Official Title: **A PHASE I OPEN-LABEL, MULTICENTER, MULTIPLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF VEMURAFENIB IN CHINESE PATIENTS WITH BRAFV600 MUTATION-POSITIVE UNRESECTABLE OR METASTATIC MELANOMA**

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Version 1: 22 May 2012

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Version 4: 23 July 2014

Version 5: 20 April 2015

PROTOCOL

TITLE:	**A PHASE I OPEN-LABEL, MULTICENTER, MULTIPLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF VEMURAFENIB IN CHINESE PATIENTS WITH BRAF^{V600} MUTATION-POSITIVE UNRESECTABLE OR METASTATIC MELANOMA**
PROTOCOL NUMBER:	YO28390
VERSION NUMBER:	5
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 22 May 2012 Version 2: 24 April 2013 Version 3: 18 September 2013 Version 4: 23 July 2014
DATE AMENDED:	Version 5: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	20-Apr-2015 14:50:42

CONFIDENTIAL STATEMENT

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol YO28390 has been amended for the following reasons:

- Safety information for vemurafenib (Zelboraf®) has been updated to include:

  New risk of progression of a preexisting RAS-mutated pancreatic adenocarcinoma (see Section 1.5.3.9.1)

  Information on pancreatitis reported with vemurafenib use (see Section 1.5.3.9.5), as well as recommended assessment for any suspected case of pancreatitis during study (see Section 4.5.1.7)

  Information on potentiation of radiation treatment toxicity reported with Vemurafenib use (see Section 1.5.3.9.6)

  Some other safety information updates according to IB version 12 (see Section 1.5.3.2)

- To improve clarity, sequence of subheadings have been adjusted (see Section 1.5.3.2), and some new subheadings have been added as appropriate (see Sections 1.5.3.4, 1.5.3.6, and 1.5.3.9).
- References have been updated as appropriate (Section 10).

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

PROTOCOL AMENDMENT, VERSION 5:
SUMMARY OF CHANGES

GLOBAL CHANGES

Section 1.5.3.8 (Deaths and Serious Adverse Events) was moved to Section 1.5.3.2 and subsequent sections were renumbered accordingly.

SECTION 1.5.3.2: Deaths and Serious Adverse Events

Deaths

Across all studies, the majority of deaths were attributed to progressive disease (PD). In the pivotal, Phase III Study NO25026, 19% of patients died in the vemurafenib group and 34% in the DTIC group. No patient died after crossing over from the DTIC group to the vemurafenib group. In ~~Studies~~ *Study* NP22657*,* ~~and NP25163,~~ 39% ~~and 25%~~ of patients *had* died *as of the 31 January 2011 clinical cutoff date. In Study NP25163, 48% (n =25) of patients died as of the end of the study*.

Serious Adverse Events

In Study NP22657, 53% of patients experienced one or more serious adverse events, and 37% experienced one or more treatment-related serious adverse events. The most common treatment-related serious adverse events included SCC of the skin (23%), BCC (7%), KA (3%), elevated liver function tests (2%), rash (2%), pyrexia (2%), and arthralgia (2%). In Study NP25163, *40*~~33~~% of patients experienced one or more serious adverse events, and 2*9*~~3~~% experienced one or more treatment-related serious adverse events. The most common treatment-related SAE was cuSCC (1*3*~~9~~%).

For a more detailed summary of deaths and serious adverse events, see the Vemurafenib IB, Section *5.5.4 and 5.5.5*~~5.1.3~~.

SECTION *1.5.3.4: New Primary Melanomas*

Eight skin lesions in 7 of 337 vemurafenib-treated patients were reported as new primary malignant melanomas in Study NO25026. No cases were reported in ~~338~~ *287* patients treated with DTIC. Cases were managed with excision and without sequelae, and patients continued treatment without dose adjustment.

SECTION 1.5.3.5: Non-Cutaneous Squamous Cell Carcinoma

Two cases of SCC of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled in a clinical trial. Pathology exam of both tumors (one a primary tonsillar tumor, the other a primary tongue tumor) revealed the presence of invasive SCC. Of note, the first patient's medical history was significant for risk factors for head and neck cancer and the tumor tissue tested positive for human papilloma virus (HPV). The second patient does not appear to possess any risk factors for head and neck cancer, and the preliminary examination of the tumor tissue did not reveal the presence of HPV genome. Full details are provided in the current IB.

~~Five cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for more than 2 years while enrolled in a clinical trial (Chapman et al. 2012). The first patient developed an upper gastrointestinal bleed, and on work-up was found to have duodenal ulceration (non-malignant), hyperplastic gastric polyps, and five colonic polyps (three of which were adenomatous). A previous colonoscopy in 2008, at the time of a jejunal resection for recurrent melanoma, documented no prior evidence of colonic polyps. All polyps were resected, and the patient subsequently resumed vemurafenib therapy. The second patient was found, on elective colonoscopy, to have seven colonic polyps (five of which were adenomatous), and all were detected and removed. This patient had not undergone a previous colonoscopy. The patient has discontinued treatment with vemurafenib. The third patient had, on elective colonoscopy, 10 colonic polyps (seven of which were adenomatous). This patient had a previous colonoscopy 7 years prior to starting vemurafenib. The fourth patient had, on elective colonoscopy, one adenomatous colonic polyp. The fifth patient had, on elective colonoscopy, three adenomatous colonic polyps. The latter two patients had histories of no prior colonoscopy. In addition, a patient on the Expanded Access Program had one colonic adenoma discovered after being on vemurafenib 0.57 years. This patient had a colonoscopy 1.3 years prior to starting vemurafenib, and a polyp was found and resected at that time.~~

SECTION *1.5.3.6*: *Adenomatous Colonic Polyps*

Five cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for more than 2 years while enrolled in a clinical trial (Chapman et al. 2012). The first patient developed an upper gastrointestinal bleed, and on work-up was found to have duodenal ulceration (non-malignant), hyperplastic gastric polyps, and five colonic polyps (three of which were adenomatous). A previous colonoscopy in 2008, at the time of a jejunal resection for recurrent melanoma, documented no prior evidence of colonic polyps. All polyps were resected, and the patient subsequently resumed vemurafenib therapy. The second patient was found, on elective colonoscopy, to have seven colonic polyps (five of which were adenomatous), and all were detected and removed. This patient had not undergone a previous colonoscopy. The patient has discontinued treatment with vemurafenib. The third patient had, on elective colonoscopy, 10 colonic polyps (seven of which were adenomatous). This patient had a previous colonoscopy 7 years prior to starting vemurafenib. The fourth patient had, on elective colonoscopy, one adenomatous colonic polyp. The fifth patient had, on elective colonoscopy, three adenomatous colonic polyps. The latter two patients had histories of no prior colonoscopy. In addition, a patient on the Expanded Access Program had one colonic adenoma discovered after being on vemurafenib 0.57 years. This patient had a colonoscopy 1.3 years prior to starting vemurafenib, and a polyp was found and resected at that time.

SECTION 1.5.3.9: Post-Approval Safety Update

1.5.3.9.1 Progression of Existing Malignancy

One case of progression of NRAS-mutated chronic myelomonocytic leukemia (CMML) occurred in a male patient with metastatic melanoma treated with vemurafenib for less than 2 weeks (Callahan et al. 2012). After the first dose of vemurafenib, laboratory results showed a marked leucoytosis and monocytosis and vemurafenib treatment was subsequently held. 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 a BRAF inhibitor, an effect that was reversed upon addition of a MEK inhibitor. Further, the cells exhibited dose-dependent and reversible activation of ERK in the NRAS-mutated leukemic clone. *A second case of progression of a preexisting RAS-mutated malignancy (pancreatic adenocarcinoma with KRAS mutation) was reported with vemurafenib in 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 or concurrent cancer associated with RAS mutation. Full details are provided in the current Vemurafenib IB.

1.5.3.9.2 Drug Reaction with Eosinophilia and Systemic Symptom (DRESS)

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

1.5.3.9.3 Liver Injury

An analysis of liver–related adverse events reported with vemurafenib use showed that 63 cases (out of an estimated exposure of approximately 20,000 patients) of medically confirmed serious adverse events were consistent with drug–induced liver injury (DILI) based on clinical chemistry criteria from the DILI Expert Working Group (Aithal et al. 2011). Of the 63 cases, two were assessed as severe, both reported as hepatic failure. There were no reported deaths among the 63 cases of liver injury; the outcome of both cases of severe liver injury was reported as completely resolved with vemurafenib discontinuation. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to ALP ratio was calculated as 1.5, which suggested a trend toward a cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

1.5.39.4 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 factors (G-CSF).

1.5.3.9.5 Pancreatitis

As of Q2 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 et al. 1995).

1.5.3.9.6 Risk of Radiation Recall and Radiation Sensitization

As of Q4 2014, an adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. This is based on 20 cases of radiation injuries, adjudicated as radiation recall (n =8) and radiation sensitization (n =12). The nature and severity of the events in all 20 cases were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation with fatal outcome in 3 cases. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Full details are provided in the current Vemurafenib IB.

1.5.3.9.7 Safety 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. Based on these data, concurrent administration of ipilimumab and vemurafenib is not recommended outside of a clinical trial. Full details are provided in the current Vemurafenib IB.

SECTION 4.5.1.7: Laboratory Assessments

The Sponsor (Roche) 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).

TABLE 5: Dose Interruption/Modification Criteria for Vemurafenib

"No dose reduction" was changed to "N/A" for Dose adjustments for resumption of treatment for Grade 1 and tolerable Grade 2 toxicities.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: **A PHASE I OPEN-LABEL, MULTICENTER, MULTIPLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF VEMURAFENIB IN CHINESE PATIENTS WITH BRAF^{V600} MUTATION-POSITIVE UNRESECTABLE OR METASTATIC MELANOMA**

PROTOCOL NUMBER: YO28390 **VERSION NUMBER:** 5

TEST PRODUCT: Vemurafenib (RO5185426)

MEDICAL MONITOR: [redacted]

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 I OPEN-LABEL, MULTICENTER, MULTIPLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF VEMURAFENIB IN CHINESE PATIENTS WITH BRAF^{V600} MUTATION-POSITIVE UNRESECTABLE OR METASTATIC MELANOMA**		
PROTOCOL NUMBER:	YO28390	**VERSION NUMBER:**	5
TEST PRODUCT:	Vemurafenib (RO5185426)		
PHASE:	I		
INDICATION:	BRAF^{V600} mutation-positive unresectable or metastatic melanoma		
SPONSOR:	F. Hoffmann-La Roche Ltd		

Objectives

Primary Objective

The pharmacokinetic (PK) objective for this study is to evaluate the pharmacokinetics of vemurafenib following 960 mg twice daily (BID) oral administration (PO) in Chinese patients with BRAF^{V600} mutation–positive unresectable or metastatic melanoma.

This is the primary objective of this study.

Secondary Objectives

The efficacy objective for this study is to describe the efficacy of vemurafenib by using best overall response rate (BORR; confirmed), duration of response, progression-free survival (PFS), and overall survival (OS) in Chinese patients with BRAF^{V600} mutation-positive unresectable or metastatic melanoma.

The safety objective for this study is to investigate the safety and tolerability of vemurafenib in Chinese patients with BRAF^{V600} mutation-positive unresectable or metastatic melanoma.

Study Design

Description of Study

This is an open-label, multicenter, Phase I study with a PK cohort and an expansion cohort. Only patients who test positive for the BRAF^{V600} mutation as determined by the cobas® 4800 BRAF^{V600} Mutation Test will be allowed to participate in this study.

Approximately 20 patients will be enrolled in the PK cohort. The dosing regimens in different periods are described as follows:

- **Period A**: Following a screening period of up to 28 days, approximately 20 patients will be enrolled into the study for PK assessment. Patients will receive 960 mg BID PO on Days 1 to 20, and on Day 21, patients will only receive their morning dose. All patients will provide blood samples on Days 1, 15, 19, and 21 for PK analysis as described in Appendix 2.
- **Period B**: Begins with Day 22 and lasts until Day 27. Study drug will be held for the purpose of characterizing the elimination profile of vemurafenib. All patients will provide blood samples on Days 22 and 24 for PK analysis as described in Appendix 2.
- **Period C**: After a pre-dose PK sample collection, starting on Day 28, all patients may resume vemurafenib 960 mg BID until the development of progressive disease (PD), unacceptable toxicity, withdrawal of consent, or other any criteria as listed in Section 4.6.

- **Follow-up period**: All adverse events (related and unrelated to study drug) occurring at any time during Periods A, B, or C up to 28 days after the last dose of study medication in Period C must be reported; drug-related adverse events must be followed until resolution. All patients who received at least one dose of vemurafenib will be followed for squamous cell carcinoma (SCC) and any new primary malignancy evaluation until 6 months after discontinuation of study treatment or death, withdrawal of consent, or loss to follow up, whichever is earlier.

After recruitment of the PK cohort is complete, approximately 25 additional Chinese patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma will be recruited into the expansion cohort.

Following a screening period of up to 28 days, all eligible patients will complete the assessments on Day 1 (see Appendix 1) as their baseline and will receive vemurafenib 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent, or any other criteria as listed in Section 4.6.

The follow-up procedures for patients in the expansion cohort are the same as for those in the PK cohort.

Number of Patients

Approximately 45 Chinese patients will be recruited into this study.

Target Population

Patients must meet the following criteria for study entry:

- Chinese male or female patients $\geq$ 18 years of age
- Histologically confirmed metastatic melanoma (surgically unresectable Stage IIIc or Stage IV, American Joint Committee on Cancer). Unresectable Stage IIIc disease must have confirmation from a surgical oncologist.
- Patients are either treatment-naïve or had received prior systemic treatments for metastatic melanoma.
- Positive $BRAF^{V600}$ mutation result determined by a designated laboratory using the cobas 4800 $BRAF^{V600}$ Mutation Test prior to administration of vemurafenib.
- Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 prior to the administration of vemurafenib
- Previous allowed chemotherapy, immunotherapy, or radiation therapy must have been completed at least 2 weeks prior to study drug administration, and all associated toxicity must be resolved (to $\leq$ Grade 1 or baseline) prior to study drug administration.
- Recovery from effects of any major surgery (excluding tumor biopsy at baseline) or significant traumatic injury at least 14 days before the first dose of study treatment
- Adequate hematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing.
  - Absolute neutrophil count $\geq$ 1.5 x 10^9/L
  - Platelet count $\geq 100 \times 10^9$/L
  - Hemoglobin $\geq$ 9 g/dL
  - Serum creatinine $\leq 1.5 \times$ the upper limit of normal (ULN) or creatinine clearance $>$ 60 mL/min by Cockroft-Gault formula
  - AST and ALT $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for patients with concurrent liver metastases)
  - Bilirubin $\leq 1.5 \times$ ULN (for patients with Gilbert's Syndrome, bilirubin $\leq 3 \times$ ULN)
  - Alkaline phosphatase $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for patients with concurrent liver metastases)
  - Albumin $\geq$ 3 g/dL

- Negative serum or urine pregnancy test within 7 days prior to commencement of dosing in pre-menopausal women. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year.
- Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician (in accordance with local requirements).
- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.
- Eastern Clinical Oncology Group Performance Status of 0 or 1
- Life expectancy > 3 months
- Be able to swallow pills

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

- Patients with active CNS lesions are excluded (i.e., those with radiographically unstable, symptomatic lesions). Note: Patients treated with stereotactic therapy or surgery are eligible if they remain without evidence of disease progression in brain for ≥ 3 months. They must also be off corticosteroid and anticonvulsant therapy for ≥ 3 weeks. Whole brain radiotherapy is not allowed with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions.
- History of or known spinal cord compression or carcinomatous meningitis
- Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study
- Active SCC that has not been excised or has not yet adequately healed post excision
- Pregnant or lactating women
- Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate vemurafenib absorption
- QTc interval ≥ 450 ms at screening ECG or history of congenital long QT syndrome
- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 Grade 3 hemorrhage within 28 days of starting the study treatment
- Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism.
- Known clinically significant active infection
- History of allogeneic bone marrow transplantation or organ transplantation
- Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study
- Patients with previous malignancy within the past 5 years are excluded other than adequately treated patients with basal cell carcinoma or SCC of the skin, melanoma in-situ, and carcinoma in-situ of the cervix and/or curatively treated cancer, from which the patient is currently disease-free, or any malignancy from which the patient has been continuously disease-free for at least 5 years. Isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer is allowed.
- Patients who have been previously treated with a BRAF inhibitor (sorafenib allowed) or MEK inhibitor
- Patients who have had at least one dose of study drug (vemurafenib) in a previous clinical trial that includes vemurafenib

- Known HIV positivity or AIDS-related illness, or hepatitis B virus or hepatitis C virus carriers (hepatitis B surface antigen positive, HCV antibody positive)
- Received any investigational treatment within 4 weeks of study drug start

Length of Study

Patient recruitment is estimated to require approximately 22 months. The data cutoff for updated analysis will occur when all patients included in the PK and expansion cohorts have completed at least 6 months of treatment (or discontinued treatment) or when > 70% of treated patients have experienced disease progression by RECIST v1.1 or death, whichever occurs later. It is expected to occur about 12 months after the first patient is enrolled.

End of Study

Patients still receiving vemurafenib at the time of updated analysis will be allowed to continue treatment until PD, unacceptable toxicity, death, loss to follow-up, or withdrawal of consent.

The study will end when the last patient has permanently discontinued treatment with vemurafenib and has completed the 6-month follow-up period for safety assessment.

