting after second dose reduction, the patient experiences skin toxicity Grade ≥ 3. Permanently discontinue cobimetinib if rash ≥ 3 persists for > 28 days despite adequate supportive care. Non-acneiform or maculo-papular rash Delay vemurafenib dosing until Grade ≤ 2. Cobimetinib dosing may continue when vemurafenib is interrupted. For Grade 3 rash, reduce vemurafenib by 1 dose level. 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 recurrent skin toxicity Grade ≥ 3. For Grade 4 rash, reduce vemurafenib by 2 dose levels. Permanently discontinue vemurafenib if after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3.

Table 10 Management of Specific Toxicities and Dose Modification Guidelines (cont.)

Adverse Event	Action
B) Photosensitivity Grade ≥ 3	a) Grade ≤ 2 photosensitivity should be managed with supportive care and treatment of both vemurafenib and cobimetinib may be continued. If Grade 2 photosensitivity does not resolve to Grade ≤ 1 after 7 days or if photosensitivity worsens to Grade ≥ 3 despite best supportive care, then both vemurafenib and cobimetinib treatment must be interrupted until the photosensitivity resolves to a Grade ≤ 1. b) If resolution to Grade ≤ 1 occurs within 28 days, treatment may be re-initiated with vemurafenib dose reduced by 1 level and without change in cobimetinib dose. 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 dose reduction of vemurafenib, then both agents should be held until the photosensitivity resolves to Grade ≤ 1 or less. The dose of vemurafenib should be reduced by another dose level. d) If photosensitivity recurs a second time to Grade ≥ 3 despite prophylactic measures and the aforementioned 2 dose reductions of vemurafenib, vemurafenib should be discontinued. The patient may continue on study treatment with cobimetinib/placebo alone.
C) New skin lesion, suggestive of any cutaneous primary malignancy. Any cutaneous primary malignancy is considered a Grade 3 event in this study.	a) Follow SCC Risk Management Plan detailed in protocol 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 cuSCC, 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 must be discontinued. d) If the lesion is not an SCC, then treatment with vemurafenib and cobimetinib may be restarted at the most recent dose level.
D) Visual symptoms ≥ Grade 2	NCI CTCAE v4.0 Eye Disorders – Other, specify:

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL

Table 10 Management of Specific Toxicities and Dose Modification Guidelines (cont.)

Adverse Event	Action
	<table><tr><td>3</td><td>Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL</td></tr><tr><td>4</td><td>Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye</td></tr></table> Interrupt cobimetinib and vemurafenib. Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography If r**etinal vein occlusion (RVO)** is diagnosed, vemurafenib and cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. If **neurosensory retinal detachment** is diagnosed, cobimetinib dosing should be interrupted until symptoms improve to Grade 1. Then cobimetinib should be dose reduced by 1 dose level when restarting. If visual symptoms of Grade $\geq$ 2 recur despite 2 dose level reductions of cobimetinib, cobimetinib should be permanently discontinued. The patient may continue on study treatment with vemurafenib alone in the event that cobimetinib/placebo is discontinued. If **uveitis/iritis** is diagnosed, Grade $\leq$ 2 uveitis/iritis can be managed with ophthalmologic input using local non-invasive therapies and/or short courses of systemic therapy. Dose reduction of study drugs is NOT required if uveitis/iritis is Grade $\leq$ 2. For Grade ≥3 uveitis/iritis, vemurafenib should be reduced by 1 dose level. If RVO, neurosensory retinal detachment or uveitis/iritis are NOT identified: ● and visual symptoms have **not resolved** to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, permanent discontinuation of both study drugs should be considered. ● and visual symptoms have **resolved** to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, resume use of vemurafenib and cobimetinib at current doses.

Table 10 Management of Specific Toxicities and Dose Modification Guidelines (cont.)	
Adverse Event	**Action**
	● If visual symptoms of Grade ≥ 2 (despite the optimal use of local / non-invasive supportive care) **recur**, vemurafenib and/or cobimetinib should be dose reduced by 1 level, depending on which agent is implicated. If visual symptoms of Grade ≥ 2 recurs despite 2 dose level reductions of both vemurafenib and cobimetinib, and maximal supportive care, 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. b) If Grade ≥3 diarrhea occurs despite adequate 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 reduced by 1 dose level, with continued supportive care or prophylaxis. • If bowel movement characteristics have NOT improved to Grade ≤ 1 or baseline with maximal supportive care by 28 days, then both drugs should be discontinued. 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 reduced by 1 dose level. The cobimetinib dose will be maintained at the previously reduced dose. e) If the diarrhea recurs at Grade ≥3 despite supportive care and dose reductions of 2 dose levels in both drugs (i.e., vemurafenib to 480 mg BID and cobimetinib to 20 mg QD), then both drugs should be permanently discontinued.
F) *Rhabdomyolysis or CPK elevations*	*Rhabdomyolysis or symptomatic CPK elevations: 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.* *If rhabdomyolysis or symptomatic CPK elevation do not improve within 4 weeks, permanently discontinue cobimetinib treatment.* *Asymptomatic CPK elevations:* *Grade ≤3: cobimetinib dosing* does *not need to modified or interrupted to manage asymptomatic Grade ≤3 CPK elevations.* *Grade 4: Interrupt cobimetinib treatment. If improved to*

Table 10 Management of Specific Toxicities and Dose Modification Guidelines (cont.)	
Adverse Event	**Action**
	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.
G) LFT elevations	a) If Grade ≤2, continue current dose of vemurafenib and cobimetinib. b) If Grade 3, hold vemurafenib. Continue current dose of cobimetinib. Upon resolution of LFT to Grade ≤1, resume vemurafenib at 1 lower dose level (e.g., 960 mg to 720 mg, or 720 mg to 480 mg). c) If Grade 4, see Section J below. d) No dose modification is required for isolated **GGT elevation** in the absence of clinically significant elevation above baseline grade in AST, ALT, ALP, bilirubin or hepatic.
H) QTcF interval prolongation on ECG Grade ≥ 3	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 9). c) Interrupt dosing of vemurafenib ECG monitoring should be performed until QTc interval decreases below 500 ms. Electrolytes abnormalities should be corrected in all cases. Continue dosing with cobimetinib at the current dose if otherwise tolerated. d) Plan to seek a cardiologist consultation or advice. e) 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. f) If QTc improves within 28 days, restart dosing of vemurafenib at 1 reduced dose level. g) Repeat 12-lead ECG monitoring at 2 weeks and 4 weeks of restarting vemurafenib at the lower dose. Additional ECG monitoring will be performed at Day 15 of each subsequent Cycle for 3 cycles, and every 3 months thereafter. h) If second increase in QTc interval to >500 ms occurs at the lower dose of vemurafenib, follow guidelines above, and reduce dose of vemurafenib by an additional dose level. i) Permanently discontinue vemurafenib if after correction of associated risk factors and dose reductions, the QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values.

Table 10 Management of Specific Toxicities and Dose Modification Guidelines (cont.)

<table>
<tr><th>Adverse Event</th><th>Action</th></tr>
<tr><td>I) Reduction in LVEF</td><td>NCI CTCAE v 4.0 EF decreased:

<table><tr><td>Grade</td><td>Description</td></tr><tr><td>1</td><td>-</td></tr><tr><td>2</td><td>Resting EF 50%–40%;
10%–19% drop from baseline</td></tr><tr><td>3</td><td>Resting EF 39%–20%;
＞20% drop from baseline</td></tr><tr><td>4</td><td>Resting EF ＜20%</td></tr></table>a) Asymptomatic decrease in LVEF
See Appendix 5.
All patients who require dose reduction of cobimetinib should have LVEF measurements at 2 weeks, 4 weeks, then every 6 weeks for 12 weeks, and then per protocol.
b) Symptomatic decrease in LVEF or symptomatic heart failure
Cardiology consultation is strongly recommended.
Hold cobimetinib. Vemurafenib may be continued.
Strong consideration should be given to permanently discontinuing cobimetinib if it is attributed to have caused the cardiac symptoms.
If cardiac symptoms resolve completely within 28 days, and LVEF returns to LLN, reduce cobimetinib by 1 dose level. The patient should have LVEF measurements at 2 weeks, 4 weeks, then every 6 weeks for 12 weeks, and then per protocol.
If cardiac symptoms resolve within 28 days, but LVEF is below LLN, see Appendix 5.
If cobimetinib is permanently discontinued, patient may continue on vemurafenib.</td></tr>
</table>

Table 10 Management of Specific Toxicities and Dose Modification Guidelines (cont.)	
Adverse Event	**Action**
J) Other Grade 4, non–hematologic adverse events related to study drug (except for GGT or CPK elevation)	a) Interrupt dosing of vemurafenib and cobimetinib. b) If adverse event resolves to Grade ≤1 within 28 days, then restart dosing of vemurafenib and cobimetinib. Vemurafenib should be decreased by 2 dose levels and cobimetinib by 1 dose level. c) If the adverse event does not resolve to Grade ≤1 by 28 days, discontinue study treatment. d) If the Grade 4 adverse event recurs (a second time), then both agents should be discontinued.
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.*

ADL = activities of daily living; BID = twice daily; CPK = creatine phosphokinase; cuSCC = cutaneous squamous cell carcinoma; EF = ejection fraction; GGT = γ glutamyltransferase; LFT = liver function test; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once daily; QTc = corrected QT interval; RVO = retinal vein occlusion; SCC = squamous cell carcinoma

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, protocol-specified safety laboratory assessments, vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to Roche)

A serious adverse event is any adverse event that meets any of the following criteria:

- Any non-cutaneous primary malignancy (related or unrelated to study treatment) that develop during or up to 12 months after study treatment completion must be reported as a serious adverse event
- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.9)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator/site to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to Roche)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

Adverse events of special interest for this study include the following:

- Any retinal vein occlusion
- Any retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or *central serous chorioretinopathy*
- Grade $\geq$ 3 photosensitivity
- Grade $\geq$ 3 rash
- Grade $\geq$ 3 elevations of AST, ALT, serum bilirubin, γ glutamyltransferase, or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- Grade $\geq$ 3 QT interval prolongation

- Cardiac events/ Grade ≥ 2 LVEF reduction
- Any cutaneous primary malignancy, including squamous cell carcinoma (SCC), keratoacanthoma (KA), basal cell carcinoma (BCC), new primary melanoma.
- *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.

The occurrence of any cutaneous primary malignancy, including SCC, KA, BCC, new primary melanoma will be considered a Grade 3 adverse event in this study. Any non–cutaneous primary malignancy will be reported as a serious adverse event (see Section 5.2.2).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events as defined in Section 5.2.1 are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for serious criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

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).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events (including new primary cancers), or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will document the event in the patient's source document and report the event on the Adverse Event eCRF.

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 11 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 11 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF 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 on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 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, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values and ECG Findings

Not every laboratory or ECG abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy

- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a manifestation of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a manifestation of a clearly discernible disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology

changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$baseline value) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- 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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol–specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of melanoma should be recorded only on the Study Completion/Early Discontinuation eCRF and do not need to be reported on the Adverse Events eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported.

The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During the post-study survival follow up, deaths attributable to progression of melanoma should be recorded on the Survival eCRF.

5.3.5.8 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective procedure became necessary because of the expected normal progression of the disease
    - The patient has not suffered an adverse event
- Hospitalization due solely to recurrence/progression of the underlying melanoma

5.3.5.10 *Adverse Events Associated with an Overdose or Error in Drug Administration*

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects. Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data*, and safety analyses will not be performed using PRO data*. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be documented in the patient's source document and reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- *A*dverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

24 HOUR MEDICAL COVERAGE (Roche Emergency Medical Call Center Help Desk): To reach the Roche Emergency Medical Call Center Help Desk please refer to your Regulatory binder for country-specific access numbers.