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum plasma concentration (C_{max}) on Days 1 and 21
- Time to maximal plasma concentration (T_{max}) on Days 1 and 21
- Area under the plasma – concentration time curve (AUC) from time 0 to 8 hours (AUC_{0-8h}) on Days 1 and 21
- AUC from time 0 to 12 hours (AUC_{0-12h} or AUC_{τ}) on Days 1 and 21
- AUC from time 0 to 168 hours (AUC_{0-168h}) beginning on Day 21
- Minimum plasma concentration (C_{min}) on Days 15, 19, and 21
- Accumulation ratio (the AUC ratio on Day 21/Day 1)
- Elimination rate constant (K_{el})
- Half-life ($t_{1/2}$)

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- BORR (confirmed)
- Duration of response
- PFS
- OS

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to NCI CTCAE v4.0
- Changes in vital signs
- Changes in clinical laboratory test results
- ECG assessments
- Dermatology evaluations for cutaneous SCC (cuSCC) surveillance
- Head, neck, anus, anal canal, and pelvic (for female patients) evaluations and computed tomography scans for non-cuSCC surveillance

Investigational Medicinal Products

Test Product

Each box of study medication contains a total of 56 film-coated tablets in aluminum blisters that are 240 mg each.

Vemurafenib tablets should be swallowed whole with a glass of water (approximately 240 mL). Vemurafenib tablets should not be chewed or crushed.

PK cohort: In Period A, patients will receive 960 mg BID PO for Days 1–20, and on Day 21, patients will receive only the morning dose. Patients will discontinue vemurafenib starting with the evening dose on Day 21.

Vemurafenib may be taken either 1 hour before or 2 hours after a meal, except on Days 1 and 21. On Days 1 and 21, patients should fast overnight for at least 8 hours before the morning dose, and continue to fast for an additional 4 hours post-dose. Patients should plan on a standard meal at 4 hours post-dose, but are allowed to have light snacks (i.e., crackers, toast, juice, and water) within the 4-hour period.

There is no study drug administration in Period B.

In Period C starting on Day 28, all patients will receive the study drug at 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent or any other criteria as listed in Section 4.6.

Expansion cohort: All patients will receive vemurafenib 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent, or any other criterion as listed in Section 4.6.

On the days of BID dosing (except Day 1 in the PK cohort), patients should be instructed to take 4 tablets in the morning and 4 tablets in the evening (total daily dose of 1920 mg [960 mg BID]) approximately 12 hours later. Both doses should be taken either 1 hour before or 2 hours after a meal.

Patients will be given a dosing diary to record the time and date of study drug administration. Administration dates and times will be recorded in the electronic Case Report Form (eCRF) by the study coordinators.

A cycle is defined as 4 weeks (28 days). A 4-week supply (Cycles 1–10) or 8-week supply (starting from Cycle 11) of study drug can be given to the patient on Day 1 of each or every other cycle. Patients will be instructed not to open a new box until the previous box has been finished and to bring their study drug and used boxes back to all clinic visits for reconciliation.

Non-Investigational Medicinal Products

Female patients of child-bearing potential who are using oral contraceptives, hormone replacement therapy, or other maintenance therapy will be asked to continue their use.

Patients taking prescribed therapies for intercurrent illnesses, or consistently dosed nutritional or herbal medicines (other than anti-cancer treatments) at the time of study entry should continue to take their medicines unless asked by the Investigator to discontinue or modify them.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the Investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drug. Hematopoietic growth factors (e.g., erythropoietin and granulocyte colony-stimulating factors) and pain medications as dictated by standard practice are acceptable while the patient is enrolled in the study. However, growth factors should not be administered prophylactically before initial treatment with study drug.

Patients who experience adverse events during the study may be treated symptomatically by the investigator as clinically indicated.

Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded on eCRF including the date, indication, description of the procedure(s), and any clinical findings.

Statistical Methods

Primary Analysis

The primary objective of the study is to evaluate the pharmacokinetics of vemurafenib following 960 mg BID oral administration in Chinese patients with BRAFV600 mutation–positive unresectable or metastatic melanoma.

For the purposes of statistical analysis, the PK population will include all patients evaluable for PK analysis, i.e., patients who provided sufficient PK data to obtain at least one of the primary PK variables. Patients will be excluded from the PK analysis if they significantly violate the inclusion or exclusion criteria, deviate significantly from sampling times or other provisions of the protocol, or if data are unavailable which may influence the analysis.

Plasma concentration on Day 1 and steady state will be listed and graphically displayed for vemurafenib.

Non-compartmental analysis using WinNonlin software will be used to obtain PK parameters of vemurafenib. All PK parameters for vemurafenib will be presented by listings and descriptive summary statistics (arithmetic mean, geometric mean, standard deviation, coefficient of variation, minimum, maximum and number of observations). Rate of elimination may be estimated using data from PK samples collected during the drug holiday period.

The following PK parameters will be reported:

- C_{max} on Days 1 and 21
- T_{max} on Days 1 and 21
- $AUC_{0\text{-}8h}$ on Days 1 and 21
- $AUC_{0\text{-}12h}$ on Days 1 and 21
- $AUC_{0\text{-}168h}$ beginning on Day 21
- C_{min} on Days 15, 19, and 21
- Accumulation Ratio
- K_{el}
- $t_{1/2}$

Determination of Sample Size

No formal sample size calculation was performed for this study. The sample size of 20 PK patients is chosen to allow acceptable variability of the PK data. Together with extra 25 patients in the expansion cohort, it would give a Clopper-Pearson 95% CI of 26%–56% for BORR assuming the target BORR (confirmed) is 40%.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AUC	area under the plasma concentration–time curve
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
BCC	basal cell carcinoma
BID	twice daily
BML	below measurable limit
BORR	best overall response rate
CFDA	China Food and Drug Administration
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximal plasma concentration
C_{min}	minimal plasma concentration
CMML	chronic myelomonocytic leukemia
CRC	colorectal cancer
CT	computerized tomography
cuSCC	cutaneous squamous cell carcinoma
CV%	coefficient of variation
DILI	drug–induced liver injury
DLT	dose-limiting toxicity
DRESS	drug reaction with eosinophilia and systemic symptoms
DTIC	dacarbazine
EC	Ethics Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factors
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol

Abbreviation	Definition
hERG	human ether-a-go-go gene
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
ILS	increase in lifespan
IMP	Investigational Medicinal Product
IND	Investigational new drug
IRC	Institutional Review Committee
IV	intravenous
KA	keratoacanthomas
KM	Kaplan Meier
K_{el}	elimination rate constant
LDH	lactate dehydrogenase
LDL-C	low density lipoprotein cholesterol
MBP	micro-precipitated bulk powder
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
OS	overall survival
PD	progressive disease
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCC	squamous cell carcinoma
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
TGI	tumor growth inhibition
TK	toxicokinetic
t_{max}	time to maximal plasma concentration

Abbreviation	Definition
$t_{½}$	elimination half-life
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON METASTATIC MELANOMA

Metastatic melanoma is one of the most deadly cancers, with a 5-year survival rate of 15% and a median overall survival (OS) of around 8 months. Approximately 160,000 new cases of melanoma are diagnosed globally each year; it is more frequent in males and Caucasians (Ries et al. 2003). According to a World Health Organization report, approximately 48,000 melanoma-related deaths occur worldwide per year (Lucas 2006). The highest rates of melanoma occur in Australia and New Zealand, where the annual incidence is more than double the highest rates recorded in Europe. Currently, the lifetime risk for development of melanoma in Australia is 1 in 25 for men and 1 in 34 for women (SUNSMART 2007, Department of Health and Ageing 2008). In Europe, approximately 26,100 males and 33,300 females are diagnosed with melanoma annually, and approximately 8300 males and 7600 females die from the disease every year (European Network of Cancer Registries 2003). In the United States in 2007, more than 58,000 people (over 33,000 men and over 25,000 women) were diagnosed with melanoma and over 8400 (more than 5500 men and almost 3000 women) died of the disease (U.S. Centers for Disease Control and Prevention 2010). Over the past several decades, a significant increase in the incidence of melanoma has been observed. The annual increase in the incidence rate varies between regions throughout the world, but in general the increase in the Caucasian population has been approximately 3%–7% per year. The number of deaths due to malignant melanoma has also increased in most fair-skinned populations throughout the world in the past few decades (Diepgen and Mahler 2002).

Malignant melanoma demonstrates a clear demographic and ethnic disparity. In China, the incidence of melanoma is relatively lower (0.52 per 100,000 patients) than in the west (varies from 3–5 per 100,000 patients in Mediterranean countries to 40–60 per 100,000 patients in Australia and New Zealand) (Zhao et al. 2006, Garbe et al. 2009, Dummer et al. 2012); Stage III and IV patients comprise 25.1% and 12.8%, respectively (China Melanoma Guide 2011). For patients with Stage IV disease, median survival time was 1.42 years, and the 5-year survival rate was 4.6% (China Melanoma Guide 2011).

Many agents tested in advanced melanoma patients have shown little or no clinical benefit over the last 3 decades since the approval of recombinant human interleukin-2 and dacarbazine (DTIC). In China, DTIC is still considered the standard first-line treatment, despite the lack of any evidence for improving OS. Metastatic melanoma continues to challenge investigators as a disease with a high-unmet medical need. Hence, the use of investigational agents as either a first-line or second-line treatment is an accepted modality of treatment in the metastatic melanoma setting.

1.2 BACKGROUND ON ROLE OF ONCOGENIC BRAF KINASE IN MELANOMA

Recent advances in the understanding of the biology of melanoma have resulted in identifying the role of BRAF kinase in melanoma. Mutated BRAF dimers constitutively activate the RAF-MEK 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., in superficial spreading and nodular melanomas) (Beeram et al. 2005, Maldonado et al. 2003, Lang and Mackie 2005, Curtin et al. 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 and may drive melanoma oncogenesis. About 90% of the BRAF mutations seen in metastatic melanoma occur in codon V600 and over 90% of the V600 mutations are V600E (1799 T>A) (Sanger Institute). Other uncommon variants, such as V600K, V600R, and V600D (in order of decreasing frequency), have also been identified, primarily in melanoma.

Nonclinical data indicate that these variant mutations, like V600E, result in constitutive activation of the BRAF kinase. Most of the transforming activity of the $BRAF^{V600E}$ is thought to result through the constitutive activation of the mitogen-activated protein kinase pathway (Gray-Schopfer et al. 2007). The therapeutic relevance of BRAF is supported by the demonstration that depletion of mRNA for oncogenic BRAF by siRNA leads to growth inhibition of melanoma cell lines in vitro (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® $BRAF^{V600}$ mutation assay and Sanger Sequencing techniques have been utilized to identify $BRAF^{V600}$ mutation status in clinical trials.

1.3 VEMURAFENIB

Vemurafenib is a low molecular weight, orally available inhibitor of oncogenic BRAF kinase. The high level of selectivity of vemurafenib for the $BRAF^{V600}$ mutation as demonstrated in biochemical, cell-based, and in vivo assays is outlined in the sections below.

In August 2011, vemurafenib was approved in the United States for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation; in October 2011 and February 2012, vemurafenib was approved in Switzerland and the European Union, respectively, for the treatment of adult patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

See the Vemurafenib Investigator's Brochure (IB) for details on nonclinical and clinical studies.

1.4 NONCLINICAL DEVELOPMENT PROGRAM

1.4.1 Nonclinical Pharmacology

In vitro biochemical and cell-based assays show that vemurafenib displays selectivity against a broad range of kinases, including the V600E oncogenic BRAF kinase (see Table 1).

Table 1 IC_{50} Values (nM) of Vemurafenib against Selected Kinases

Kinase	V600E BRAF	WT BRAF	RAF1	PTK6	KIT	KDR
Vemurafenib (nM)	44	110	44	240	610	5300

IC_{50} = half-maximal inhibitory concentration.

As shown in Table 2, cell lines bearing BRAF mutations are selectively sensitive to inhibition by vemurafenib.

Table 2 Inhibition of Proliferation: IC_{50} Values of Vemurafenib in a Variety of Cell Lines

Cell Line:	A375	WM2664	COLO829	COLO205	SKMel2	SW620	H1299
Tumor:	Melanoma	Melanoma	Melanoma	Colorectal	Melanoma	Colorectal	NSCLC
Oncogene:	$BRAF^{V600E}$	$BRAF^{V600D}$	$BRAF^{V600E}$	$BRAF^{V600E}$	NRAS	KRAS	KRAS
IC_{50} (μM):	0.55	0.42	0.08	0.04	9.2	6.5	13

IC_{50} = half-maximal inhibitory concentration; NSCLC = non-small cell lung cancer.

In vivo activity for vemurafenib was assessed in a mouse xenograft study in which HT29 cells were implanted into the right lateral flank of female athymic NCr nu/nu mice. Treatment with vemurafenib demonstrated dose-dependent tumor growth inhibition (TGI) at doses of 25 mg/kg, 50 mg/kg, and 75 mg/kg twice daily (BID), and the TGI of vemurafenib at doses of 75 mg/kg and 100 mg/kg BID was equivalent. Similarly, there was a dose-dependent increase in life span (ILS) with vemurafenib at doses of 25 mg/kg, 50 mg/kg, and 75 mg/kg BID, with an equivalent ILS at doses of 75 mg/kg and 100 mg/kg BID. Vemurafenib at all doses significantly improved survival versus vehicle. This benefit was biologically significant according to National Cancer Institute (NCI) criteria (>25% ILS). Pharmacokinetic (PK) measurements at the end of the dosing period indicated that the dose-response relationship in efficacy correlates with the drug exposures, and the efficacy observed with the lowest dose of 25 mg/kg BID of vemurafenib occurs at an area under the plasma–concentration time curve (AUC) of 1250 μM•h (Data Package 2006).

Please refer to the Vemurafenib IB for a detailed description of the nonclinical pharmacology data.

1.4.2 Nonclinical Metabolism and Pharmacokinetics

A series of in vitro and in vivo studies have been conducted with vemurafenib to assess nonclinical pharmacokinetics and metabolism (Flaherty et al. 2010, Kopetz et al. 2010). The single-dose pharmacokinetics of vemurafenib were evaluated in the mouse, rat, dog, and monkey. Multiple-dose pharmacokinetics were assessed during general toxicity and toxicokinetic (TK) studies in rats and beagle dogs. The metabolic disposition and drug–drug interaction potential of vemurafenib were investigated in various in vitro systems.

The volume of distribution was modest and clearance was low in both rats and dogs following intravenous (IV) injection (Flaherty et al. 2010, Kopetz et al. 2010). Vemurafenib was absorbed and widely distributed to tissues, and mainly eliminated via biliary excretion in rats. Drug levels in the rat CNS were undetectable following a single oral dose of 100 mg/kg of vemurafenib.

Data demonstrate that in vitro protein binding of vemurafenib is high (>99%). In vitro evaluation using hepatocytes from multiple species suggested minimal metabolism of vemurafenib by human, dog, and monkey hepatocytes. Vemurafenib is not an inhibitor and/or an irreversible inactivator of CYP3A4/5 in vitro. Inhibition of CYP2C9 is observed in vitro (half-maximal inhibitory concentration [IC_{50}] ~6 µM), indicating a potential for interactions with drugs mainly eliminated by the enzyme. CYP enzyme activity is not induced in the in vitro human hepatocyte induction assay. Vemurafenib is a weak substrate of P-glycoprotein (P-gp) and is a P-gp inhibitor. Thus, vemurafenib may have potential for P-gp mediated drug – drug interactions when co-administered with other P-gp substrates.

1.4.3 Nonclinical Toxicology and Safety Pharmacology

The toxicology of vemurafenib was evaluated in single-dose and a series of repeat-dose toxicity and TK studies for up to 26 weeks in Sprague-Dawley rats and 13 weeks in beagle dogs (oral gavage administration once daily). A corn oil formulation of vemurafenib was used for single-dose toxicology, 28-day repeat-dose toxicology, and safety pharmacology studies. Due to limited systemic exposures with the corn oil formulation, a new formulation developed for nonclinical and clinical studies, hereafter referred to as micro-precipitated bulk powder (MBP) formulation, achieved higher systemic exposures for the 13- and 26-week repeat-dose toxicology studies, the in vivo micronucleus assay, and reproductive and developmental toxicology studies. Refer to the Vemurafenib IB for a more detailed description of the nonclinical toxicology and safety pharmacology studies.

Repeat-Dose Toxicity:

In rats given vemurafenib in the corn oil formulation for 28 days, higher cholesterol levels and slightly higher heart weights were observed in the 1000 mg/kg/day group, and minimal to moderate microscopic lymphangiectasis (dilated lymphatic vessels) in the

jejunum was seen in the 100 mg/kg/day and 1000 mg/kg/day groups. These findings were not considered adverse, as there was no overall impact on animal health. Importantly, the ame findings were not observed in rats that received vemurafenib in the MBP formulation for 26 weeks. Systemic exposures achieved in rats were greater with the MBP formulation than the corn oil formulation. The no observed adverse effect level (NOAEL) for rats was 450 mg/kg/day (MBP formulation) for 26 weeks ($AUC_{0–24h}$ = 2602 μM • h), the highest dose levels examined.

In dogs, once daily vemurafenib doses up to 450 mg/kg/day in the MBP formulation for 13 weeks were well tolerated with no treatment-related adverse findings up to the NOAEL of 450 mg/kg/day, which was the highest dose level tested. However, the systemic vemurafenib exposures achieved in dogs at the highest dose level (mean UC_{0-24h} = 825 μM • h) were below the mean steady-state exposure in patients receiving 960 mg BID in the ongoing Phase I study (mean AUC_{0-24h} = 1795 μM • h).