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide

medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information and List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

For reports of serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/ Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during study treatment or within 6 months after the last dose of study drug. All women of childbearing potential will have a serum pregnancy test at screening.

A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF.
The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information and List of Investigators").

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during study treatment or within 6 months after the last dose of study drug.

A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy.

An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any abortion associated with a pregnancy occurring during the study or within 6 months of the last dose of study drug should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug during the study or within 6 months of the last dose of study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 New Non-Cutaneous Primary Cancers

In fulfillment of a post-marketing requirement as a condition of vemurafenib approval in the United States (for the treatment of locally-advanced Stage IIIC or metastatic melanoma), all non-melanoma, new non-cutaneous primary cancers will be reported to the U.S. FDA every 12 months after the first patient enrolls and for 12 months after the last patient has completed study treatment.

5.5 FOLLOW UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY TREATMENT ADVERSE EVENTS

At the end-of-study-treatment visit and at the 4-week after end-of-study-treatment visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, serious adverse event (including new primary malignancies), or other adverse event of *special interest* occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information and List of Investigators").

During survival follow-up, deaths attributed to progression of melanoma should be recorded only on the Survival eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against the cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Cobimetinib IB
- Vemurafenib IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Progression-Free Survival

The type 1 error (α) for the analysis of the primary endpoint of PFS is 0.05 (2-sided).

Approximately 500 patients will be randomized to treatment. The final analysis of the primary endpoint of PFS will take place when approximately 206 PFS events have occurred. Statistical considerations are based on the following assumptions:

- Stratified log-rank test at 0.05 significance level (2-sided)
- 6 months median PFS for the vemurafenib + placebo arm
- 11 months median PFS for the vemurafenib + cobimetinib arm
- Accrual ramp-up time of 9 months to reach 65 patients per month thereafter for a total enrollment period of approximate 14 months
- 5% dropout rate

- No interim analysis of PFS

A total of 206 PFS events provides >95% power to detect an improvement in median PFS from 6 months in the vemurafenib + placebo arm to 11 months in the vemurafenib + cobimetinib arm (corresponding to a hazard ratio of 0.55, and the minimal detectable difference [MDD] is 0.76).

6.1.2 Overall Survival

See Section 6.9.2 for a description of the planned interim analysis and final analysis of OS. The type 1 error (α) for the analysis of the secondary endpoint of OS is 0.05 (2-sided).

The final analysis of OS will be performed after the occurrence of approximately 250 deaths. A total of 250 deaths provides approximately 80% power to detect an improvement in median OS from 15 months in the vemurafenib + placebo arm to 21.4 months in the vemurafenib + cobimetinib arm (corresponding to a hazard ratio for death of 0.70) at an overall 2-sided 0.05 significance level.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations, and patient disposition will be summarized for randomized patients by treatment arm. Study treatment administration will be summarized by treatment arm for all treated patients.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline and disease characteristics (including disease stage and LDH) will be summarized.

6.4 EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will include all randomized patients (intent-to-treat analysis), and patients will be grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Analysis

The primary analysis will be a comparison of PFS between the 2 treatment arms using a stratified log-rank test at an overall 0.05 significance level (2-sided).

The statistical hypothesis of this study is as follows:

H_0: $PFS_{(Arm\ A)} = PFS_{(Arm\ B)}$

H_1: $PFS_{(Arm\ A)} \neq PFS_{(Arm\ B)}$

where $PFS_{(Arm\ A)}$ represents the survival function of PFS in the vemurafenib + placebo arm and $PFS_{(Arm\ B)}$ represents the survival function of PFS in the vemurafenib + cobimetinib arm.

PFS as assessed by Investigator will be the primary endpoint evaluated. PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment using RECIST v1.1. Data from patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data from patients with no post-baseline tumor assessment will be censored at the randomization date. The hazard ratio for PFS will be estimated using a stratified Cox model. Two-sided 95% CIs for the hazard ratio will be provided. The stratified analyses will incorporate 2 stratification factors: geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c). Results from an unstratified log-rank test and the unstratified hazard ratio will also be presented. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and the Kaplan-Meier curves will be provided.

6.4.2 Secondary Efficacy Analyses

Secondary efficacy endpoints are OS, ORR, DOR, and PFS assessed by independent review.

OS is defined from randomization until death from any cause. For patients who are alive at the time of analysis data cutoff, OS time will be censored at the last date the patient was known to be alive. Survival time for patients with no post-baseline survival information will be censored on the date of randomization.

The final analysis of ORR will take place at the time of final analysis of PFS. BORR will be assessed by the investigator according to the RECIST v1.1. Confirmed ORR is defined as the total number of patients whose best overall response is CR or PR divided by the population evaluable for ORR. Confirmation of response (partial response or complete response) will be done no earlier than 28 days. In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval not less than 6 weeks. Treatment difference in BORR will be tested using a chi-square test with Schouten correction, and a 95% Hauck-Anderson CI will be calculated for the difference in BORRs between treatment groups. In addition, a 95% Clopper-Pearson CI will be calculated for the BORR.

DOR is defined as the interval 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 a confirmed overall response of CR or PR. Median duration of response will be estimated using the Kaplan-Meier method, and the 95% CI will be calculated using the method of Brookmeyer and Crowley (1982). Since the

determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed on this endpoint.

6.5 SAFETY ANALYSES

Safety will be assessed through summaries of all adverse events, including serious adverse events, adverse events of special interest, and adverse events leading to discontinuation of study treatment.

Adverse events will be summarized using MedDRA by mapped term, appropriate thesaurus level, and toxicity grade. adverse events will be graded by the investigator using NCI CTCAE v4. The following safety parameters will be summarized by treatment arm:

- All adverse events
- All adverse events leading to discontinuation of study treatment
- All deaths
- Serious adverse events
- Adverse events of special interest (see Section 5.2.3 for a list of adverse events of special interest for this study)

In addition, exposure to study treatment (vemurafenib, cobimetinib, placebo), including cumulative dose and treatment duration, will be summarized by treatment arm. Selected laboratory data will be summarized by treatment arm and toxicity grade (NCI CTCAE v4.0).

6.6 PHARMACOKINETIC ANALYSES

Summary statistics will be used as appropriate to perform the descriptive analysis of the plasma concentrations of vemurafenib and cobimetinib. Cobimetinib and vemurafenib concentrations will be measured as shown in Appendix 2. Cobimetinib and vemurafenib plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a pop PK analysis approach. Nonlinear mixed-effect modeling will be used for the estimation of pop PK parameters for cobimetinib and vemurafenib. Covariates such as patient demographics (e.g., age, sex, body size), total protein, serum albumin, liver function tests (e.g., AST, ALT, ALP), and serum creatinine will be tested for significance on PK parameters of interest. The PK data in this study might be pooled with PK data from other studies.

The PK data will be combined with the safety (e.g., QTc) and efficacy (e.g., PFS) data for exposure–response modeling as data permit. PK and PK–pharmacodynamic analyses may be reported in separate stand-alone reports. Additional analyses may be explored as warranted by the data.

6.7 PATIENT-REPORTED OUTCOMES

Quality of life, as measured by EORTC QLQ-C30, will be evaluated for patients with a baseline assessment and at least one post-baseline QLQ-C30 assessment that generate a score. Total QLQ-C30, each domain score (e.g., physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), as well as symptom scales, will be examined at baseline, and change from baseline for each timepoint by use of descriptive statistics.

Repeated measures mixed-effects models will be the primary models for the formal comparison of the QLQ-C30 multiple-item subscale scores between treatment arms. Each model will have a term for intercept, a term for a linear time trend term (in weeks), a term for treatment group, and a term for treatment-by-time interaction. Repeated measures over time will be accounted for by unstructured covariance structure (using the REPEATED statement in SAS® PROC MIXED).

Health economic measures, as assessed by the EQ-5D, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D assessment that generate a score. Scores at baseline and change from baseline scores for each timepoint will be quantified with descriptive statistics.

Following approval of v5 of the protocol, PRO data will no longer be collected.

6.8 BIOMARKER ANALYSES

Biomarker analyses will be provided in a separate report. Descriptions of biomarker analyses will be provided in a Biomarker Analysis Plan.

6.9 INTERIM ANALYSES

6.9.1 Interim Efficacy Analyses of Primary Endpoint

No interim analyses of the primary endpoint (PFS) will be performed.

6.9.2 Analysis of Overall Survival

The OS analyses plan for this study protocol (v5) and the statistical analysis plan (SAP) have been revised. The study will incorporate 2 OS analyses (1 interim and 1 final analysis). The first OS interim analysis was performed at the time of the primary PFS analysis (16 months after the first patient was randomized). The originally planned final analysis for OS at 385 events is anticipated to occur in the second quarter of 2017. The rapid development of other potentially effective therapies for patients with metastatic melanoma provides more treatment options for patients following disease progression, which may potentially confound the OS benefit of vemurafenib + cobimetinib in future OS analyses. Therefore, in order to minimize this potential impact while maintaining a statistically robust evaluation of the OS benefit associated with the combination, the protocol-defined OS analyses have been revised.

The revised plan for OS analyses is to perform the final OS analysis at approximately 250 deaths without further interim analyses. The type 1 error rate would be strictly controlled at the 0.05 level by the continued use of the Lan-DeMets implementation of the O'Brien-Fleming use function as pre-specified in the original protocol and SAP.

The final OS analysis will be performed after the occurrence of approximately 250 deaths (projected to occur at approximately 31 months after the first patient was randomized). The Lan-DeMets implementation of the O'Brien and Fleming use function will be used to control the overall type I error for the OS comparison at a 2-sided, 0.05 significance level. Table 12 summarizes the assumptions and characteristics of the interim and final analyses for OS.

Table 12 Assumptions and Characteristics of the Interim and Final Analyses for Overall Survival

Assumptions	Findings
HR targeted	0.70
Targeted median (vemurafenib + placebo)	15 months
Targeted median (vemurafenib + cobimetinib)	21.4 months
Projected enrollment period	12.7 months
First interim OS (to be performed at time of final PFS analysis)	
Estimated cutoff date [a]	16 months after FPI
Projected number of events (% of final events)	85[c] (34%)
Projected MDD [b] (p-value)	0.45 (<0.000242)
Final OS	
Number of events (% of final events)	250 (100%)
Estimated cutoff date [a]	31 months after FPI
Projected MDD [b] (p-value)	0.78 (<0.0499)
Power	80%
α level (2-sided)	0.05

FPI = first patient in; HR = hazard ratio; MDD = minimally detectable difference; PFS = progression free survival; OS = overall survival.

[a] Estimated data cutoff time from study enrollment date. Analysis results will be available after data cleaning.

[b] The largest observed HR that is projected to be statistically significant.

[c] The actual number of events observed at the interim analysis in July 2014

7. DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) and the Sponsor will be responsible for the data management of this study, including quality checking of the data. Data obtained manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

ePRO data was collected using an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs must be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients used an ePRO device to capture PRO data. The data was transmitted via to a centralized database at the ePRO vendor. The data can be reviewed by site staff via secure access to a method.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor or designee direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in

accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or

authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the final OS analysis.

9. STUDY DOCUMENTATION, MONITORING AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol

amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

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

This study will be sponsored by F. Hoffmann-La Roche Ltd and managed with the support of a CRO, which will provide clinical monitoring, sample management, and project management support. Approximately 180 centers globally may participate in the study and will randomize approximately 500 patients.