A 39-week chronic toxicity study was initiated using the same MBP formulation with increased dosing frequency (BID) to aid in establishing the maximum tolerated dose (MTD) and to characterize potential target organ toxicity in dogs at exposures approaching those achieved in patients in the ongoing Phase I clinical trial. This 39-week toxicity study was prematurely terminated because the dogs were not able to tolerate the highest vemurafenib dose levels (300 mg/kg and 450 mg/kg BID or 600 mg/kg/day and 900 mg/kg/day). The exposures achieved at these dose levels (mean AUC_{0-24h} = 1195 and 1295 μM • h for 600 mg/kg/day and 900 mg/kg/day, respectively) were still below the steady-state exposures observed in patients given 960 mg BID (mean AUC_{0-24h} = 1795 μM • h). Two moribund dogs (1 male and 1 female) in the high-dose group were euthanized due to intolerable clinical signs (emesis, significant reduction in food intake, body weight loss, hypoactivity, elevated body temperature, and dehydration) even after study drug interruption and preventive measures (i.e., canned food and subcutaneous fluid) failed to produce improvement.

Histopathologic examination of tissues from the two euthanized dogs revealed treatment-related adverse findings of hepatotoxicity (2 dogs), which correlated with elevations in liver enzymes, and focal bone marrow necrosis only in the sternum but not in the femur or in the spleen (1 dog) without hematological changes. No changes in cartilages or growth plates in bones were observed. No treatment-related adverse findings were observed in the rest of the tissues in these two moribund euthanized dogs. Overall, these findings suggest that dogs are more sensitive to the adverse effects of vemurafenib than humans. A new 13-week repeat-dose BID toxicology and TK study in dogs with a 4-week interim necropsy and a 4-week recovery period has been initiated to investigate the extent, progression, and the reversibility of the observed findings (Vemurafenib IB).

Genotoxicity:

No signs of genotoxicity were identified in a standard battery of tests (in vitro Ames, chromosome aberration, and in vivo micronucleus assays) conducted with vemurafenib.

Reproductive and Developmental Toxicity:

In rats, no adverse effects were observed in maternal or fetal generations treated with vemurafenib doses up to 250 mg/kg/day. The NOAEL for embryo/fetal development toxicity in rats was 250 mg/kg/day ($AUC_{0\text{-}24h} = 3245$ µM • h), the highest dose examined (Roche Reference No. 10482 2008).

In rabbits, maternal toxicities (reduced food consumption and decreased body weight gain) were observed at 450 mg/kg/day, but there was no evidence of embryofetal toxicity, or any evidence of teratogenicity. The NOAEL for embryo-fetal development toxicity in rabbits was 450 mg/kg/day ($AUC_{0\text{-}24h} = 1376$ µM • hr), the highest dose examined (Roche Reference No. 10483 2008).

Safety Pharmacology:

A series of in vitro and in vivo experiments have been performed to evaluate potential effects of vemurafenib on the cardiovascular system. The results of these studies can be summarized as follows:

- Vemurafenib did not inhibit the human ether-a-go-go-related gene (hERG) (IKr) channel in a rubidium flux hERG screen up to the maximum soluble concentration of 25 µM and was inactive against the hERG (IKr) channel in the 63 panel receptor screen at 10 µM.
- In a Good Laboratory Practice (GLP) patch clamp assay, the IC_{50} for inhibition of the hERG channel in serum-free conditions was 1.24 µM. This value is approximately 120-fold higher than the IC_{50} for the target inhibition (pERK).
- A GLP Purkinje cell assay was negative, with no effects on conduction at vemurafenib concentrations up to 8 µM.

In an ECG radiotelemetry study in dogs, a single oral administration of vemurafenib at doses up to 1000 mg/kg (estimated $C_{max} = 42$ µM, ≤ 1-fold to efficacious maximal plasma concentration [C_{max}; 85 µM] in patients) resulted in no significant effects on heart rate, arterial blood pressure, body temperature, or ECG parameters. Furthermore, all ECGs were qualitatively and quantitatively within normal limits in dogs given up to 450 mg/kg/day (maximum feasible dose in the MBP formulation) in the 13-week repeat-dose toxicity study (up to steady-state $C_{max} = 91$ µM).

No adverse effects were observed after single oral dose administration of vemurafenib up to 1000 mg/kg (estimated $C_{max} = 160$ µM, 2-fold to efficacious C_{max} in patients treated 720 mg to 960 mg BID) in rats in the CNS and respiratory safety pharmacology studies.

Phototoxicity:

Vemurafenib absorbs ultraviolet (UV) light significantly between 240 nm and 450 nm. Therefore, vemurafenib was assessed for possible phototoxic potential in vitro by the 3T3 fibroblast Neutral Red uptake assay. Vemurafenib was shown to be phototoxic in vitro on cultured murine fibroblasts after UVA irradiation. However, vemurafenib did not induce phototoxic skin reaction in an in vivo 7-day phototoxicity study in female hairless rats at dose levels up to 450 mg/kg (maximum feasible dose; predicted exposure ~1500 µM • h).

1.5 CLINICAL DEVELOPMENT PROGRAM

1.5.1 Description of Clinical Studies

1.5.1.1 Phase I Dose-Finding Study (PLX 06-02) and other Phase I Studies

The dose of vemurafenib was established in a multicenter, Phase I dose escalation study with a total of 55 patients, of whom 49 had a diagnosis of melanoma (Flaherty et al. 2010; Vemurafenib IB).

The pharmacokinetics of the marketed formulation has been evaluated in Phase I clinical pharmacology studies including a drug interaction study (Study NP22676; n = 20), a study to evaluate the pharmacokinetics of vemurafenib at 240 mg to 960 BID doses using the 240 mg MPB tablets (Study NP25163; n = 50), and a mass balance study (Study NP25158; n = 6).

1.5.1.2 Two Phase I Extension Cohorts

Once the recommended Phase II dose of 960 mg BID had been identified, a cohort of 32 additional patients with metastatic melanoma and prospectively identified $BRAF^{V600}$ mutations were enrolled in the extension phase of this study (Flaherty et al. 2010). A different cohort of 21 patients with metastatic colorectal cancer (CRC) and identified $BRAF^{V600}$ mutations were treated in the extension phase with the established dose of 960 mg BID (Kopetz et al. 2010). The primary objective of these extension cohorts was to determine clinical response rate. Secondary objectives were safety and additional PK and pharmacodynamic evaluations.

1.5.1.3 Phase II Single-Arm Study (NP22657/BRIM-2)

In this open-label, multicenter Phase II study, 132 patients were enrolled and treated with oral vemurafenib 960 mg BID, without scheduled dose interruption, until either progression of disease, unacceptable toxicity, withdrawal of consent, or any other reason as specified in the protocol (Sosman et al. 2012; Vemurafenib IB).

The primary objective of this study was to evaluate the efficacy of vemurafenib in previously treated metastatic melanoma patients with $BRAF^{V600E}$ mutation-positive status by the companion diagnostic using best overall response rate (BORR), as assessed by an independent review committee (IRC) using the Response Evaluation Criteria in Solid Tumors (RECIST, v1.1) guidelines for metastatic melanoma. Secondary objectives

included BORR assessed by the Investigator, duration of response, progression-free survival (PFS), OS, safety/toxicity, effect on QT interval, quality of life using Functional Assessment of Cancer Therapy-Melanoma (v4), validation of the cobas 4800 $BRAF^{V600}$ mutation test, and additional PK and pharmacodynamic parameters.

1.5.1.4 Phase III Randomized Controlled Study (NO25026/BRIM-3)

This randomized, open-label, multicenter Phase III study planned to enroll approximately 680 patients with treatment-naïve metastatic melanoma confirmed by histopathology (unresectable Stage IIIC or Stage IV) and identified $BRAF^{V600E}$ mutation by the companion diagnostic (Chapman et al. 2011; Vemurafenib IB). Patients were randomly assigned to be treated with either vemurafenib 960 mg orally (PO) BID every day or IV DTIC 1000 mg/m^2 on Day 1 every 3 weeks. OS and PFS were defined as co-primary endpoints (Study NO25026, protocol version C). The Data Safety and Monitoring Board Charter provided guidance outlining the statistical criteria that could enable crossover of patients from the DTIC arm to the vemurafenib arm based on the 50% OS interim analysis. Major secondary study objectives included comparisons of BORR, time to response, duration of response, time to treatment failure, and tolerability/safety. Further assessments of the PK profile of vemurafenib, validation of the cobas 4800 $BRAF^{V600}$ mutation test, evaluation of quality of life, and additional pharmacodynamic analyses were planned. See the Vemurafenib IB for more detailed information.

1.5.2 Clinical Pharmacokinetics of Vemurafenib

The pharmacokinetics of vemurafenib was first evaluated in study PLX06-02, the first-in-human dose ranging study that led to the selection of 960 mg orally administered BID dose as the recommended dose for further clinical development. During the course of PLX06-02 development, several vemurafenib formulations and dose strengths were evaluated. The 240-mg film-coated tablet of vemurafenib was subsequently selected as commercial formulation based on its pharmacokinetic properties, which were characterized in Study NP25163 at dose range of 240–960 mg BID in patients with BRAFV600 mutation–positive metastatic melanoma.

Studies NP25163, NP22657, NP22676, and NO25026 were conducted to characterize the pharmacokinetics of the 240 mg vemurafenib tablets at 960 mg BID, including marked accumulation after multiple doses and relative constant exposure throughout the dose interval at steady state. The time to steady state was formally evaluated in Study NP25163 using the individual based statistical approach, where 5 of 12 patients (41.6%) in the 960 mg BID cohort achieved steady state on Day 15, while the remaining patients reached 60%–80% of the projected steady-state exposure.

At steady state, daily fluctuations in the concentration–time profiles were small, with C_{max} values approximately 1.2-fold higher than pre-dose values. Minimum plasma concentration (C_{min}) vemurafenib concentrations averaged 53–60 µg/mL across studies and remained constant for patients continuing on the treatment regimen.
In Study NP22676, vemurafenib mean steady-state $AUC_{0\text{-}24h}$ exposure was

approximately 1200 µg • h/mL (~2400 µM • h), which is in the range of exposure required for tumor regression in the less sensitive xenograft model, HT29. In Study NP25163, vemurafenib was shown to be dose proportional over the dose range of 240, 480, 720, and 960 mg BID, with an overlap in the ranges of individual exposures between doses. A population PK analysis utilizing 458 patients from Studies NO25026, NP22657, and NP25163 estimated the half-life to be approximately 57 hours.

In all clinical studies and at all dose levels evaluated, vemurafenib exhibits relatively high inter-patient variability (coefficient of variation [CV%]) and wide range between minimum and maximum individual values (approximately 15- to 27-fold for $AUC_{0\text{-}8h}$ and 12- to 14-fold for C_{max}).

In Studies NP25163 and NP22657, the inter-patient variability (CV%) for both AUC and C_{max} was generally higher after the first dose (Day 1; range, 57.6%–69.9%) than after multiple doses (Day 15; range, 27.9%–38.4%). The reason for these differences is not known. The CV% values for trough (range, 32%–49%) and post-dose (range, 34%–43%) are consistent across studies. Vemurafenib trough and post-dose values in individual patients depend on dose modification throughout the course of the treatment. However, the inter-patient variability (CV%) and the width of the range of individual values are independent of dose reduction or treatment interruption. These results suggest that dose modification alone cannot explain the inter-patient variability in trough values observed in these studies. The impact of food intake at the time of measurement may have an impact on the variability of trough and post-dose measurements as food intake was not strictly controlled across all studies, particularly the Phase II and Phase III studies. At this time, no clear explanation is available to explain the inter-patient variability.

The relative proportions of vemurafenib and its metabolites were characterized in a mass balance study (NP25158) following oral administration of a single dose of ^{14}C-vemurafenib to melanoma patients. In this study, the majority of the parent molecule and metabolites were eliminated in the feces, accounting for an average of 94% of the input radioactivity (renal elimination accounted for $<1\%$ of the input radioactive dose, constituting a negligible elimination path for vemurafenib). The parent compound was the predominant component in all analyzed plasma samples with metabolites representing $<5\%$ of the total chromatographic radioactivity.

Over the first 96 hours, each metabolite accounted for $<0.5\%$ of the total administered dose in urine and $\leq 6\%$ of the total administered dose in feces. In the absence of absolute bioavailability, the fraction absorbed of the oral dose cannot be reliably estimated. Based on mass spectrometry, no new metabolites have been detected in plasma and feces in this study that have not been observed in in vitro studies with rat and human hepatocytes and in vivo studies in rats and dogs. The chemical structures of metabolites have not been identified.

For drug-drug interaction results, please see Section 4.4.3.

1.5.3 Safety

Vemurafenib has a manageable safety profile based on the adverse events (AE) observed across clinical trials. Treatment-related adverse events were noted to emerge within the first 1–2 months of initiation of treatment. Adverse events leading to dose modifications (interruption and/or dose reduction) occur in almost 40% of patients treated at 960 mg BID; however, the majority of these events are successfully managed by a treatment interruption interval of 1 week and/or a dose reduction to 720 mg BID. It was reported in the pivotal Phase III study NO25026 that 7% of adverse events reported resulted in treatment discontinuation.

The most frequently reported adverse events in vemurafenib-treated patients (≥ 30% patients) in the pivotal Phase III NO25026 study and pooled safety population (Phase I PLX06-02 and Phase II NP22657 studies and post approval safety study MO25515) were (preferred terms) arthralgia, rash, alopecia, fatigue, nausea, pruritus, diarrhea, skin papilloma, hyperkeratosis, and photosensitivity. The majority of these events were mild or moderate in intensity. Table 3 summarizes adverse drug reactions (ADRs) that occurred in at least 10% of patients treated with vemurafenib in either the Phase III NO25026 or Phase 2 NP22657 study. These events were considered ADRs based on their consistent occurrence across trials; differences in treatment duration and/or patient populations may be contributing factors to differences in the incidence of ADRs between studies.

Table 3 Summary of ADRs[1] Occurring in ≥10% of Patients in the Vemurafenib Treatment Arm

ADRs	Phase III Study: Treatment-Naive Patients						Phase II Study: Patients who Failed at least One Prior Systemic Therapy		
	Vemurafenib n=336			Dacarbazine n=287			Vemurafenib n=132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Skin and subcutaneous tissue disorders									
Rash	37	8	-	2	-	-	54	7	-
Photosensitivity reaction	33	3	-	4	-	-	52	3	-
Alopecia	45	<1	-	2	-	-	38	-	-
Pruritis	23	1	-	1	-	-	32	2	-
Hyperkeratosis	24	1	-	<1	-	-	30	-	-
Rash maculo-papular	9	2	-	<1	-	-	21	6	-
Actinic keratosis	8	-	-	3	-	-	17	-	-
Dry skin	19	-	-	1	-	-	19	-	-
Rash papular	5	<1	-	-	-	-	13	-	-
Erythema	14	-	-	2	-	-	10	-	-
Palmar-plantar erythrodysaesthesia síndrome	8	<1	-	1	-	-	10	2	-
Musculoskeletal and connective tissue disorders									
Arthralgia	53	3	-	3	<1	-	68	8	-
Myalgia	13	-	-	1	-	-	24	<1	-
Pain in extremity	18	<1	-	6	2	-	10	-	-
Musculoskeletal pain	8	<1	-	4	<1	-	12	-	-
Back pain	8	-	-	5	<1	-	11	<1	-
Arthritis	2	<1	-	-	-	-	10	2	-
General disorders and administration site conditions									
Fatigue	38	2	-	33	2	-	57	4	-
Oedema peripheral	17	<1	-	5	-	-	23	-	-
Pyrexia	19	<1	-	9	<1	-	19	2	-
Asthenia	11	<1	-	9	<1	-	2	-	-

Table 3 Summary of ADRs1 Occurring in ≥ 10% of Patients in the Vemurafenib Treatment Arm (cont.)

ADRs	Phase III Study: Treatment-Naive Patients						Phase II Study: Patients who Failed at least One Prior Systemic Therapy		
	Vemurafenib n=336			Dacarbazine n=287			Vemurafenib n=132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders									
Nausea	35	2	-	43	2	-	42	3	-
Diarrhoea	28	<1	-	13	<1	-	32	<1	-
Vomiting	18	1	-	26	1	-	28	2	-
Constipation	12	<1	-	24	-	-	17	-	-
Nervous system disorders									
Headache	23	<1	-	10	-	-	29	-	-
Dysgeusia	14	-	-	3	-	-	11	-	-
Neuropathy peripheral	2	-	-	<1	-	-	11	<1	-
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)									
Skin papilloma	21	<1	-	-	-	-	31	-	-
SCC of skin[2]	24	22	-	<1	<1	-	23	23	-
Seborrhoeic keratosis	10	<1	-	1	-	-	14	-	-
Investigations									
γ-glutamyltransferase increased	5	3	<1	1	-	-	15	6	4
Weight decreased	8	<1	-	2	-	-	10	<1	-
Metabolism and nutrition disorders									
Decreased appetite	18	-	-	8	<1	-	23	-	-
Respiratory, thoracic and mediastinal disorders									
Cough	8	-	-	7	-	-	15	-	-
Injury, poisoning and procedural complications									
Sunburn	10	-	-	-	-	-	14	-	-

Table 3 Summary of ADRs1 Occurring in ≥ 10% of Patients in the Vemurafenib Treatment Arm (cont.)

ADR = adverse drug reaction; incl. = including; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SCC = squamous cell carcinoma.

[1] ADRs reported using MedDRA and graded using NCI-CTCAE v 4.0 for assessment of toxicity.

[2] All cases of cutaneous SCC were to be reported as Grade 3 per instructions to study investigators, and no dose modification or interruption was required.

The following clinically relevant ADRs were reported in < 10% of patients in the vemurafenib-treated group in the Phase III and Phase II studies:

- Skin and subcutaneous tissue disorders: keratosis pilaris, panniculitis, erythema nodosum, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
- Nervous system disorders: dizziness, VIIth nerve paralysis
- Neoplasms benign, malignant and unspecified (includes cysts and polyps): basal cell carcinoma (BCC)
- Infections and infestations: folliculitis
- Eye disorders: retinal vein occlusion, uveitis
- Vascular disorders: vasculitis

Refer to the Vemurafenib IB for updated safety information.