Randomization will occur through an IxRS. Central facilities will be used for certain study assessments (i.e., ECG, specified laboratory tests, pharmacokinetics, dermatology). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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 the Sponsor 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.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor 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 authorship requirements. Any formal publication

of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Assessments and Procedures

Period	Screening	Study Treatment											End-of-study treatment	Follow-up after treatment discontinuation		
Cycle		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycles 7 +		4 wks	12 wks	6 mths
Day		1	15	1	15	1	15	1	1	1	15	1				
Informed consent[1]	X															
Tumor tissue for $BRAF^{V600}$ mutation testing[1]	X															
Randomization[2]		X														
Medical history and demographics	X															
Interval medical history		X	X	X	X	X		X	X	X		X	X			
Physical exam including HEENT, vital signs, height, weight[3]	X	X	X	X	X	X		X^{3}	X	X		X^{3}		X		
Anal and gynecological exam[3A]	X															

Appendix 1 Schedule of Assessments and Procedures (cont.)

Period	Screening	Study Treatment											End-of-study treatment	Follow-up after treatment discontinuation		
Cycle		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycles 7 +		4 wks	12 wks	6 mths
Day		1	15	1	15	1	15	1	1	1	15	1				
ECOG Performance Status	X	X	X	X	X	X		X	X	X		X				
12-lead ECG[5]	X	Per vemurafenib IB for patients receiving vemurafenib. If clinically indicated for patients receiving only cobimetinib/placebo[5]														
ECHO or MUGA[6]	X			X					X			X[6]	X[6]			
Hematology[7]	X	X		X		X		X	X	X		X				
Chemistry and LFTs[8]	X	X	X	X	X	X	X	X	X	X		X				
Serum pregnancy tests[9]	X															
Fasting blood glucose and lipid panel[10]	X															
CT/MRI brain[11]	X	As clinically indicated														
Radiologic tumor assessment[12]	X	Per local standard of care[12]														

Appendix 1 Schedule of Assessments and Procedures (cont.)

Period	Screening	Study Treatment											End-of-study treatment	Follow-up after treatment discontinuation		
Cycle		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycles 7 +		4 wks	12 wks	6 mths
Day		1	15	1	15	1	15	1	1	1	15	1				
Mandatory whole blood sample for genotyping		X														
PK blood samples [13]		X	X		X											
Vemurafenib administration[14]		X	X	X	X	X	X	X	X	X	X	X				
Cobimetinib administration[14]		X	X	X	X	X	X	X	X	X	X	X				
Drug accountability[15]		X	X	X	X	X		X	X	X		X	X			
Concomitant medications[16]	X[16]	X	X	X	X	X		X	X	X		X	X			
Adverse events[17]		X	X	X	X	X		X	X	X		X	X	X[17]		
Survival assessment and subsequent anti-cancer therapy[18]															X[18]	→

Appendix 1 Schedule of Assessments and Procedures (cont.)

Period	Screening	Study Treatment											End-of-study treatment	Follow-up after treatment discontinuation		
Cycle		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycles 7 +		4 wks	12 wks	6 mths
Day		1	15	1	15	1	15	1	1	1	15	1				
Dermatologic exam[19]	X			X					X			X[19]	X[19]			
Ophthalmologic exams[20]	X			X					X			X[20]	X[20]			
Tumor biopsy for biomarker analyses[21]	X				X								X[21A]			
Blood samples for biomarker[22]		X				X			X				X			
Cutaneous SCC tumor tissue or suspicious neoplasms[23]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
CT/MRI of chest to monitor for SCC[24]		Per local standard of care [24]														

Appendix 1 Schedule of Assessments and Procedures (cont.)

Period	Screening	Study Treatment											End-of-study treatment	Follow-up after treatment discontinuation		
Cycle		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycles 7 +		4 wks	12 wks	6 mths
Day		1	15	1	15	1	15	1	1	1	15	1				
Optional whole blood sample for RCR		X														

CT = computerized tomography scan; ECG = electrocardiogram; ECHO = echocardiogram; HEENT = head, ears, eyes, nose and throat; LFT = liver function test; MRI = magnetic resonance imaging scan; MUGA = Multiple Gated Acquisition; RCR = Roche Clinical Repository; SCC = squamous cell carcinoma

→ Assessment or procedure is performed throughout the study.

Schedule of Assessments – Footnotes

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

Unless otherwise specified, assessments that are done every 2 weeks should be performed within a ± 2 days window. Assessments performed monthly, should be performed within a window of ± 3 days.

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 Cycle 1 Day 1 unless otherwise noted. Assessments performed as standard of care before signed informed consent form but within the screening window may be used for screening. Screening exams for ECG, hematology, and chemistry must be performed within 14 days of first dose. Melanoma tissue must be tested for $BRAF^{V600}$ mutation using the cobas® 4800 BRAF V600 mutation may be performed at a Roche-designated Central Reference Laboratory or at a non-Roche-designated laboratory. If a non-Roche-designated laboratory is used for $BRAF^{V600}$ mutation testing, documentation of the test procedures and results must be included as source documentation. Testing requires an FFPE tumor block or 5 unstained sections. BRAFV600 mutation testing must be performed prior to additional screening tests and requirements. Standard-of-care tests or examinations may be performed concurrently with the BRAFV600 mutation testing. The 28-day window (Day-28 to Day-1) for performing screening assessments opens at the time the first additional screening assessment is performed after the cobas® 4800 BRAF V600 mutation test result is available.

2. Randomization can be done up to 72 hours prior to Cycle 1 Day 1. Following approval of protocol v6, treatment assignment will be unblinded and patients who have been receiving vemurafenib plus placebo who provide consent may cross over to receive vemurafenib plus cobimetinib if this is considered by the physician to be in the patient's best interest.
3. Physical exam will be performed during screening and subsequently at each study visit. After initial screening physical exam, a symptom-directed exam that contains an evaluation of the oral cavity, oropharynx, neck, 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. Note: If vital signs and physical examination are assessed within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1. 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 at each study visit that a physical exam is performed. Blood pressure and heart rate measurements will be recorded after a 5-minute rest in a seated position. Height will be collected only at screening/baseline.