1.5.3.1 Dose-Limiting Toxicities

Five patients experienced dose-limiting toxicities (DLTs) in Study PLX06-02 (1 patient at 720 mg BID; 4 patients at 1120 mg BID). One DLT, Grade 4 pancytopenia, was observed at 720 mg BID. Upon resolution of the pancytopenia after 9 days of study drug interruption, the patient was rechallenged with vemurafenib at a lower dose of 360 mg BID without recurrence of the pancytopenia. In the 1120 mg BID cohort, 4 of 6 patients developed protocol-defined, non–life-threatening DLTs (including Grade 3 rash with pruritus, fatigue, and/or arthralgia) that resolved with temporary drug interruption. All 4 patients were rechallenged at a lower dose of 720 mg BID and continued in the study. No occurrence of pancytopenia was observed in the 1120 mg BID dose cohort.

Approximately 40% of patients who received the MBP formulation had their vemurafenib dose interrupted and/or reduced because of an AE.

The majority of adverse events that led to dose interruption and/or reduction were of Grade 3 severity and included a broad range of events, most of which resolved with no sequelae.

1.5.3.2 *Deaths and Serious Adverse Events*

Deaths

Across all studies, the majority of deaths were attributed to progressive disease (PD). In the pivotal, Phase III Study NO25026, 19% of patients died in the vemurafenib group

and 34% in the DTIC group. No patient died after crossing over from the DTIC group to the vemurafenib group. In *Study* NP22657, 39% of patients *had* died *as of the 31 January 2011 clinical cutoff date. In Study NP25163, 48% (n =25) of patients died as of the end of the study.*

Serious Adverse Events

Across all three studies (NO25026, NP22657, and NP25163), the most commonly reported vemurafenib-related serious adverse event (SAE) was cuSCC. In Study NO25026, 42% and 18% of patients in the vemurafenib and DTIC groups, respectively, experienced one or more serious adverse event. Thirty-one percent and 5% of patients in the vemurafenib and DTIC groups, respectively, experienced one or more treatment-related serious adverse event.

The most common treatment-related serious adverse events in the vemurafenib group were cuSCC (17%) and KA (9%). All occurrences of cuSCC/KA were required to be reported as Grade 3 and serious. No other treatment-related serious adverse events occurred in > 1% of patients in either treatment group. Severe dermatologic reactions have been reported in patients receiving vemurafenib, including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. One notable treatment-related serious adverse events occurred in a vemurafenib-treated patient after the 1 March 2011 clinical cutoff date for safety. This patient developed toxic epidermal necrolysis. The event improved slightly after the patient was given treatment, but was not resolved at last report. The patient was discharged from the hospital and permanently discontinued treatment with vemurafenib.

Four of 37 DTIC patients (11%) who crossed over to receive vemurafenib experienced serious adverse events after the start of vemurafenib. These events included pyrexia, anemia, convulsion, lower respiratory tract infection, and cellulitis; only the episode of pyrexia was judged by the Investigator to be related to treatment.

The serious adverse events data at the 1 February 2012 cutoff date were generally consistent with data reported with the 1 March 2011 cutoff in study NO25026. Forty-seven percent (47%) of patients experienced serious adverse events in the vemurafenib group versus 18% of patients in the DTIC group, compared with 42% and 18%, respectively, at the 1 March 2011 cutoff. Although there were some increases in the incidence of serious adverse events that were reported, similar to the increases described for Grade ≥ 3 adverse events, there was no overall change in the types of adverse events that were reported.

In Study NP22657, 53% of patients experienced one or more serious adverse events, and 37% experienced one or more treatment-related serious adverse events. The most common treatment-related serious adverse events included SCC of the skin (23%), BCC (7%), KA (3%), elevated liver function tests (2%), rash (2%), pyrexia (2%), and arthralgia (2%). In Study NP25163, *40*% of patients experienced one or more serious adverse

events, and 29% experienced one or more treatment-related serious adverse events. The most common treatment-related SAE was cuSCC (13%).

For a more detailed summary of deaths and serious adverse events, see the Vemurafenib IB, Section *5.5.4 and 5.5.5*.

1.5.3.3 Cutaneous Squamous Cell Carcinoma

As of cutoff date for safety data of September 2, 2011, in Studies NO25026, NP22657, and NP25163, 79 (23.5%), 34 (25.8%), and 10 (19.2%) patients, respectively, developed cutaneous squamous cell carcinomas (SCC) and keratoacanthomas (cuSCC/KA). Most cuSCC cases were KAs: 58/79 (73.4%), 30/34 (88.2%), and 10/10 (100%) in Studies NO25026, NP22657, and NP25163, respectively.

1.5.3.4 *New Primary Melanomas*

Eight skin lesions in 7 of 337 vemurafenib-treated patients were reported as new primary malignant melanomas in Study NO25026. No cases were reported in *287* patients treated with DTIC. Cases were managed with excision and without sequelae, and patients continued treatment without dose adjustment.

1.5.3.5 Non-Cutaneous Squamous Cell Carcinoma

Two cases of SCC of the head and neck have been reported in 2 patients treated with vemurafenib in excess of 300 days while enrolled in a clinical trial. Pathology exam of both tumors (one a primary tonsillar tumor, the other a primary tongue tumor) revealed the presence of invasive SCC. Of note, the first patient's medical history was significant for risk factors for head and neck cancer and the tumor tissue tested positive for human papilloma virus (HPV). The second patient does not appear to possess any risk factors for head and neck cancer, and the preliminary examination of the tumor tissue did not reveal the presence of HPV genome. Full details are provided in the current IB.

Surveillance measures, including regular dermatologic and head and neck examinations and chest computed tomography (CT) scans, has been established to monitor for and treat SCC (both cutaneous and non-cutaneous) in patients receiving vemurafenib in clinical trials (see Section 4.5.1.9).

1.5.3.6 *Adenomatous Colonic Polyps*

Five cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for more than 2 years while enrolled in a clinical trial (Chapman et al. 2012). The first patient developed an upper gastrointestinal bleed, and on work-up was found to have duodenal ulceration (non-malignant), hyperplastic gastric polyps, and five colonic polyps (three of which were adenomatous). A previous colonoscopy in 2008, at the time of a jejunal resection for recurrent melanoma, documented no prior evidence of colonic polyps. All polyps were resected, and the patient subsequently resumed vemurafenib therapy. The second patient was found, on elective colonoscopy, to have seven colonic polyps (five of which were adenomatous),

and all were detected and removed. This patient had not undergone a previous colonoscopy. The patient has discontinued treatment with vemurafenib. The third patient had, on elective colonoscopy, 10 colonic polyps (seven of which were adenomatous). This patient had a previous colonoscopy 7 years prior to starting vemurafenib. The fourth patient had, on elective colonoscopy, one adenomatous colonic polyp. The fifth patient had, on elective colonoscopy, three adenomatous colonic polyps. The latter two patients had histories of no prior colonoscopy. In addition, a patient on the Expanded Access Program had one colonic adenoma discovered after being on vemurafenib 0.57 years. This patient had a colonoscopy 1.3 years prior to starting vemurafenib, and a polyp was found and resected at that time.

1.5.3.7 Hypersensitivity Reactions

A case of hypersensitivity reaction with rash, fever, rigors, and hypotension 8 days after starting vemurafenib 960 mg BID was reported in a clinical trial. Similar symptoms were observed upon re-initiation of treatment with a single dose of 240 mg vemurafenib. The patient discontinued vemurafenib permanently and recovered without sequelae.

1.5.3.8 ECG Analysis

In the nonclinical GLP patch clamp in vitro assay, the IC_{50} for inhibition of the hERG channel in serum-free conditions was 1.24 µM. The mean C_{max} at steady state attained in melanoma patients with vemurafenib 960 mg BID has exceeded the IC_{50} for hERG blockade in vitro, albeit with a high degree of protein binding in humans.

However, QTc prolongation was observed in the ECG substudy of NP22657. The effects of single and multiple doses of vemurafenib (960 mg BID) on ECG measurements, including the QT interval, were evaluated in 132 adult patients with metastatic melanoma in the Phase II Study NP22657.

Ninety-one patients (68.9%) exhibited either normal ECG values throughout the study (n = 25) or developed new abnormal but clinically insignificant ECG changes (n = 66). However, 41 patients (31.1%) exhibited new ECG changes considered to be abnormal and potentially significant. No patients developed new abnormal U waves, but 19 patients (14.4%) had new abnormal T-waves. Vemurafenib did not cause a meaningful change from the time-matched baseline ECG in either the QRS or the PR (PQ) interval.

Two patients (1.5%) developed treatment-emergent QTcP values > 500 ms (NCI Common Terminology Criteria for Adverse Events [CTCAE] Grade 3), while 49 (37.1%) and 6 (4.5%) of patients exhibited treatment-emergent, QTcP values > 450 ms and > 480 ms, respectively. No patients had treatment-emergent uncorrected QT values > 500 ms. Treatment-emergent, individual QTcP changes > 30 ms from baseline were observed in 58 (43.9%) patients, but only 1 patient (0.8%) exhibited a QTcP change > 60 ms from baseline.

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

None of the QT prolongation events were serious or led to premature withdrawal from treatment or dose modification/interruption; none were clearly associated with prolongation of cardiac repolarization, arrhythmia, or any other cardiac function disorder. Refer to the Vemurafenib IB for additional details.

1.5.3.9 Post-Approval Safety Update

1.5.3.9.1 *Progression of Existing Malignancy*

One case of progression of NRAS-mutated chronic myelomonocytic leukemia (CMML) occurred in a male patient with metastatic melanoma treated with vemurafenib for less than 2 weeks (Callahan et al. 2012). After the first dose of vemurafenib, laboratory results showed a marked leucoytosis and monocytosis and vemurafenib treatment was subsequently held. 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 a BRAF inhibitor, an effect that was reversed upon addition of a MEK inhibitor. Further, the cells exhibited dose-dependent and reversible activation of ERK in the NRAS-mutated leukemic clone. *A second case of progression of a preexisting RAS-mutated malignancy (pancreatic adenocarcinoma with KRAS mutation) was reported with vemurafenib in 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 or concurrent cancer associated with RAS mutation. Full details are provided in the current Vemurafenib IB.

1.5.3.9.2 *Drug Reaction with Eosinophilia and Systemic Symptom (DRESS)*

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

1.5.3.9.3 *Liver Injury*

An analysis of liver–related adverse events reported with vemurafenib use showed that 63 cases (out of an estimated exposure of approximately 20,000 patients) of medically confirmed serious adverse events were consistent with drug–induced liver injury (DILI)

based on clinical chemistry criteria from the DILI Expert Working Group (Aithal et al. 2011). Of the 63 cases, two were assessed as severe, both reported as hepatic failure. There were no reported deaths among the 63 cases of liver injury; the outcome of both cases of severe liver injury was reported as completely resolved with vemurafenib discontinuation. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to ALP ratio was calculated as 1.5, which suggested a trend toward a cholestatic pattern of liver injury. The analysis did not reveal any risk factors or populations at risk.

1.5.3.9.4 *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 factors (G-CSF).

1.5.3.9.5 *Pancreatitis*

As of Q2 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 et al. 1995).

1.5.3.9.6 *Risk of Radiation Recall and Radiation Sensitization*

As of Q4 2014, an adverse drug reaction of potentiation of radiation treatment toxicity has been identified in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. This is based on 20 cases of radiation injuries, adjudicated as radiation recall (n =8) and radiation sensitization (n =12). The nature and severity of the events in all 20 cases were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation with fatal outcome in 3 cases. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Full details are provided in the current Vemurafenib IB.

1.5.3.9.7 *Safety 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. Based on these data, concurrent administration of ipilimumab and

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

1.5.4 Clinical Efficacy

Clinical efficacy data to support the use of vemurafenib for the treatment of patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma is primarily based on results from three studies (NO25026, NP22657, and PLX06- 02). All three studies were multicenter, international, and open label.

- NO25026, Phase 3: clinical cutoff: 31 March 2011; vemurafenib n = 337; DTIC n = 338. Updated analyses are also provided based on a clinical cutoff date of 1 February 2012.
- NP22657, Phase 2: clinical cutoff: 31 January 2011; n = 132. Updated analyses are also provided based on a clinical cutoff date of 1 February 2012.
- PLX06-02, Phase 1: clinical cutoff: 3 June 2010. Dose escalation phase: (patients with solid tumors); vemurafenib original formulation, n = 26, vemurafenib MBP formulation, n = 30. Treatment extension phase: metastatic melanoma patients, n = 32, metastatic CRC patients, n = 21. Updated analyses for the melanoma extension cohort patients are provided based on a clinical cutoff date of 17 July 2012.

In all three studies (NO25026, NP22657, and PLX06-02) in which vemurafenib was used to treat previously untreated or previously treated patients with BRAFV600 mutation-positive metastatic melanoma, consistent, robust, and clinically meaningful benefits were observed.

In the Phase 3 Study (NO25026), as of the 31 March 2011 cutoff date, after a median 5.19 months of follow-up in the vemurafenib arm, the Kaplan-Meier (KM) estimate of median survival among patients randomized to vemurafenib was not reached (95% CI: 9.59 months, not reached). Among patients randomized to DTIC, after a median 4.46 months of follow-up, the KM estimate of median survival was 7.89 months (95% CI: 7.26 months, 9.63 months). The KM estimate of the 6-month survival rate among patients randomized to vemurafenib was 83% (95% CI: 79%, 87%) and 63% (95% CI: 57%, 69%) among patients randomized to DTIC. The hazard ratio (HR) for death was 0.44 (95% CI: 0.33, 0.59) in favor of vemurafenib. Treatment with vemurafenib demonstrated a clinically meaningful and statistically significant improvement in PFS compared with dacarbazine treatment ($p < 0.0001$). There was a statistically significant improvement in BORR (confirmed) as assessed by the investigator with vemurafenib (48.4%; 95% CI: 41.6%, 55.2%) compared with DTIC (5.5%; 95% CI: 2.8%, 9.3%, $p < 0.0001$).

In updated analyses (1 February 2012 cutoff date), the survival benefit of vemurafenib treatment compared with DTIC treatment was again observed. With a median of 12.5 months of follow up for vemurafenib patients, updated OS analyses showed that

vemurafenib treatment is associated with a nearly 4 month improvement in median survival compared with DTIC (13.6 months vs. 9.7 months, respectively). The HR for death in this analysis was 0.70 (95% CI: 0.57, 0.87) in favor of vemurafenib. Updated PFS analyses showed that vemurafenib treatment was associated with an approximately 5-month improvement in median PFS compared with DTIC (6.9 months vs. 1.6 months, respectively); the PFS HR was 0.38 (95% CI: 0.32, 0.46) in favor of vemurafenib. In these analyses, data were censored as specified in the Statistical Analysis Plan at the time of crossover for DTIC patients who crossed over to receive vemurafenib treatment.

In the Phase 2 Study NP22657, with a 31 January 2011 clinical cutoff date, after a median duration of follow-up of 10.4 months, the primary endpoint of BORR (confirmed) as assessed by the IRC was 53% (95% CI: 44.2%, 61.8%). Secondary endpoints that were supportive of antitumor activity as assessed by the IRC included median response duration and OS. The median response duration was 6.7 months (95% CI: 5.6 months, 8.6 months), and the median OS had not been reached (95% CI: 11.2 months, not reached). Median PFS was 6.1 months (95% CI: 5.5 months, 6.9 months).

In updated analyses, with a 1 February 2012 clinical cutoff date, with a median follow-up of 13.4 months, BORR, duration of response, and PFS were similar to the prior analysis. The KM estimate of median OS was 15.9 months (95% CI: 11.2 months, 19.3 months), and the estimate of median PFS was 6.8 months (95% CI: 5.5–7.9 months).

In the Phase 1 Study (PLX06-02), a BORR (confirmed) of 56% was observed (duration of follow-up not available) with a median duration of response of 227 days (7.6 months), median PFS of 233 days (7.8 months), and a 1-year survival rate of 57%.

In updated analyses of survival (using a 17 July 2012 cutoff date), the median OS in the melanoma cohort was 13.8 months, and the 2-year survival rate was 38%.

Consistent with in vitro evidence demonstrating strong inhibition of vemurafenib across cell lines expressing variant $BRAF^{V600}$ mutations, improvement in OS, PFS, and BORR was also observed in patients with $BRAF^{V600K}$ mutations identified by Sanger sequencing in the NO25026 study, and in BORR in the NP22657 study.

While acknowledging the limited number of patients in these analyses, these data support the clinical activity of vemurafenib in metastatic melanomas harboring less common activating $BRAF^{V600}$ mutations.

For updated efficacy information, refer to the Vemurafenib IB.

1.6 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Metastatic melanoma represents a major clinical challenge, as it is an essentially incurable disease with few satisfactory treatment options. Current first-line treatment options have yielded low response rates and, although ipilumumab has demonstrated an

OS advantage, it is associated with significant toxicities (Robert et al. 2011). Furthermore, no biomarkers for patient selection or reliably predicting development of severe immune-related toxicity are known for ipilimumab.

Vemurafenib is a highly selective inhibitor of the oncogenic BRAF kinase, which has been identified in a large number of malignant melanomas. Results from Phase I, II, and III studies in the West have shown that vemurafenib was associated with consistent, robust, and clinically meaningful benefits as measured by all primary and secondary efficacy endpoints, in treatment-naïve or previously treated patients with $BRAF^{V600}$ mutation-positive metastatic melanoma. To date, no other first- or second-line treatment options for metastatic melanoma have shown consistent improvement in all three efficacy parameters (OS, PFS, and BORR) in this population with high unmet medical need. These data indicate that vemurafenib is an effective treatment option in this patient population.