3A Visual inspection of the anus and digital examination of the anal canal will be performed at screening, thereafter per local standard of care for vemurafenib-treated patients, and at other times as clinically indicated to monitor for SCC. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated. All female patients will undergo pelvic examination including visual inspection of the uterine cervix and Pap smear at screening, thereafter per local standard of care, and at other times as clinically indicated to monitor for cervical carcinoma.

4. Following approval of v5 of the protocol, QoL assessments will no longer be conducted.
5. ECG monitoring for patients receiving vemurafenib will be conducted in accordance with the vemurafenib IB. Ongoing ECG monitoring is no longer required for patients continuing to receive only cobimetinib/placebo unless clinically indicated.
6. All patients will undergo evaluation of left ventricular function, either by ECHO or MUGA at the following timepoints:
   - Screening
   - Cycle 2, Day 1 ± 1 week
   - On Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ± 2 weeks
   - On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles) ± 2 weeks
   - On Day 1 of Cycles 29, 35, 41, 47 etc. (every 6 treatment cycles) ± 2 weeks
   - End-of-study-treatment visit

   Evaluation of left ventricular function does not need to be performed at end-of-study-treatment visit if it has been performed within the last 12 weeks. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of left ventricular function must be performed by the same method for each patient.

   For patients who cross over from placebo to cobimetinib treatment, the ECHO/MUGA schedule must begin again, with exams at the following timepoints:
   - Within 28 days of, but not after the first day of cross over

- Start of second cycle after cross over, Day 1 ±1 week
- On Day 1 of Cycles 5, 8, and 11 after cross over (every three treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, and 23 after cross over (every four treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 after cross over, etc. (every six treatment cycles) ±2 weeks
- End-of-study-treatment visit

7. Hematology includes hemoglobin, hematocrit, WBC with differential (neutrophils, lymphocyte, monocyte, eosinophil and basophil counts, and other cells), and platelet count. Screening hematology values must be obtained within 14 days of Cycle 1 Day 1. Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
8. Chemistry includes BUN, creatinine, sodium, potassium, chloride, bicarbonate, phosphorus, magnesium, total calcium, albumin, LDH, and CPK. LFTs include ALT, AST, total bilirubin, ALP, and GGT. Screening chemistry values must be obtained within 14 days of Cycle 1 Day 1. Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
9. For women of childbearing potential, a serum pregnancy test is required at screening within 14 days prior to Cycle 1 Day 1. Women who have had amenorrhea for >12 months but <2 years should have an FSH test at screening for eligibility purposes.
10. This is performed only during screening. Both blood glucose and lipid panel must be obtained after at least an 8-hour fast. Lipid panel should include total cholesterol, low-density lipoprotein and triglycerides.
11. All patients must have a screening brain CT or MRI to assess for brain metastasis, and subsequently only as clinically indicated.
12. The frequency, method, and evaluation criteria for tumor assessments will be determined by the investigator per local clinical practice. Response may be assessed using RECIST v1.1. Assessments should include CT scans of the chest, abdomen and pelvis, with an evaluation of all known or suspected sites of disease, whenever possible. The same radiographic procedure used at screening should be used throughout the study.
13. PK sample for analysis of vemurafenib concentration will be collected in sodium heparin tubes and will require 2mL of venous blood at each timepoint. PK sample for analysis of cobimetinib concentration will be collected in K2-EDTA tubes and will require 3mL of venous blood at each timepoint. The time and date of all PK samples must be documented. Plasma samples for vemurafenib and cobimetinib concentration measurement will be collected at the following time-points:
    - 1–4 hours after the first dose on Cycle 1, Day 1
    - Pre-dose on Cycle 1, Day 15 ± 3 days
    - 2–4 hours post-dose on Cycle 1, Day 15 ± 3 days
    - Pre-dose on Cycle 2, Day 15 ± 3 days
14. For both investigational drugs, dosing will continue until disease progression, consent withdrawal, or unacceptable toxicity. Dispense a sufficient number of vemurafenib and cobimetinib to last until the next visit. Extra medications 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).

15. Provide a medication diary. Instruct patient to record the time and date they take each study drug dose in the diary and to return all unused capsules at each study visit to assess compliance. Collect and review medication diary, collect unused medications, and assess compliance at each subsequent visit. At least 7 days off cobimetinib are required prior to starting a new treatment cycle.
16. Review and capture of all concomitant medications will be performed at each study visit. Concomitant medications are defined as any prescription medications, over-the-counter preparations and supplements used by a patient within 7 days prior to Cycle 1, Day 1 and continuing through the study completion visit.
17. All adverse events and serious adverse events will be collected. All adverse events or serious adverse events occurring after study discontinuation will be recorded until 28 days after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever occurs first. Any second non-cutaneous primary malignancy (related or unrelated to study treatment) that develop during or up to 12 months after study treatment completion must be reported as a serious adverse event.
18. Survival assessment will be used to collect overall survival during long-term follow-up; patient should be followed up every 12 weeks until death, withdrawal of consent, or loss to follow-up. Subsequent anti-cancer therapy information will be collected at the same time as survival assessment.
19. Dermatology evaluation: Complete evaluation of the skin by a dermatologist, or qualified equivalent medical specialist, will be conducted at baseline (up to 28 days prior to Cycle 1, Day 1), Cycle 2, Day 1 (±1 week), and per local standard of care thereafter while receiving study treatment and at the end-of-study-treatment visit. Dermatologic examination does not need to be performed at end-of-study-treatment visit if one has been performed within the last 12 weeks.
20. All patients will undergo ophthalmologic examination at the following timepoints:
    - Screening
    - Cycle 2, Day 1±1 week
    - On Day 1 of Cycles 5, 8 and 11 (every 3 treatment cycles)±2 weeks
    - On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles)±2 weeks
    - On Day 1 of Cycles 29, 35, 41, 47 etc. (every 6 treatment cycles)±2 weeks
    - End-of-study-treatment visit

    Ophthalmologic examination does not need to be performed at end-of-study-treatment visit if one has been performed within the last 12 weeks. Baseline ophthalmologic examination evaluates for evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension and glaucoma. Ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (spectral domain OCT, if not available, may be substituted with time domain OCT).

For patients who cross over from placebo to cobimetinib treatment, the ophthalmologic examination schedule should begin again, with exams at the following timepoints:

- Within 28 days of, but not after the first day of cross over
- Start of second cycle after cross over, Day 1 ±1 week
- On Day 1 of Cycles 5, 8 and 11 after cross over (every three treatment cycles) ±2 weeks
- On Day 1 of Cycles 15, 19, 23 after cross over (every four treatment cycles) ±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 after cross over, etc. (every six treatment cycles) ±2 weeks
- End-of-study-treatment visit

21. Biopsies of accessible melanoma lesions are mandatory upon patient's consent to participate in the trial. Either FFPE or fresh-frozen biopsies (or both) will be obtained at 3 timepoints:
    - Baseline sample: during screening within 28 days of Cycle 1 Day 1
    - On treatment cycle: on Cycle 2, Day 15 (±1 week)
        - Disease progression sample: at time of progressive disease

    Baseline sample biopsies should be completed at least 48 hours before the initiation of study drug therapy on Cycle 1 Day 1. Archival tissue may be submitted in place of newly obtained tumor tissue for the baseline sample biopsy. It is highly recommended that the biopsy at disease progression be collected within 3 days after last study treatment. Excisional biopsies, punch biopsies, 14-gauge core needle biopsies are acceptable. Fine needle aspiration (FNA) biopsies are not acceptable.

21A. Biopsy will only be performed if patient has accessible lesion and disease progression.

22. Blood samples for biomarker analysis will be obtained on Day 1 of Cycles 1, 3, and 5, and at the time of disease progression. Blood sample required at each timepoint: one 6-mL blood sample anticoagulated in EDTA.

23. If a patient develop any cutaneous lesion(s) suspicious for SCC or KA during the study, biopsy tissue and a paired normal skin biopsy must be obtained for central pathology review. Only one normal skin biopsy is required per patient, regardless of the number of SCC lesions identified and biopsied during the study. Any suspicious lesions (cutaneous or non-cutaneous) thought to be malignant must also be sent for central pathology review and may undergo molecular characterization.
    - Any second non-cutaneous primary malignancy (related or unrelated to study treatment) that develop during or up to 12 months after study treatment completion must be reported as a serious adverse event and tumor tissue sent for central pathology review.

24. Patients will undergo CT/MRI of the chest to monitor for the occurrence of SCC while on study treatment and per local standard of care.

Appendix 2 Schedule of Pharmacokinetic Assessments

Visit	Timepoint	Sample Type
Cycle 1, Day 1	1-4 hours after the first dose of vemurafenib and cobimetinib	vemurafenib PK cobimetinib PK
Cycle 1, Day 15 ± 3 days	Prior to doses of vemurafenib and cobimetinib	vemurafenib PK cobimetinib PK
Cycle 1, Day 15 ± 3 days	2-4 hours after the dose of vemurafenib and cobimetinib	vemurafenib PK cobimetinib PK
Cycle 2, Day 15 ± 3 days	Prior to doses of vemurafenib and cobimetinib	vemurafenib PK cobimetinib PK

PK = pharmacokinetic.

Appendix 3 New Response Evaluation Criteria in Solid Tumors – Version 1.1 – Excerpt From Original Publication with Addition of Supplementary Explanations

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 computed tomography (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 $\geq$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 $\geq$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.

Appendix 3 New Response Evaluation Criteria in Solid Tumors – Version 1.1 (cont.)

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography (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.
- 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 magnetic resonance imaging (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 3 New Response Evaluation Criteria in Solid Tumors – Version 1.1 (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). 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 intravenous (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.

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 CA-125 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 partial response (PR) and complete response (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 the section titled “Measurable Tumors at Baseline”). 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.

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 that 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 ≥ 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 $\times$ 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 ≥ 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.

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’).

Appendix 3 New Response Evaluation Criteria in Solid Tumors – Version 1.1 (cont.)

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 (CRFs) 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.

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 assigning 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 CRF:

- 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.

- 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.)

Appendix 3 New Response Evaluation Criteria in Solid Tumors – Version 1.1 (cont.)

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.
- When the patient has only non-measurable disease: this circumstance arises in some Phase III 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

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.

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.

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 timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Appendix 3 New Response Evaluation Criteria in Solid Tumors – Version 1.1 (cont.)

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.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint 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 timepoint.

BEST OVERALL RESPONSE: ALL TIMEPOINTS

The best overall response will be determined by statistical programming once all the data for the patient is known.

Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al, New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228-247.