As there is very limited information on vemurafenib in the treatment of Asian patients (only 4 Asian patients were treated with vemurafenib, 1 in the Phase 1 study PLX06-02, 3 in an ongoing safety Study MO25515), and to safely apply clinical information obtained in Caucasians to support usage of vemurafenib to treat Chinese melanoma patients, the Study YO28390 is planned to investigate the pharmacokinetics, safety, and efficacy of vemurafenib in Chinese patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma. This study will comply with the International Conference on Harmonisation (ICH) Guidance E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data) and regulatory requirements of the People's Republic of China.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The PK objective for this study is to evaluate the pharmacokinetics of vemurafenib following 960 mg BID oral administration in Chinese patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

This is the primary objective of this study.

2.2 SECONDARY OBJECTIVES

The efficacy objective for this study is to describe the efficacy of vemurafenib by using BORR (confirmed), duration of response, PFS, and OS in Chinese patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

The safety objective for this study is to investigate the safety and tolerability of vemurafenib in Chinese patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

This is an open-label, multicenter, Phase I study with a PK cohort and an expansion cohort. Only patients who test positive for the $BRAF^{V600}$ mutation as determined by the cobas 4800 $BRAF^{V600}$ Mutation Test will be allowed to participate in this study. Approximately 45 Chinese patients will be recruited into this study. Patient recruitment is estimated to require approximately 22 months.

3.1.1.1 Pharmacokinetic Cohort

Approximately 20 patients will be enrolled in the PK cohort. The study design scheme for the PK cohort is in Table 4.

Table 4 Study Design Scheme for PK Cohort

Screening	Period A	Period B	Period C (extension phase)	Follow-up
Days –28 to –1	Days 1–21	Days 22–27	Day 28 and beyond	After completion of study treatment
No vemurafenib administration	Vemurafenib 960 mg BID	Vemurafenib holiday	Vemurafenib 960 mg BID	No vemurafenib administration

BID = twice daily.

The dosing regimens in different periods are described as follows:

- **Period A**: Following a screening period of up to 28 days, approximately 20 patients will be enrolled into the study for PK assessment. Patients will receive 960 mg BID PO on Days 1 to 20, and on Day 21, patients will only receive their morning dose. All patients will provide blood samples on Days 1, 15, 19, and 21 for PK analysis as described in Appendix 2.
- **Period B**: Begins with Day 22 and lasts until Day 27. Study drug will be held for the purpose of characterizing the elimination profile of vemurafenib. All patients will provide blood samples on Days 22 and 24 for PK analysis as described in Appendix 2.
- **Period C**: After a pre-dose PK sample collection, starting on Day 28, all patients may resume vemurafenib 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent, or any other criterion as listed in Section 4.6.
- **Follow-up period**: All adverse events (related and unrelated to study drug) occurring at any time during Periods A, B, or C up to 28 days after the last dose of study medication in Period C must be reported; drug-related events must be followed until resolution. All patients who received at least one dose of vemurafenib will be followed for SCC evaluation until 6 months after discontinuation of study treatment or death, withdrawal of consent, or loss to follow-up, whichever is earlier.

3.1.1.2 Expansion Cohort

After recruitment of the PK cohort is complete, approximately 25 additional Chinese patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma will be recruited into the expansion cohort.

Following a screening period of up to 28 days, all eligible patients will complete the assessments on Day 1 (see Appendix 1) as their baseline and will receive vemurafenib 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent, or any other criterion as listed in Section 4.6.

The follow-up procedures for patients in the expansion cohort are the same as for those in the PK cohort.

For detailed information on the safety and efficacy evaluations for both cohorts, please refer to the Schedule of Assessments (see Appendix 1). PK samples will be obtained according to the schedule outlined in Appendix 2.

3.2 END OF STUDY

Patients still receiving vemurafenib at the time of updated analysis will be allowed to continue treatment until PD, unacceptable toxicity, death, loss to follow-up, or withdrawal of consent.

The study will end when the last patient has permanently discontinued treatment with vemurafenib and has completed the 6-month follow-up period for safety assessment.

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase I, open-label, multicenter, multiple-dose study. The purpose of the study is to investigate the pharmacokinetics, safety, and efficacy of vemurafenib in Chinese patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

In the PK portion of the study (Periods A and B), the PK profile after the first dose (Day 1) and at steady-state will be evaluated to determine the accumulation ratio of vemurafenib in Chinese patients. To achieve the complete steady-state in plasma in all patients, the 21-day continuous BID dosing (Days 1–21) in Period A will be employed. This is based on the results from the PK dose ranging Study NP25163, which demonstrated that more than 14 days of continuous dosing may be required to complete the approach to steady state in plasma in certain patients. The 6-day “drug holiday” in Period B (Days 22–27) is used for assessing the elimination phase of vemurafenib at steady state because > 95% of plasma clearance of drug occurred within 7 days in Study NP25163. Since 10 evaluable patients had been sufficient for solid PK data in NP 25163, total 20 patients will be recruited for the PK cohort and at least 10 patients are expected to complete the PK portion of the study.

After recruitment of the PK cohort is complete, an additional 25 patients will be enrolled into the expansion cohort for efficacy and safety assessments. All patients will receive vemurafenib 960 mg BID until the development of PD, unacceptable toxicity, consent withdrawal, or any other criterion as listed in Section 4.6. The purpose of the expansion cohort is to collect additional safety and efficacy results in Chinese patients.

3.3.1 Rationale for Test Product Dosage

A regimen of 960 mg BID has been chosen in this study to characterize the pharmacokinetics of vemurafenib and collect additional safety and efficacy results in Chinese patients. This is the regulatory authority-approved starting dose for vemurafenib to treat mutation-positive unresectable or metastatic melanoma in the United States, Switzerland, and European Union, and was also the MTD determined in a first-in-human study conducted in Caucasian patients (Study PLX 06-02).

In global registration studies, a high incidence of at least one temporary interruption and/or dose reduction (approximately 40%–50%) due to treatment-emergent adverse events at the MTD of 960 mg BID was observed; however, permanent discontinuation of study drug for toxicity was rare.

A risk management plan specific for this study in Chinese patients based largely on the global studies risk management plan (see Section 5.1) and dose reduction guidelines will be used to manage symptomatic adverse events and possible QTc prolongation in this bridging study.

3.3.2 Rationale for Patient Population

The mechanism of action of vemurafenib and existing nonclinical and clinical data all suggest that the activity of the drug is limited to patients whose tumors are positive for the V600 mutation(s) of the BRAF gene. Patients whose tumors are not positive for the mutation will not be treated with vemurafenib.

The global clinical trial program included treatment-naïve and previously treated patients with $BRAF^{V600}$ mutation–positive unresectable or metastatic melanoma. Results from global Phase II and III studies have shown that vemurafenib demonstrates high response rates and improves the OS and PFS in patients with metastatic melanoma who carry the $BRAF^{V600}$ mutation.

Therefore, the BRAFV600 mutation status for eligible patients must have been determined using the cobas 4800 BRAFV600 Mutation Test. This includes previously untreated patients or those previously treated but without prior exposure to any BRAF (sorafenib allowed) or MEK inhibitor therapy, having locally advanced and unresectable or metastatic melanoma, are eligible.

3.4 OUTCOME MEASURES

3.4.1 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- C_{max} on Days 1 and 21
- Time to maximal plasma concentration (T_{max}) on Days 1 and 21
- AUC from time 0 to 8 hours (AUC_{0-8h}) on Days 1 and 21
- AUC from time 0 to 12 hours (AUC_{0-12h} or AUC_{τ}) on Days 1 and 21
- AUC from time 0 to 168 hours (AUC_{0-168h}) beginning on Day 21
- C_{min} on Days 15, 19, and 21
- Accumulation ratio (the AUC ratio on Day 21/Day 1)
- Elimination rate constant (K_{el})
- Half-life ($t_{1/2}$)

3.4.2 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- BORR (confirmed)
- Duration of response
- PFS
- OS

3.4.3 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and intensity (severity) of adverse events and serious adverse events, graded according to NCI CTCAE v4.0
- Changes in vital signs
- Changes in clinical laboratory test results
- ECG assessments
- Dermatology evaluations for cuSCC surveillance
- Head, neck, anus, anal canal, and pelvic (for female patients) evaluations and CT scans for non-cuSCC surveillance

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll Chinese patients ≥18 years of age who are $BRAF^{V600}$ mutation positive and have histologically confirmed metastatic melanoma (unresectable Stage IIIC or Stage IV). Patients may be either treatment-naïve or have received prior systemic treatments for metastatic melanoma. Written informed consent must be obtained from patients prior to performing any study-related procedures.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Chinese male or female patients $\geq$ 18 years of age.
- Histologically confirmed metastatic melanoma (surgically unresectable Stage IIIc or Stage IV, American Joint Committee on Cancer). Unresectable Stage IIIc disease must have confirmation from a surgical oncologist.
- Patients are either treatment-naïve or had received prior systemic treatments for metastatic melanoma.
- Positive $BRAF^{V600}$ mutation result determined by a designated laboratory using the cobas 4800 $BRAF^{V600}$ Mutation Test prior to administration of vemurafenib.
- Measurable disease by RECIST v1.1 prior to the administration of vemurafenib.
- Previous allowed chemotherapy, immunotherapy, or radiation therapy must have been completed at least 2 weeks prior to study drug administration, and all associated toxicity must be resolved (to $\leq$ Grade 1 or baseline) prior to study drug administration.
- Recovery from effects of any major surgery (excluding tumor biopsy at baseline) or significant traumatic injury at least 14 days before the first dose of study treatment.
- Adequate hematologic, renal, and liver function as defined by laboratory values performed within 28 days prior to initiation of dosing.
    - Absolute neutrophil count $\geq$ 1.5 x 10^9/L
    - Platelet count $\geq 100 \times 10^9$/L
    - Hemoglobin $\geq$ 9 g/dL
    - Serum creatinine $\leq 1.5 \times$ the upper limit of normal (ULN) or creatinine clearance $>$ 60 mL/min by Cockroft-Gault formula
    - AST and ALT $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for patients with concurrent liver metastases)
    - Bilirubin $\leq 1.5 \times$ ULN (for patients with Gilbert's Syndrome, bilirubin $\leq 3 \times$ ULN)
    - Alkaline phosphatase $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for patients with concurrent liver metastases)
    - Albumin $\geq$ 3 g/dL
- Negative serum or urine pregnancy test within 7 days prior to commencement of dosing in pre-menopausal women. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for $\geq$ 1 year.
- Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician (in accordance with local requirements).

- Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry.
- ECOG PS of 0 or 1.
- Life expectancy > 3 months.
- Be able to swallow pills.

4.1.2 Exclusion Criteria

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

- Patients with active CNS lesions are excluded (i.e., those with radiographically unstable, symptomatic lesions). Note: Patients treated with stereotactic therapy or surgery are eligible if they remain without evidence of disease progression in brain for ≥ 3 months. They must also be off corticosteroid and anticonvulsant therapy for ≥ 3 weeks. Whole brain radiotherapy is not allowed with the exception of patients who have had definitive resection or stereotactic therapy of all radiologically detectable parenchymal lesions.
- History of or known spinal cord compression or carcinomatous meningitis.
- Anticipated or ongoing administration of anti-cancer therapies other than those administered in this study.
- Active SCC that has not been excised or has not yet adequately healed post excision.
- Pregnant or lactating women.
- Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate vemurafenib absorption.
- QTc interval ≥ 450 ms at screening ECG or history of congenital long QT syndrome.
- NCI CTCAE v4.0 Grade 3 hemorrhage within 28 days of starting the study treatment.
- Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), serious cardiac arrhythmia requiring medication, uncontrolled hypertension, cerebrovascular accident or transient ischemic attack, or symptomatic pulmonary embolism.
- Known clinically significant active infection.
- History of allogeneic bone marrow transplantation or organ transplantation.
- Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study.

- Patients with previous malignancy within the past 5 years are excluded other than adequately treated patients with BCC or SCC of the skin, melanoma in-situ, and carcinoma in-situ of the cervix and/or curatively treated cancer, from which the patient is currently disease-free, or any malignancy from which the patient has been continuously disease-free for at least 5 years. Isolated elevation in prostate-specific antigen in the absence of radiographic evidence of metastatic prostate cancer is allowed.
- Patients who have been previously treated with a BRAF inhibitor (sorafenib allowed) or MEK inhibitor.
- Patients who have had at least one dose of study drug (vemurafenib) in a previous clinical trial that includes vemurafenib.
- Known HIV positivity or AIDS-related illness, or hepatitis B virus or hepatitis C virus (HCV) carriers (hepatitis B surface antigen positive, HCV antibody positive).
- Received any investigational treatment within 4 weeks of study drug start.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a single-arm Phase I, open-label, multicenter, multiple-dose study.

Twenty patients will be enrolled into the PK cohort, and after the recruitment of PK cohort is complete, an additional 25 patients will be enrolled into the expansion cohort for efficacy and safety assessments.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Vemurafenib is supplied in 240-mg film-coated tablets packed in aluminium blisters for oral administration. For additional information for vemurafenib film-coated tablets, please refer to IB.

Vemurafenib will be stored at the clinical site under recommended storage conditions as indicated on the study drug label. Patients will be requested to store vemurafenib at the recommended storage conditions noted on the label out of the reach of children or other cohabitants.

Vemurafenib will be labeled in compliance with Good Manufacturing Procedures. The drug label will include the contents, protocol number, batch number, and storage conditions, as well as any other required information mandated by local health authorities (e.g., “For Investigational Use Only”).

4.3.2 Dosage, Administration, and Compliance

Each box of study medication contains a total of 56 film-coated tablets in aluminum blisters that are 240 mg each.

Vemurafenib tablets should be swallowed whole with a glass of water (approximately 240 mL). Vemurafenib tablets should not be chewed or crushed.

PK cohort:

In Period A, patients will receive 960 mg BID PO for Days 1–20, and on Day 21, patients will receive only the morning dose. Patients will discontinue vemurafenib starting with the evening dose on Day 21.

Vemurafenib may be taken either 1 hour before or 2 hours after a meal, except on Days 1 and 21. On Days 1 and 21, patients should fast overnight for at least 8 hours before the morning dose, and continue to fast for an additional 4 hours post-dose. Patients should plan on a standard meal at 4 hours post-dose, but are allowed to have light snacks (i.e., crackers, toast, juice, and water) within the 4-hour period.

There is no study drug administration in Period B.

In Period C starting on Day 28, all patients will receive the study drug at 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent, or any other criterion as listed in Section 4.6.

Expansion Cohort:

All patients will receive vemurafenib 960 mg BID until the development of PD, unacceptable toxicity, withdrawal of consent, or any other criterion as listed in Section 4.6.

On the days of BID dosing (except Day 1 in the PK cohort), patients in both cohorts should be instructed to take 4 tablets in the morning and 4 tablets in the evening (total daily dose of 1920 mg [960 mg BID]) approximately 12 hours later. Both doses should be taken either 1 hour before or 2 hours after a meal. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.

Patients will be given a dosing diary to record the time and date of study drug administration. Administration dates and times will be recorded in the eCRF by the study coordinators.

A cycle is defined as 4 weeks (28 days). A 4-week supply (Cycles 1–10) or 8-week supply (starting from Cycle 11) of study drug can be given to the patient on Day 1 of each or every other cycle. Patients will be instructed not to open a new box until the previous box has been finished and to bring their study drug and used boxes back to all clinic visits for reconciliation.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (vemurafenib) will be provided by the Sponsor. The investigational site will acknowledge

receipt of IMPs, and 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-Trial Access to Vemurafenib

The Sponsor does not intend to provide vemurafenib or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.4 CONCOMITANT THERAPY

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 screening to the study completion/early termination visit. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

Female patients of child-bearing potential who are using oral contraceptives, hormone replacement therapy, or other maintenance therapy will be asked to continue their use.

Patients taking prescribed therapies for intercurrent illnesses, or consistently dosed nutritional or herbal medicines (other than anti-cancer treatments) at the time of study entry should continue to take their medicines unless asked by the Investigator to discontinue or modify them.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the Investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drug. Hematopoietic growth factors (e.g., erythropoietin and G-CSF) and pain medications as dictated by standard practice are acceptable while the patient is enrolled in the study. However, growth factors should not be administered prophylactically before initial treatment with study drug.

Patients who experience adverse events during the study may be treated symptomatically by the investigator as clinically indicated.

Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded on eCRF including the date, indication, description of the procedure(s), and any clinical findings.

4.4.2 Prohibited Therapy

All concomitant medication or treatment required by the patient will be at the discretion of the treating physician. The following medications and treatments are not allowed while the patient is on study:

- St. John's wort or hyperforin.
- Any concomitant therapy intended for the treatment of melanoma, either approved by health authorities or experimental, including chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy, investigational agents, or herbal therapy.
- 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) are not allowed 30 days prior to the first dose of study drug and during the study for the patients in PK cohort.
- Radiotherapy for the treatment of disease during study, except limited field radiotherapy for palliative bone pain due to preexisting bone metastasis if not considered a target lesion for RECIST assessments.

Patients who require the use of any of these agents will be discontinued from study treatment.

4.4.3 Medication Precautions in case of Drug–Drug Interactions

Results from an in vivo drug–drug interaction study in patients with cancer demonstrated that vemurafenib is a moderate CYP1A2 inhibitor, a weak CYP2D6 inhibitor and a CYP3A4 inducer.

The results from this clinical study demonstrate that co-administration of vemurafenib increased the AUC of caffeine (CYP1A2 substrate) 2.6-fold and increased the AUC of dextromethorphan (CYP2D6 substrate) by 47%, while it decreased the AUC of midazolam (CYP3A4 substrate) by 39%, suggesting vemurafenib may inhibit CYP1A2 and CYP2D6 activity and induce CYP3A4 activity. Concomitant use of vemurafenib with agents with narrow therapeutic windows 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.

Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR monitoring when vemurafenib is used concomitantly with warfarin.

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. Thus, 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) are not allowed for the patients in PK cohort. For the patients in the expansion cohort, these strong CYP3A4 inhibitors or inducers should be used with caution when co-administered with vemurafenib.

A more extensive list of medications whose metabolism might be affected by vemurafenib can be found in Appendix 7 , which includes a non-exhaustive list of CYP1A2, CYP3A4, and CYP2C9 substrates. For further information see Vemurafenib IB.

4.4.3.1 Medications that Affect the QT Interval

Certain medications could affect the QT interval on ECG measurements required in this study. Specifically, anti-emetics other than those belonging to the 5-HT_3 receptor antagonist class (i.e., granisetron, ondansetron, dolasetron, palonosetron) are preferred since the latter have the potential to prolong the QT interval. Investigators are advised to avoid or take precautions in closely monitoring patients who are on medications or herbal and vitamin supplements that may increase the QT interval. Alternative treatment options for medications known to affect the QT interval should be discussed with each patient prior to his or her inclusion into this study. A list of medications that may cause QT interval prolongation is provided in Appendix 8. Please refer to http://www.azcert.org/ for additional information and references.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, 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 the screening visit.

Demographic data will include age, gender, and self-reported race/ethnicity.

4.5.1.2 Vital Signs

Vital signs will include measurements of pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and body temperature.

4.5.1.3 Physical Examinations

A complete physical examination will include evaluation of the head, eyes, ears, nose, and throat; heart and vascular system; lungs and respiratory system; abdomen and abdominal organs; gastrointestinal system; skin and musculoskeletal system; and

neurological system. Changes from normal or from baseline abnormalities should be recorded at each subsequent examination. New or worsened abnormalities should be recorded as adverse events, if appropriate.

As part of tumor assessments, physical examination should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, splenomegaly, and skin metastases.

4.5.1.4 Pharmacokinetic Assessments

Blood samples will be collected to evaluate the pharmacokinetics as specified in Appendix 2 for the PK cohort. At each PK assessment timepoint, venous blood samples (2 mL) will be collected to measure concentrations of vemurafenib.

PK plasma samples will be obtained on Day 1 to characterize the single dose PK profile of vemurafenib, on Days 15 and 19 for C_{min} during the treatment, and as noted in Appendix 2 on Days 21–28 to characterize the PK profile of vemurafenib after achieving steady state.

The total volume blood loss for PK assessments will be approximately 58 mL during this study.

The procedures for the collection, handling, and shipping of the PK laboratory samples are specified in a separate laboratory manual.

Fasting Requirements

Vemurafenib may be taken either 1 hour before or 2 hours after a meal with or without food, except on Days 1 and 21 of PK sampling in Period A.

On Days 1 and 21 in Period A, patients should fast overnight for at least 8 hours before the morning dose, and continue to fast for an additional 4 hours post-dose. Patients should plan on a standard meal at 4 hours post-dose on Days 1 and 21 of PK sampling, and are allowed to have light snacks (i.e., crackers, toast, juice, and water) within the 4-hour period.

Period A

PK plasma samples for vemurafenib will be obtained on Days 1, 15, 19, and 21.
PK sampling will be obtained pre-dose, and at 1, 2, 4, 5, 8, and 12 hours post-dose on Days 1 and 21. PK sampling will be obtained pre-dose on Days 15 and 19.
The pre-dose PK samples can be taken up to 1 hour before the dose. The pre-dose PK sample CANNOT be taken after the dose. Post-dose PK samples have a window of 15 minutes.

Period B

Two PK samples will be taken approximately 4 hours apart on Days 22 (i.e., at 24 hours [±15 minutes] and 28 hours [±1 hour] after the morning dose on Day 21). Two PK samples will be taken approximately 4 hours apart on Day 24: at 72 hours (±15 minutes) and 76 hours (± 1 hour) after the morning dose on Day 21. The 24- and 72-hour post-dose PK samples (after the morning dose on Day 21) have a window of ± 15 minutes. The 28- and 76-hour post-dose PK samples (after the morning dose on Day 21) have a window of ± 1 hour.

Period C

On Day 28, one PK sample will be taken pre-dose (morning). The pre-dose PK samples can be taken up to 1 hour before the dose. The pre-dose PK sample CANNOT be taken after the dose.

One PK sample will be taken at the time of all RECIST/BORR assessments for all patients, including the PK cohort and expansion cohort.

Unscheduled PK Sampling

One unscheduled PK sample should be taken as close as possible to the time of onset of an AE/SAE leading to dose adjustment or treatment interruption, and as close as possible to the time of first (unconfirmed) diagnosis of disease progression.

4.5.1.5 Performance Status

PS will be measured using the ECOG PS Scale (see Appendix 5). It is recommended that, where possible, a patient's PS be assessed by the same person throughout the study. Refer to Appendix 1 for details on when ECOG PS is collected. All patients will be evaluated continually throughout trial to see if performance status score changes.

4.5.1.6 Tumor and Response Evaluations

The activity of vemurafenib will be determined by the assessment of tumor responses in patients with measurable disease according to RECIST (v1.1).

Tumor assessments are to be performed as scheduled according to the calendar days regardless of treatment delays. On-study tumor assessments are to be performed every 8 weeks (2 cycles) from the date of first dose of study drug until the development of PD, or withdrawal of consent. The date of first dose of study drug should always be used as the baseline when calculating when the next tumor assessment is due. Because in this study disease progression must be documented by CT or MRI scan, CT or MRI scan should also be performed whenever disease progression is suspected (e.g., symptomatic deterioration). The determination of anti-tumor efficacy will be based on tumor assessments made according to the RECIST v1.1 (Appendix 3). An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation or at the next scheduled tumor assessment if it is to occur > 4 weeks after

the initial response. The CT scans should be performed with contrast agents unless contraindicated for medical reasons. The same imaging modality should be used throughout the study to measure disease. Tumor evaluation by positron emission tomography scan or by ultrasound cannot be a substitute for CT or MRI scans. CT or MRI scans will include chest, brain, abdomen, and pelvis at screening. Brain must be included in subsequent tumor assessments if a patient has brain metastases; otherwise brain will only be evaluated when clinically indicated. A bone scan is required at screening. Repeat bone scans are required every 16 weeks only if bone metastases are present at baseline; otherwise a repeat bone scan is required only if new bone metastases are suspected. A bone scan is also required at the time of determination of response for patients who have bone metastases.

Measurable lesions that have been previously irradiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.

If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment. If at any time during treatment phase there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled tumor assessment should be performed.

All scans will be evaluated locally at each center by designated radiologist (separate from the principal investigator), who will read and evaluate all scans for the subjects enrolled in this study at his own center.

4.5.1.7 Laboratory Assessments

All laboratory assessment will be evaluated locally at each center. Normal ranges for the study laboratory parameters must be supplied. Laboratory safety tests shall be collected at timepoints specified in Appendix 1, Schedule of Assessments.

Hematology, serum biochemistry, viral serology/detection, and urinalysis will be done as part of regular safety assessments.

- Hematology: hemoglobin, hematocrit, white blood cells, absolute neutrophil count, and platelet count
- Biochemistry: urea (BUN), ALT, AST, bilirubin, alkaline phosphatase, amylase, creatinine, albumin, phosphorus, serum electrolytes (sodium, potassium, magnesium, chloride, bicarbonate), glucose, total protein, total calcium, γ-glutamyltransferase, total cholesterol, triglyceride, LDL-C, HDL-C, and LDH (LDH will be obtained only at screening and baseline (Day 1 pre-dose).

  Note: total cholesterol, triglyceride, LDL-C, and HDL-C will be collected from patients who have fasted overnight (for at least 8 hours)

- Viral serology/detection: hepatitis B (hepatitis B surface antigen) and HCV antibody and anti-HIV antibody.
- Urinalysis: urinalysis must include a determination of glucose, protein, hemoglobin (blood), bilirubin, ketones, pH, and specific gravity. A microscopic exam should be performed for 2 + or higher hemoglobin or protein levels (must include sediment, RBC, WBC, casts, crystals, epithelial cells, bacteria).
- Serum for the pregnancy test at screening if a urine test was not used

The Sponsor (Roche) 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).

4.5.1.8 Electrocardiograms

For the PK cohort, a triplicate 12-lead ECG assessment will be performed at screening, Cycle 1 Day 1 (pre-dose and 2 and 4 hours post-dose), Cycle 1 Day 15 (pre-dose), Day 21 (pre-dose and 2, 4, and 24 hours post-dose), Day 28 - the first day of Period C (pre-dose), and pre-dose on Cycle 3 Day 1. After Cycle 3, ECG assessments will be performed at the beginning of every other treatment cycle (i.e., Day 1 of Cycles 5, 7, 9, etc.) and at the end of Study Completion/Early Termination visit. All ECGs will be taken at least 15 minutes before the scheduled PK sampling or any other type of blood draw.

For the expansion Cohort, 12-lead ECG assessment will be performed at screening, Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 Day 1. After Cycle 3, ECG assessments will be performed at the beginning of every other treatment cycle (i.e., Day 1 of Cycles 5, 7, 9, etc.) and at the end of study treatment visit. ECGs should be performed at least 15 minutes prior to the first daily administration of study drug and drawing of any blood samples.

Machine-read automated ECG intervals will be captured on the eCRF including, heart rate, RR, QRS, QT, QTc interval (using Fredericia correction formula), and any clinically significant ECG abnormalities, including U wave and T wave abnormalities.

Triplicate ECGs will be obtained as three 10-second recordings in close succession and not more than 2 minutes apart. Patients must be in a supine position for 5 minutes prior to the ECG. The ECGs should be reviewed promptly by a qualified physician and any clinically important finding recorded on the appropriate eCRF. The investigator is responsible for providing the interpretation of all ECGs.

All ECG recordings must be performed using a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements. Digital ECG recording is recommended.

4.5.1.9 Dermatological Evaluations and Additional Assessments for SCC Surveillance

Dermatological evaluations and additional assessments will be completed to monitor for and treat SCC. The SCC surveillance plan includes thorough skin examinations by a dermatologist or other qualified physician, a head, neck, anus, anal canal, and pelvic (for female patients) exam by the treating physician, and a CT scan of the chest.

A complete dermatological history of prior medications and cuSCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, and photochemotherapy for psoriasis) must be collected.

In patients who develop cuSCC or any suspicious skin lesions during the trial, the patient may choose to continue or discontinue from the trial in consultation with the investigator. If the patient elects to continue in the trial, definitive treatment (i.e., surgical excision) of any SCC/KA or other suspicious lesion(s) is required.

Schedule of Dermatology Evaluations

- At screening (any time up to 28 days prior to Day 1), Cycle 2 Day 1, and Cycle 3 Day 1. After Cycle 3, these assessments will be performed at the beginning of every other treatment cycle (i.e., Day 1 of Cycles 5, 7, 9, etc.) and at the Study Completion/Early Termination visit. These assessments will be repeated at Months 3 and 6 after the last study treatment or until death, withdrawal of consent, or loss to follow-up, whichever is earlier:
    - A window of + 21 days applies to the schedule of study visits for purposes of dermatology evaluation (with exception of screening).
    - Patients should consult their treating physician as needed for any new skin lesion while on study drug.
- The occurrence of any other skin changes, including rash and photosensitivity, should be reported to the study investigator, and patients will be referred to a dermatologist for further evaluation as required.
- Non-cuSCC: risk management (treating physician)
    - A thorough head and neck examination to monitor for non-cutaneous SCC, consisting (at a minimum) of a visual inspection of the oral mucosa and lymph node palpation, must be performed by the treating physician for all patients enrolled in this clinical trial. A head and neck exam will be performed at screening, Cycle 2 Day 1, and Cycle 3 Day 1. After Cycle 3, these assessments will be performed every other treatment cycle (Day 1 of Cycle 5, 7, 9, etc.) and at the end of study treatment visit. These assessments will be repeated at Months 3 and 6 after the study treatment or until death, withdrawal of consent, or loss to follow-up, whichever is earlier.

- All patients will undergo digital and visual examination of the anus and anal canal at baseline and at the end of study treatment (28 days after the last dose of study treatment) and female patients must also have a visual pelvic examination (including evaluation of the uterine cervix) at baseline and at the end of study treatment (28 days after the last dose of study treatment) as additional measures to monitor for the occurrence of SCC of the anus, anal canal, and cervix, respectively.

Chest CT Scans

- Chest CT scans must be done at baseline (i.e., up to 28 days prior to the start of treatment), every 6 months while on study treatment, and 6 months after discontinuation of study treatment or until death, withdrawal of consent, or loss to follow-up, whichever occurs earlier. A window of ± 21 days of scheduled study visit is allowed for collection of the chest CT scan (with exception of screening). The routinely scheduled CT scan of the chest for assessment of response and progression of the underlying malignancy can be used for the assessment of SCC risk while the patient is on study drug.

4.5.1.10 Mandatory Samples for Determination of Patient Eligibility

The following mandatory samples will be collected for determination of patient eligibility:

A sample of formalin-fixed paraffin-embedded tumor will be submitted for all patients being considered for this trial. This sample will consist of five serially cut unstained sections of 5 microns in thickness. The sample can also be one formalin-fixed, paraffin-embedded block. If archived tumor tissue is not available, a biopsy will be taken. Tumor samples will be submitted to a designated testing site where DNA will be isolated and tested using the cobas 4800 $BRAF^{V600}$ Mutation Test.

DNA samples will be retained from the tumor specimens for subsequent re-testing, if necessary. These samples will be stored in the central reference laboratory until the New Drug Application has been reviewed and approved by the China Food and Drug Administration (CFDA).

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. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening and baseline assessments are outlined in Schedule of Assessments in Appendix 1. Consent must be obtained within 42 days of study treatment start (Day 1). An original signed consent form will be retained by the investigator and the patient will receive a copy to take home.

A screening assessment should be performed between –28 and –1 days before the start of the study treatment (Day 1). Submission of tumor tissue for BRAF mutation status can occur prior to Day –28 but must occur after consent has been obtained. If a new biopsy (separate from the one used to make the diagnosis of melanoma) is necessary to obtain tumor tissue for BRAF mutation status, the biopsy must occur after consent has been obtained. All screening assessments are outlined in the Schedule of Assessments (see Appendix 1). Patients must fulfill all entry criteria to be accepted into the study.

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

A screen failure log must be maintained by the investigator. See Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

All treatment assessments must be performed within ± 3 days of the scheduled visit dates except where indicated otherwise (see Appendix 1). Assessments should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

In the PK cohort, all assessments must be performed on the day of the specified visit in Periods A and B (please refer to Appendix 2 for the time window for PK sampling); beginning from Period C (Cycle 2), a ±3 day window is permitted for completion of the scheduled visit in order to accommodate holidays, travel delays, site closures, or for other reasons (see Appendix 1). Assessments of tumor response and progression should be performed according to RECIST v1.1 (see Appendix 3).

See Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Study Completion/Early Termination Visit

Patients who complete the study treatment or discontinue early from the study will be asked to return to the clinic within 28 days after their last dose of vemurafenib for a Study Completion/Early Termination visit.

See Appendix 1 for the schedule of assessments performed at the Study Completion/Early Termination visit.

4.5.2.4 Follow-Up Assessments

After the Study Completion/Early Termination visit, the following data will be collected until either death, withdrawal of consent, or the patient is lost to follow up:

- Survival status
- All adverse events (with exception of SCC) will be collected until 28 days after the last dose of study treatment.

- Dermatological evaluation until 6 months after the last dose of study drug
- Non-cutaneous SCC evaluation until 6 months after the last dose of study drug
- Chest CT at 6 months after study treatment completion

Patients who discontinue study treatment for reasons other than disease progression or death should continue to collect scheduled tumor assessments every 2 cycles until patient death or progressive disease. Adverse events should be followed as outlined in Section 5.5 and 5.6

Please see Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

CT or MRI scan should be performed whenever disease progression is suspected (e.g., symptomatic deterioration). The results should be recorded in corresponding pages of eCRF.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator may discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients may 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
- Disease progression (defined using RECIST v1.1 methodology; see Appendix 3)
- Change in patient eligibility
- Noncompliance with protocol requirements

4.6.1.1 Discontinuation from Study Drug

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

- Pregnancy
- Disease progression
- Unacceptable toxicity

In the follow-up portion of the study, patients who stop study treatment due to disease progression will also be followed for survival every 3 months until death, withdrawal of consent, or loss to follow-up. All patients who received at least one dose of vemurafenib will be followed for SCC evaluation until 6 months after discontinuation of study drug or until death, withdrawal of consent, or loss to follow-up, whichever is earlier.

See Appendix 1 for assessments done at the Study Completion/Early Termination Visit.

Patients who discontinue study drug prematurely will be asked to return to the clinic for a Study Completion/Early Termination visit (see Section 4.5.2.3) and may undergo follow-up assessments (see Section 4.5.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely 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.

4.6.2 Study and Site Discontinuation

The Sponsor 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.
- 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 replace a site at any time. Reasons for replacing 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 ICH guideline for Good Clinical Practice (GCP) or local regulations

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Real-time safety monitoring will occur on an ongoing basis for all patients enrolled in this study, using the NCI CTCAE v4.0. Complete details of the safety evaluation to be performed in this study are provided below, including expedited reporting of SAEs to the study Sponsor.

The most common AEs in vemurafenib-treated patients (≥30% patients) in the pivotal Phase III NO25026 study and pooled safety population (Phase I PLX06-02 and Phase II NP22657 studies and post-approval safety study MO25515) were (preferred terms)

arthralgia, rash, alopecia, fatigue, nausea, pruritus, diarrhea, skin papilloma, hyperkeratosis, and photosensitivity. The majority of these events were mild or moderate in intensity.