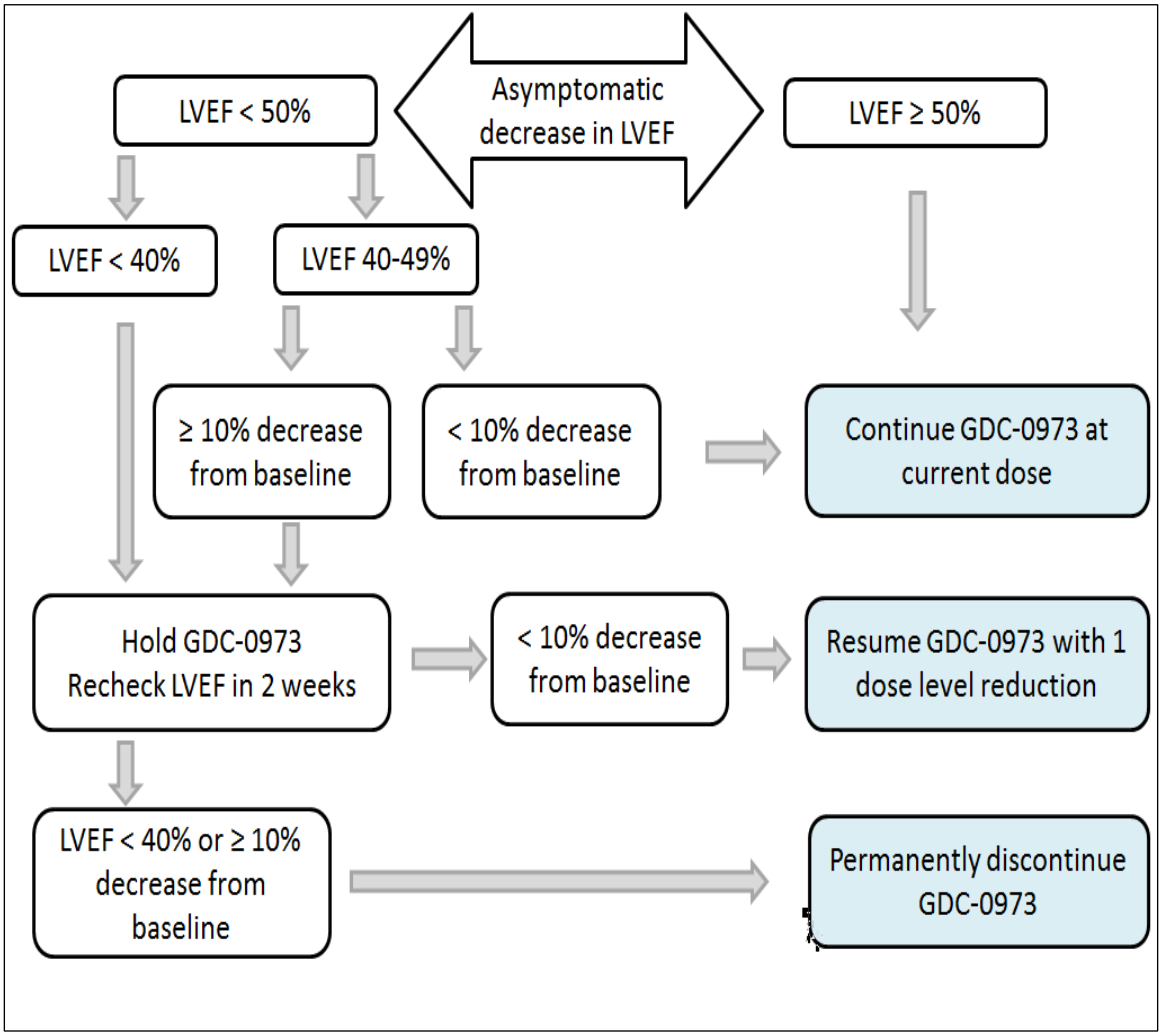
Appendix 4 ECOG Performance Status

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: Oken, MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Appendix 5 Guidelines for Management of Asymptomatic Reduction in Ejection Fraction



Appendix 6 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.

Appendix 6 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 (cont.)

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 adverse events 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 serious adverse events: 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 serious adverse events 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: 1-866-286-9573 and ask for the physician on call. From Australia, call 1-800-031-902 and ask for the physician on call. *(Note, the number for Australia cannot be dialed from a mobile phone.)*

Appendix 7 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 8 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 9 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 10 Cobas® 4800 BRAF V600 Mutation Test Information

The **cobas**® 4800 BRAF V600 Mutation Test is a real-time polymerase chain reaction (PCR) test intended to be used to identify melanoma patients whose tumors carry the $BRAF^{V600}$ mutation for treatment with vemurafenib monotherapy. Its primary use is the detection of the $BRAF^{V600}$ 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 I 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 $BRAF^{V600}$ 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 II and Phase III clinical trials of vemurafenib in locally-advanced/unresectable 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 11 Impact of Vemurafenib on Concomitant Medications

Concomitant use of vemurafenib and agents with narrow therapeutic indices that are metabolized by CYP1A2, CYP2D6, and CYP3A4 is not recommended as vemurafenib may alter their concentrations. If co-administration cannot be avoided, caution should be exercised. The following is a list of sensitive or narrow therapeutic substrates of CYP1A2, CYP2C9, CYP3A4, and CYP2D6. Other drugs that may have narrow therapeutic index should also be avoided (based on updated information).

Substrates of Cytochrome Enzymes			
CYP 1A2 [1]	**CYP 2C9 [1]**	**CYP 3A4 [2]**	**CYP2D6 [1]**
Alosetron	Celecoxib	Alfentanil	Atomoxetine
Caffeine	Phenytoin	Amiodarone	Desipramine
Duloxetine	S-warfarin	Astemizole	Dextromethorphan
Melatonin	Torsemide	Carbamazepine	Metoprolol
Ramelteon		Cisapride	Nebivolol
Tacrine		Cyclosporine	Paroxetine
Theophylline		Diergotamine	Perphenazine
Tizanidine		Diltiazem	Thioridazine
		Ergotamine	Tolterodine
		Fentanyl	Venlafaxine
		HIV protease inhibitors: amprenavir, Indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)	
		Itraconazole	
		Ketoconazole	
		Macrolide antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin	
		Mibefradil	
		Pimozide	
		Quinidine	
		Rifabutin	
		Sirolimus	
		Tacrolimus	
		Terfenadine	
		Vincristine	
		Verapamil	

[1] Exposure of these drugs may be increased following vemurafenib treatment.

[2] Exposure of these drugs may be decreased following vemurafenib treatment.