The inclusion and exclusion criteria for this study (see Section 4.1) and safety monitoring plan are designed to minimize the risk of toxicity to patients.

Each safety assessment will include pertinent patient history since the previous assessment, physical examination, and clinical laboratory tests.

All AEs will be considered treatment related unless clearly attributed to disease progression or to another clear etiology identified by the investigator.

5.1.1 Dose Delays and Modifications

Missed or delayed doses (>4 hours after normal administration time) should be skipped and not administered as a double dose at the next administration. Missed doses should be recorded in the patient diary.

Management of symptomatic adverse drug reactions (e.g., arthralgia, fatigue, rash) other than cuSCC adverse reactions may require temporary interruption and/or dose reduction of vemurafenib treatment. If dose reduction is needed, dose reduction in 240-mg BID decrements is recommended based on individual safety and tolerability. Dose escalation after dose reduction is generally not recommended unless under special circumstances—i.e., increased likelihood of clinical benefit for the dose increase and no safety concerns. This should only be done after discussion with the Sponsor. Dose increases above 960 mg BID will NOT be allowed.

For Grade 1 and tolerable Grade 2 toxicities, patients may continue full dose.
For intolerable Grade 2 toxicities or Grade 3 toxicities, dosing will be interrupted until resolution to Grade 1 or less and dose reductions in 240-mg BID decrements are required for the first (i.e., to 720 mg BID) and second (i.e., to 480 mg BID) occurrence. On the third appearance of intolerable Grade 2 or Grade 3 toxicity despite two dose reductions, it is recommended that patients discontinue vemurafenib. Dose reduction below 480 mg BID will NOT be allowed during the study.

For Grade 4 toxicities, patients should discontinue study treatment or, based on investigator judgment, interrupt until resolution to Grade 1 or less with dose reduction of 50% upon restarting study drug. Patients should permanently discontinue vemurafenib for a second occurrence of any Grade 4 toxicities.

For all patients receiving vemurafenib treatment, if QTc (using Fredericia's correction formula) increases to >500 msec or if a change from baseline of ≥60 msec is observed on study, vemurafenib treatment should be temporarily interrupted and QTc interval

should be monitored weekly until it is < 500 msec or returns to baseline before reinstituting therapy at a reduced dose.

Appropriate electrolyte evaluation (potassium, magnesium, and calcium levels) should be monitored and any electrolyte abnormalities, especially hypokalemia, should be corrected prior to reinstitution of therapy. Other cardiac risk factors (hypertension, CHF, bradyarrhythmias, diabetes, etc.) should be corrected per standard of care.

If the QTc interval does not improve within 28 days after interruption of vemurafenib dosing, permanently discontinue vemurafenib.

Upon re-initiation of vemurafenib treatment, patients should have their dose reduced by one dose level (see Section 5.1.1, Table 5). ECG and electrolytes should be monitored at the following intervals:

- Pre-dose on morning of study drug resumption (time 0 hour)
- 2 and 4 weeks after resuming study drug
- Once a cycle for 3 consecutive cycles after study drug resumption
- Every 2 cycles thereafter

Vemurafenib treatment should be permanently discontinued if QTc increases to >500 ms AND changes from baseline exceed 60 ms.

Vemurafenib treatment should be permanently discontinued if patients experience SJS, TEN, or DRESS.

More than 28 days interruption of dosing for whatever reason is considered permanent discontinuation from the study treatment

Exceptions will be granted for reversible laboratory abnormalities with no clinical sequelae and/or clinical significance in the opinion of the investigator and Sponsor (see Table 5).

Table 5 Dose Interruption/Modification Criteria for Vemurafenib

Dose Modifications		
Toxicity Grade (CTCAE) [a]	Vemurafenib dose changes during current treatment period	Dose adjustments for resumption of treatment
	Grade 1 and tolerable Grade 2 toxicities	
	No dose reduction	*N/A*
	Grade 2 (intolerable toxicities) or Grade 3	
1st Appearance	Interrupt until resolved (Grade 0-1)	Reduce by 240 mg twice daily
2nd Appearance	Interrupt until resolved (Grade 0-1)	Reduce by 240 mg twice daily
3rd Appearance	Discontinue permanently	
	Grade 4	
1st Appearance	Discontinue permanently or interrupt until resolved (Grade 0-1)	Reduce to 480 mg twice daily (50% of starting dose)
2nd Appearance	Discontinue permanently	

CTCAE = Common Terminology Criteria for Adverse Events.
[a] The intensity of clinical AEs graded by the CTCAE v4.0.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, SAEs and non-serious AEs of special interest (AESIs); measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified 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 GCP, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE 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
- AEs 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 the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death). This does not include any AE 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 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the AE 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)

  A new primary malignancy (other than cuSCC or new primary melanoma) or progression or recurrence of a prior malignancy (other than the disease under study) will be categorized as a serious adverse event.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (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 AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor immediately (within 24 hours) after learning of the event (see Section 5.4.2 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious AESIs are required to be reported by the investigator to the Sponsor immediately (within 24 hours) after learning of the event (see Section 5.4.2 for reporting instructions). AESIs for this study include the following:

- Grade 3 or greater photosensitivity
- Grade 4 elevations of AST, ALT, serum bilirubin, OR cases of elevated ALT or AST in combination with either an elevated serum bilirubin value or clinical jaundice (see Section 5.3.5.6)
- cuSCC
- Grade 3 or greater QT interval prolongation
- Suspected transmission of infectious agents via a medical product

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, the Investigator will assess seriousness (see Section 5.2.2 for seriousness 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 AEs at each patient contact. All AEs, 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 SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).

After initiation of study drug, all AEs, 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, SAEs, or other AEs 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?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. Table 6 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 6 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 AE [d]

AE = adverse event; 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 an SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5 2 2

[d] Grades 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE 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 AE 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 AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE 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 AEs based on signs and symptoms should be nullified and replaced by one AE 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, AEs 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 AEs 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 gastrointestinal 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 AEs 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 AE 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 AE 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

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE 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

The Investigator must review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase 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 sign of a 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 AE. 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 AE. 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

The Investigator must 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 AE.

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 AE 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 $\geq 35\%$ 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 immediately (within 24 hours) after learning of the event, either as an SAE or a non-serious AESI (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 AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of metastatic melanoma should be recorded only on the Study Completion/Early Discontinuation 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).

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 post-study survival follow-up, deaths attributed to progression of metastatic melanoma should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting 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 Lack of Efficacy or Worsening of Primary Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. Because in this study the expected pattern of disease progression will be solely based on RECIST v1.1. CT or MRI scan should also be performed whenever disease progression is suspected (e.g., symptomatic deterioration).

If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or PK sampling)
- 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 surgery became necessary because of the expected normal progression of the disease
  - The patient has not suffered an AE
- Hospitalization due solely to progression of the underlying cancer

5.3.5.11 Overdoses

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor immediately (within 24 hours) after learning of the event, regardless of relationship to study drug:

- SAEs
- Non-serious AESIs
- Pregnancies

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (within 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 SAEs to the local health authority and Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

MEDICAL MONITOR (ROCHE MEDICAL RESPONSIBLE) CONTACT INFORMATION

Primary Contact

Medical Monitor: [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: [redacted]

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

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 & List of Investigators").

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

For reports of SAEs and non-serious AESIs, investigators should record all case details that can be gathered immediately (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.

If the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to

Roche Safety Risk Management or its designee immediately (within 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 the study or within 12 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the Investigator immediately (within 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 immediately (within 24 hours) after learning of the pregnancy, using the fax numbers provided to Investigators (see "Protocol Administrative and Contact Information & 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 the study or within 86 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the Investigator immediately (within 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 spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (within 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 should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (within 24 hours) after learning of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each AE 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 SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (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 SAEs, non-serious AESIs, 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 ADVERSE EVENTS

At the Study Completion/Early Termination visit, the investigator should instruct each patient to report to the investigator any subsequent AEs 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, SAE, or other AE of concern 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 & List of Investigators").

During post-study survival follow-up, deaths attributed to progression of melanoma should be recorded only on the Study Completion/Early Discontinuation eCRF}.

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

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

- Vemurafenib IB
- Vemurafenib Core Data Sheet

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

For the purpose of the primary objective analysis, PK (primary) analysis will include only PK cohort patients and will be conducted when the last patient in PK cohort completes the PK blood draw on Day 28. A primary Clinical Study Report that describes these PK results as well as appropriate efficacy and safety for patients will be generated for filing purposes.

The data cutoff for updated analysis will occur when all patients included in the PK and expansion cohorts have completed at least 6 months of treatment (or discontinued treatment) or when $>$70% of treated patients have experienced disease progression by RECIST v1.1 or death, whichever occurs later. It is expected to occur about 12 months after the first patient is enrolled.

The final analysis will occur after the last patient has permanently discontinued treatment with vemurafenib.

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation was performed for this study. The sample size of 20 PK patients is chosen to allow acceptable variability of the PK data. Together with extra 25 patients in the expansion cohort, it would give a Clopper-Pearson 95% CI of 26%–56% for BORR assuming the target BORR (confirmed) is 40%.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, major protocol violations, and discontinuations from the study will be summarized descriptively for the treated population. The incidence of treatment discontinuation will be tabulated. Major protocol violations, including violations of inclusion/exclusion criteria, will be summarized for the treated population.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics such as age, sex, race, weight, ECOG PS, and baseline disease characteristics such as histologic subtype and primary location of disease will be summarized for the treated population. Descriptive baseline summaries of continuous data will present mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

6.4 PHARMACOKINETIC ANALYSES

The primary objective of the study is to evaluate the pharmacokinetics of vemurafenib following 960 mg BID oral administration in Chinese patients with BRAFV600 mutation-positive unresectable or metastatic melanoma.

For the purposes of statistical analysis, the PK population will include all patients evaluable for PK analysis, i.e., patients who provided sufficient PK data to obtain at least one of the primary PK variables. Patients will be excluded from the PK analysis if they significantly violate the inclusion or exclusion criteria, deviate significantly from sampling times or other provisions of the protocol, or if data are unavailable which may influence the analysis.

Plasma concentration on Day 1 and steady state will be listed and graphically displayed for vemurafenib.

Non-compartmental analysis using WinNonlin software will be used to obtain PK parameters of vemurafenib. All PK parameters for vemurafenib will be presented by listings and descriptive summary statistics (arithmetic mean, geometric mean, standard deviation, coefficient of variation, minimum, maximum, and number of observations). Rate of elimination may be estimated using data from PK samples collected during the drug holiday period.

The following PK parameters will be reported:

- C_{max} on Days 1 and 21
- T_{max} on Days 1 and 21
- $AUC_{0\text{-}8h}$ on Days 1 and 21
- $AUC_{0\text{-}12h}$ on Days 1 and 21
- $AUC_{0\text{-}168h}$ beginning on Day 21
- C_{min} on Days 15, 19, and 21
- Accumulation Ratio
- K_{el}
- $t_{1/2}$

6.5 EFFICACY ANALYSES

Efficacy endpoints include BORR (confirmed), PFS, and OS. BORR, PFS, and OS analyses will include all patients who received at least one dose of vemurafenib. All efficacy data will be summarized using descriptive statistics.

The BORR is defined as the number of patients whose confirmed objective response is complete response or partial response divided by the total number of treated patients. PR/CR must be confirmed by repeated assessment that should be performed no less than 4 weeks after the criteria for response are first met. Patients without a post-baseline tumor assessment will be considered as non-responders.

An estimate of BORR (confirmed) and its 95% CI will be calculated using Clopper-Pearson method.

Duration of response (DOR) is defined as the time from the initial response to disease progression or death among patients who have experienced a CR or PR during study. At the time of analysis, patients who have not progressed or have died after achieving a response will be censored at the last tumor assessment date. DOR will be estimated using Kaplan-Meier methodology.

PFS is defined as the time between date of first treatment and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment with use of RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the first treatment date.

KM methodology will be used to estimate median PFS and 6-month PFS rate and the KM curve will be constructed to provide a visual description. The 95% CI for median PFS will be calculated using the Brookmeyer and Crowley method.

OS is defined as the time from the date of first treatment to the date of death, regardless of the cause of death. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive.

KM methodology will be used to estimate median OS and 6-month survival rate and the KM curve will be constructed to provide a visual description. The 95% CI for median OS will be calculated using the Brookmeyer and Crowley method.

6.6 SAFETY ANALYSES

Safety analyses will include all patients who receive at least one dose of study treatment (the safety population).

Drug exposure will be summarized to include treatment duration, dosage, and dose intensity.

Verbatim description of AEs will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v4.0. All AEs occurring during or after the first study treatment will be summarized by NCI CTCAE grade. In addition, SAEs, severe AEs (Grade 3 and above), and AEs leading to discontinuation or interruption of study treatment will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. In addition, the following events: cuSCC, photosensitivity, liver laboratory abnormalities, and events potentially related to QT interval prolongation will be summarized separately, including incidence, time to first onset of the event, and the total number of episodes.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by grade.

Changes in vital signs will be summarized.

All deaths and causes of death will be summarized.

Concentration–QTc effect relationship will be explored with various QT-RR correction methods (i.e., Bazett, Fridericia, population (study-specific), and if warranted by the changes in the heart rate, individual correction will be made). Vemurafenib concentration–QTc effect relationships may be explored and this concentration–QTc data may be pooled with corresponding data from other studies to enhance the analysis of the concentration–QTc effect relationship. The concentration–QTc analysis may use linear and nonlinear mixed effect modeling techniques.

6.7 EXPLORATORY ANALYSES

Exploratory analyses include the following:

Descriptive tables with side-by-side PK parameters in Chinese and Caucasian patients will be presented, with exploratory statistical comparison for descriptive purposes only.

Statistical output will be 2-sided 90% CI of the geometric mean ratio (test/reference) for steady-state AUC and C_{max}. Test = Chinese (current study); reference = Caucasian (dose-specific PK data from eCTD). Acceptance criterion for CI width will not be pre-specified for purposes of this analysis.

Final conclusion on PK comparability will be determined in the context of the benefit–risk ratio for vemurafenib in patients with life-threatening melanoma where no comparably efficacious therapy exists in China.

6.8 INTERIM ANALYSES

Not applicable.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered 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 Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data (vemurafenib concentration–time 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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and will 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 should 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 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 7.5.

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

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, 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 GCP 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).

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 EC submission. The final EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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 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 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.

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 EC by the Principal Investigator and reviewed and approved by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also responsible for promptly informing the 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 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 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 CFDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the 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 study (i.e., last patient last visit).

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 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 ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

This study is sponsored by Roche. Approximately two to three study centers in China will participate in this study, enrolling a total of approximately 45 patients. Roche will provide clinical operations oversight, data management support, and medical monitoring. Tumor tissue from consenting patients will be sent to a central laboratory for analysis of $BRAF^{V600}$ mutation status. Blood samples for pharmacokinetics will be sent to a central laboratory for analysis. Sample analysis will be performed by an external vendor or Roche.

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. The Sponsor is responsible for promptly informing the EC of any amendments to the protocol. Approval must be obtained from the EC 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).

10. REFERENCES

Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011;89:806-15.

Ascierto P, Streicher HZ, Sznol M. Melanoma: A model for testing new agents in combination therapies. J Translational Med 2010;8:38.

Australian Government Dept. of Health and Ageing. 2008. http://www.skincancer.gov.au/internet/skincancer/publishing.nsf/Content/fact-2. Accessed 23 April 2012.

Beeram M, Patnaik A, Rowinsky EK. Raf: a strategic target for therapeutic development against Cancer. J Clin Oncol 2005;23:6771-6790.

Callahan MK, Rampal R, Harding JJ, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. N Engl J Med 2012;367:2316-21.

Chapman PB, Hauschild A, Robert C, et al; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.

Chapman PB, Metz D, Supelveda AR, et al. Development of colonic adenomas and gastric polyps in BRAF mutant melanoma patients treated with vemurafenib. Pigment Cell Melanoma Res [abstract]. 2012;25:847.

China Melonoma Guideline, 2011.

Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353:2135-2147.

Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol 2002;146(Suppl.61):1-6.

Dummer R, Keilholz U, Pentheroudakis G, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii86-91.

European Network of Cancer Registries No. 4, November 2003.

Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 2010;363:809-819.

Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol 27:3-9, 2009.

Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature 2007;445:851-857.

Harding JJ, Lacouture ME, Pulitzer M, et al. Hypersensitivity skin reactions in melanoma patients treated with vemurafenib after ipilimumab therapy J Clin Oncol 2012;30(S; abstract 8515).

Hingorani SR, Jacobetz MA, Robertson GP, Herlyn M, Tuveson DA. Integrating BRAF/MEK inhibitors in combination therapy for melanoma. Cancer Research 2003;63:5198-5202.

Investigator's Brochure RO5185426: [Please refer to current version, including any addendums].

Kopetz S, Desai J, Chan E, et al. PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. J Clin Oncol 2010;28:3534.

Lang J, Mackie RM. Prevalence of exon 15 BRAF mutations in primary melanoma of the superficial spreading, nodular, acral, and lentigo maligna subtypes. J Invest Dermatol. 2005;125:575-579.

Lankisch PG, Droge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. Gut 1995;37:565-567

Lucas R. Global Burden of Disease of Solar Ultraviolet Radiation, Environmental Burden of Disease Series, July 25, 2006; No. 13. News release, World Health Organization.

Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst 2003;95:1878-1890.

Ribas A, Hodi FS, Callahan M, et al. Correspondence: hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 2012;368:1365-1366

Ries LAG, et al., eds. SEER Cancer Statistics Review, 1975–2000. Bethesda, MD: National Cancer Institute; 2003: Tables XVI-1-9.

Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-2526. Epub 2011 Jun 5.

Sanger. http://www.sanger.ac.uk/genetics/CGP/cosmic/. Accessed 23 April 2012.

Smalley KSM, Herlyn M, et al. Targeting BRAF/MEK in melanoma: new hope or another false dawn? Expert Tev Dermatol 2007;2:179-190.

Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutated advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707-14.

Sumimoto H, Miyagishi M, Miyoshi H, et al. Inhibition of growth and invasive ability of melanoma by invasion of mutated BRAF with lentivirusmediated RNA interference. Oncogene 2004;23:6031-6039.

SUNSMART Cancer Council Victoria. 2007. http://www.sunsmart.com.au. Accessed 23 April 2012.

US Centers for Disease Control and Prevention. Skin Cancer Statistics. Updated 23 November 2010. http://www.cdc.gov/cancer/skin/statistics/index.htm. Accessed 13 April 2012.

Zhao P, Chen W, et al. Chinese Cancer Registry Annual Report 2009-cancer incidence and mortality in Chinese cancer registration areas in 2006 [R]. Beijing: Military Medical Science Press 2010;74-79:170-174.

Appendix 1 Schedule of Assessments

Protocol Activities		Screening Period (28 Days)	Study Treatment [1] 28 Day Cycle								Day of Last Study Dose	Completion/ Early Termination Visit [18]	Post-Treatment Follow-Up
			Cycle1						Cycle2	Cycle3 +			
			Period A for PK Cohort				Period B for PK Cohort		Period C for PK Cohort				
	-42 to -28	-28 to -1	1 [2]	15	19	21	22	24	28 +	57+			Every 3 months
Informed consent [3]	X	X											
Submission of tumor tissue for BRAF mutation status [4]	X	X											
Medical history and demographics		X											
Physical examination [5]		X	(X)						X	X		X	
ECOG PS		X	X						X	X		X	
Laboratory tests													
Hematology/ biochemistry/ urinalysis (PK cohort)[6]		X	(X)			X			X	X		X	
Hematology/ biochemistry/ urinalysis (expansion cohort)[6]		X	(X)						X	X		X	
LDH		X	(X)										

Appendix 1
Schedule of Assessments (cont.)

Protocol Activities		Screening Period (28 Days)	Study Treatment [1] 28 Day Cycle								Day of Last Study Dose	Completion/ Early Termination Visit [18]	Post-Treatment Follow-Up
			Cycle1						Cycle2	Cycle3 +			
			Period A for PK Cohort				Period B for PK Cohort		Period C for PK Cohort				
	-42 to -28	-28 to -1	1 [2]	15	19	21	22	24	28 +	57+			Every 3 months
HBsAg and HCV, HIV antibody		X											
Pregnancy test (serum or urine) [7]		X											
Triplicate 12-lead ECG (PK cohort) [8]		X	X	X		X			X	X		X	
Triplicate 12-lead ECG (expansion cohort) [9]		X	X	X					X	X		X	
PK blood sampling: PK cohort [10]			X	X	X	X	X	X	X	X	X	X	
PK blood sampling: expansion cohort [11]			X							X	X	X	
Tumor assessment [12]		X								X			
Dermatology evaluation [13]		X							X	X		X	X

Appendix 1
Schedule of Assessments (cont.)

Protocol Activities		Screening Period (28 Days)	Study Treatment [1] 28 Day Cycle								Day of Last Study Dose	Completion/ Early Termination Visit [18]	Post-Treatment Follow-Up
			Cycle1						Cycle2	Cycle3 +			
			Period A for PK Cohort				Period B for PK Cohort		Period C for PK Cohort				
	-42 to -28	-28 to -1	1 [2]	15	19	21	22	24	28 +	57+			Every 3 months
Non-cuSCC Evaluation [13]		X							X	X		X	X
Chest CT scan for presence of SCC [14]		X								X			X
Adverse events [15]			X									X	X
Concomitant and previous medications [15]		X	X									X	X
Patient diary for study drug administration			X										
Survival assessment [16]													X
Study treatment: administration of vemurafenib [17]			X										

ECOG PS = Eastern Clinical Oncology Group Performance Status; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus; non-cuSCC = non-cutaneous squamous cell carcinoma; PK = pharmacokinetic.

( ) - Need not be repeated on Day 1 if tests have been performed within 7 days before Day 1 (start of study treatment).

Appendix 1
Schedule of Assessments (cont.)

Notes: Clinic visits are completed on Day 1 of every 4 week cycle for Cycles 1–10 (every 4 weeks). Starting from Cycle 11, clinic visits will be completed on Day 1 of every other cycle (every 8 weeks). All assessments should be performed within ± 3 day of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

1. **Study treatment:** All assessments should be performed prior to dosing with study medications unless otherwise indicated. All cycles are 28 days in duration. Enough study drugs for treatment will be dispensed at each clinic visit.
2. **Cycle 1/Day 1:** Blood chemistry, hematology, LDH, physical examination and triplicate 12-lead ECG not required if acceptable screening assessment is performed within 7 days prior to the start of study treatment.
3. **Informed consent:** Must be obtained prior to undergoing any trial specific procedure.
4. **Submission of tumor tissue for BRAF mutation status:** Tumor tissue must be submitted for $BRAF^{V600}$ mutation screening (one formalin-fixed, paraffin-embedded block or at least 5 serially cut unstained 5 micron sections cut from one block, mounted on slides). A biopsy will be taken if no archived tumor tissue is available. Submission of tumor tissue for $BRAF^{V600}$ mutation status can occur prior to the 28-day screening period as long as the submission is after informed consent (Informed consent must be obtained within 42 days of the first dose). DNA from the tumor tissue will be retained for subsequent re-testing, if necessary.
5. **Physical examination:** Includes an examination of major body systems, height (at screening only), weight, blood pressure, and pulse rate at baseline and on Day 1 of each clinical visit.
6. **Hematology, biochemistry, urinalysis:** Obtain at screening, baseline (Day 1), Day 1 of Cycles 2–10, Day 1 of every other cycle starting from Cycle 11, and at the completion /early termination visit. All lipid parameters should be obtained after the patient has fasted overnight (for at least 8 hours). For the PK cohort, hematology / biochemistry / urinalysis should also be obtained at Day 21 Cycle 1. Required tests are listed in Section 4.5.1.7.
7. **Pregnancy test:** All female patients of child-bearing potential are required to have a negative pregnancy test at screening within 7 days prior to commencement of dosing.
8. **12-lead ECG (PK cohort):** A triplicate 12-lead ECG assessments will be performed at screening, Cycle 1 Day 1 (pre-dose and 2 and 4h post-dose), Cycle 1 Day 15(pre-dose), Cycle Day 21 (pre-dose and 2, 4, and 24 hours post-dose), Day 28 - the first day of Period C (pre-dose), and pre-dose on Cycle 3 Day 1; after Cycle 3, ECG assessments will be performed every other treatment cycle (Day 1 of Cycle 5, 7, 9 etc.) and at the study completion/early termination visit. All ECGs will be taken at least 15 minutes before the scheduled PK sampling or any other type of blood draw.

Appendix 1
Schedule of Assessments (cont.)

9. **12-lead ECG (expansion cohort):** A triplicate 12-lead ECG assessments will be performed at screening, Cycle 1 Day 1 and Day 15, Cycle 2 Day 1, and Cycle 3 Day 1; after cycle 3, ECG assessments will be performed every other treatment cycle (Day 1 of Cycle 5, 7, 9 etc.) and at the study completion/early termination visit. ECGs should be performed at least 15 minutes prior to the first daily administration of study drug and any blood draws.
10. **PK blood sampling (PK cohort):** Schedule of PK sampling, See Appendix 2. One unscheduled PK sample should be taken at the time of onset of AE/SAE leading to dose adjustment/treatment interruption and as close as possible to the time of first (unconfirmed) diagnosis of disease progression.
11. **PK blood sampling (Expansion Cohort):** PK sample will be taken at pre-dose on Cycle 1 Day 1, and at the time of all RECIST/BORR assessments. One unscheduled PK sample should be taken at the time of onset of AE/SAE leading to dose adjustment/treatment interruption and as close as possible to the time of first (unconfirmed) diagnosis of disease progression.
12. **Tumor assessments:** All patients must have a brain CT and/or MRI at screening to assess for brain metastasis. After the baseline assessment, if no brain metastasis, subsequent brain CT and/or MRI should only be obtained as clinical indicated. A bone scan is required at screening. Repeat bone scans are required every 16 weeks only if bone metastases are present at baseline. A bone scan is also required at the time of determination of response for patients who have bone metastases. Radiological tumor assessments (CT and/or MRI scans; bone scans only if clinically indicated) of chest, abdomen, pelvis will be obtained to assess extent of disease at the following timepoints: screening (anytime within 28-day period), Cycle 3 Day 1 and every 2 cycles thereafter until documented disease progression. Tumor assessments can be completed within ± 7 days of scheduled visit. If at any time during treatment phase there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled tumor assessment should be performed. If a bone scan is used for progressive disease, then a corresponding CT scan needs to be completed. All tumor assessment will be performed based on a calendar schedule beginning from the date of first dose of study treatment.
13. **Dermatology evaluation and non-cuSCC evaluation:** Dermatology evaluation and non-cuSCC evaluation are required at screening, Cycle 2 Day 1, and Cycle 3 Day 1; after Cycle 3, these assessments will be performed every other treatment cycle (Day 1 of Cycles 5, 7, 9, etc.) and at the study completion/early discontinuation visit. These assessments will be repeated 3 and 6 months after last study treatment or until death, withdrawal of consent, or loss to follow-up, whichever is earlier. A window of + 21 days is acceptable. Refer to section 4.5.1.9 for detailed information.
14. **Chest CT scan for presence of SCC:** Chest CT scans must be done at baseline (i.e., up to 28 days prior to the start of treatment), an every 6 months while on study treatment and 6 months after discontinuation of study treatment or until death, withdrawal of consent, or loss to follow-up. A window of ± 21 days of scheduled study visit is allowed for collection of the chest CT scan (with exception of screening).

Appendix 1
Schedule of Assessments (cont.)

15. **Adverse events and concomitant medications/treatments:** Assess concomitant medications at baseline and continually report along with adverse events throughout study treatment. Adverse events of special interest and concomitant medications will be followed for up to 28 days post last dose of vemurafenib during the follow up period. Drug-related adverse events will be followed until resolution. After this period, collect any serious adverse events/adverse events that the investigator considers having a causal relationship with vemurafenib, regardless of time elapsed since post last dose of vemurafenib and even if the study has stopped.

16. **Survival follow up:** Patients who discontinue study treatment for reasons other than disease progression or death should continue to collect scheduled tumor assessments every 2 cycles until patient death or progressive disease. Post-progressive disease survival status will be collected every 3 months. The study will be closed when all patients enrolled have been followed until progression, death or loss to follow-up. Telephone contact is acceptable for survival follow up.

17. **Administration of vemurafenib:** For the PK cohort, in Period A, the study drug is administered twice daily on Days 1 to 20. The study drug is administered in the morning (AM) only on Day 21. The patient does NOT take the evening dose on Day 21. Patients in the PK cohort should resume twice-daily vemurafenib administration starting from Day 28.

18. **End of treatment visit:** Patients who complete study treatment or discontinue study treatment early will be asked to return to the clinic 28 $\pm$ 3 days after the last dose of study drug for an end of treatment visit.

Appendix 2 Schedule of Pharmacokinetic Assessments

Periods	Screening	Cycle 1		Cycle 2+	Follow-up after End of Study Treatment
		Period A	Period B	Period C	
Day	Day –28 to –1	Days 1–21	Days 22–27	Day 28 and Beyond	Every 3 Months
Pharmacokinetics: PK sampling in PK cohort	N/A	*Days 1 and 21* Pre-dose and 1, 2, 4, 5, 8, and 12 hours post-dose *Days 15 and 19* Pre-dose	*Day 22* 24 hours (± 15 minutes) and 28 hours (± 1 hour) after the morning dose on Day 21 *Day 24* 72 hours (± 15 minutes) and 76 hours (± 1 hour) after the morning dose on Day 21	*Day 28* Pre-dose (morning) At the time of onset of AE/SAE leading to dose adjustment/treatment interruption; As close as possible to the time of first (unconfirmed) diagnosis of disease progression; At the time of all RECIST/BORR assessments	Prior to stopping study drug at the clinic visit and at the final visit (at the time of progression or withdrawal)
Pharmacokinetics: PK sampling in expansion cohort	N/A	Day 1: Pre-dose (morning)	N/A	At the time of onset of AE/SAE leading to dose adjustment/treatment interruption; As close as possible to the time of first (unconfirmed) diagnosis of disease progression; At the time of all RECIST/BORR assessments	Prior to stopping study drug at the clinic visit and at the final visit (at the time of progression or withdrawal)

AE = adverse event; BORR = best overall response rate; N/A = not applicable; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Appendix 3 New Response Evaluation Criteria in Solid Tumors Quick Reference – Version 1.1

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness ≤ 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Appendix 3 New Response Evaluation Criteria in Solid Tumors Quick Reference – 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, PET scan, or plain films 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 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) because 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 Quick Reference – 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). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken because 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. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward.

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.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds

or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1.1.1). 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 lesions (even if size is greater than 10mm by CT scan)

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost

always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.” In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

Response Criteria

Definitions of the criteria used to determine objective tumor response for target lesions include the following:

- 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.

Appendix 3 New Response Evaluation Criteria in Solid Tumors Quick Reference – Version 1.1 (cont.)

Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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 case report form:

If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked (Note: It is less likely that this rule will be used for lymph nodes because 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).

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 preexisting 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.

^{18}F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation.

The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

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

A response assessment is assumed to occur at each protocol-specified timepoint. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

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" because 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.

Table 1 Response Evaluation Criteria in Solid Tumors

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; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Appendix 3 New Response Evaluation Criteria in Solid Tumors Quick Reference – Version 1.1 (cont.)

Table 2: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (because disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (eCRF).

In trials where confirmation of response is required, repeated "NE" timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Appendix 3 New Response Evaluation Criteria in Solid Tumors Quick Reference – Version 1.1 (cont.)

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.
The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 and 2.

Conditions that define "early progression, early death, and non-evaluability" are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false-positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Appendix 4 American Joint Committee on Cancer TNM Staging for Melanoma

Clinical stage grouping for Stage IV melanoma is defined as any T, any N, and any M1

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 5 ECOG Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described below:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

* As published in Am J Clin Oncol: Oken 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 6 Alternative and Preferred Methods for Patients Unable to Tolerate Radiological Contrast Agents

For patients who cannot tolerate radiological contrast agents, the following methods are preferred and should be used as alternative means for collecting radiological assessments in these patients.

- For CT contrast contraindication: unenhanced CT of the chest, enhanced MRI of the abdomen/pelvis
- For MRI contrast contraindication: CT of the chest, unenhanced MRI of the abdomen/pelvis, and MRI of the thorax on systems that can acquire the entire data set in a single breath-hold or are gated in place of the chest CT

Appendix 7 Impact of Vemurafenib on Concomitant Medications

Substrates		
CYP 1A2[a]	CYP 2C9[a]	CYP3A4[b]
Amitriptyline	**NSAIDs:**	**Macrolide antibiotics:**
caffeine	diclofenac	clarithromycin
clomipramine	ibuprofen	erythromycin
clozapine	lornoxicam	telithromycin
cyclobenzaprine	meloxicam	Anti-arrhythmics:
estradiol	S-naproxen_Nor	quinidine_3OH
fluvoxamine	piroxicam	
haloperidol	suprofen	**Benzodiazepines:**
imipramine N-DeMe		alprazolam
mexilletine	**Oral Hypoglycemic:**	diazepam_3OH
naproxen	tolbutamide	midazolam
olanzapine	glipizide	triazolam
ondansetron	Angiotensin II	
phenacetin_	Blockers:	**Immune Modulators:**
acetaminophen	losartan	cyclosporine
propranolol	irbesartan	tacrolimus (FK506)
riluzole	Sulfonylureas:	HIV Antivirals:
ropivacaine	glyburide	indinavir
tacrine	glibenclamide	nelfinavir
theophylline	glipizide	ritonavir
tizanidine	glimepiride	saquinavir
verapamil	tolbutamide	Prokinetic:
(R)warfarin	amitriptyline	cisapride
zileuton	celecoxib	
zolmitriptan	fluoxetine	**Antihistamines:**
	fluvastatin	astemizole
	glyburide	chlorpheniramine
	nateglinide	terfenadine
	phenytoin-4-OH2	
	rosiglitazone	**Calcium Channel Blockers:**
	tamoxifen	amlodipine
	torsemide	diltiazem
	S-warfarin	felodipine
		lercanidipine

Appendix 7
Impact of Vemurafenib on Concomitant Medications (cont.)

Substrates		
CYP 1A2[a]	CYP 2C9[a]	CYP3A4[b]
		nifedipine2 nisoldipine nitrendipine verapamil **HMG CoA Reductase Inhibitors:** atorvastatin cerivastatin lovastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone **Miscellaneous:** alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-Ndemethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan

Appendix 7
Impact of Vemurafenib on Concomitant Medications (cont.)

Substrates		
CYP 1A2[a]	CYP 2C9[a]	CYP3A4[b]
		lidocaine
		methadone
		nateglinide
		ondansetron
		pimozide
		propranolol
		quetiapine
		quinine
		risperidone
		salmeterol
		sildenafil
		sirolimus
		tamoxifen
		taxol
		terfenadine
		trazodone
		vincristine
		zaleplon
		ziprasidone
		zolpidem

[a] Exposure of these drugs may be increased following vemurafenib treatment.
[b] Exposure of these drugs may be decreased following vemurafenib treatment.

Appendix 8 Medications that Affect the QT Interval

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	