Official Title: **A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB (RO5185426) ADJUVANT THERAPY IN PATIENTS WITH SURGICALLY RESECTED, CUTANEOUS BRAF-MUTANT MELANOMA AT HIGH RISK FOR RECURRENCE**

NCT Number: NCT01667419

Document Date: Protocol Version 10: 24 Oct 17

PROTOCOL

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PROTOCOL NUMBER:	GO27826
VERSION NUMBER:	10
EUDRACT NUMBER:	2011-004011-24
IND NUMBER:	73620
TEST PRODUCT:	Vemurafenib (RO5185426)
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 24 February 2012
DATES AMENDED:	Version 2: 23 April 2012 Version 3: 27 June 2012 Version 4: 25 March 2013 Version 5: 28 August 2013 Version 6: 20 December 2013 Version 7: 18 April 2014 Version 8: 14 April 2015 Version 9: 14 March 2017 Version 10: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Oct-2017 19:11:10

PROTOCOL AMENDMENT, VERSION 10: RATIONALE

Protocol GO27826 has been amended as a result of the primary analysis of efficacy and safety (data cutoff 17 April 2017) and an analysis of secondary malignancies (data cutoff 3 July 2017; approximately 94 weeks after the last patient started study treatment). The study did not meet its primary endpoint. A statistically meaningful disease-free survival benefit for vemurafenib treatment was not demonstrated in Cohort 2, as required by hierarchical testing defined in the Statistical Analysis Plan. Safety analysis showed that patients treated in this study had a safety profile consistent with that of patients treated with vemurafenib for unresectable or metastatic melanoma with *BRAF*^{V600} mutation, an approved indication. The analysis of secondary malignancies demonstrated that overall incidences of cutaneous squamous cell carcinoma (including keratoacanthoma) among the vemurafenib-treated patients in this study was similar to the incidence reported in vemurafenib-treated patients with unresectable or metastatic melanoma with *BRAF*^{V600} mutation across studies: approximately 20%.

Changes to the protocol are summarized below:

- The end of study definition has been refined (see Sections 3.2, 6.4, 6.9, and Appendix 1), the length of patient follow-up has been reduced (see Sections 3.1, 3.2, 4.4.2, 4.5, 4.6, 5.1, 5.3, 5.4, 5.5, and Appendix 1), and in patients who had polyp(s) found at the 3-month post-treatment colonoscopy, a further colonoscopy after an additional 3 years is not required (see Sections 4.5, 5.1, and Appendix 1). The last patient in the treatment phase took their last dose of study medication on 14 September 2016. The reduction in the length of follow-up and earlier closure of the study is based on the following considerations:

  The primary endpoint was not met; therefore, long-term overall survival data are no longer required, as registration plans are no longer being pursued.

  No new safety signals were identified in the primary analysis; therefore, there is no need for additional safety monitoring.

  An extensive safety database exists for vemurafenib, with more than 6,200 patients having been treated in company-sponsored clinical trials and a cumulative market exposure to vemurafenib of more than 45,016 patients.
- The reporting of the term “sudden death” has been updated to also require the presumed cause of death (Section 5.3.5.7).
- Event reporting for hospitalization has been clarified (Section 5.3.5.9).

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

PROTOCOL AMENDMENT, VERSION 10:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1: DESCRIPTION OF STUDY

During Years 3, 4, and 5 of the study, physical examination will be performed every 13±2 weeks, and the aforementioned imaging studies will be performed every 26±4 weeks until recurrence of melanoma or an occurrence of a new primary melanoma or ~~for 5 years after Cycle 1, Day 1~~*until end* of study ~~treatment~~ *(see Section 3.2)*, whichever occurs earlier.

In addition, all patients will undergo contrast-enhanced MRI of the brain (or CT if MRI is generally not available or is contraindicated) every 52±4 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or ~~for 5 years after Cycle 1, Day 1~~*until end* of study ~~treatment~~ *(see Section 3.2)*, whichever occurs earlier.

SECTION 3.2: END OF STUDY

All patients will be followed for melanoma recurrence or occurrence of new primary melanoma *and overall survival for at least 2 years after Cycle 1, Day 1 of study treatment. Patients may be followed for melanoma recurrence or occurrence of new primary melanoma* for up to 5 years and OS for up to 6 years after Cycle 1, Day 1 of study treatment. Patients who exhibit recurrence of melanoma or a new primary melanoma ~~prior to completion of Year 5 of~~*during* the study will be followed for OS. ~~No study related observations (including survival status) are planned after the completion of Year 6 of follow up.~~

~~Data cutoff for~~ *The end of* the ~~final, prospectively~~ *study is* defined ~~OS analysis is projected~~*as the date of the last patient, last visit, which is expected* to occur ~~at~~ approximately ~~72~~ *6* months after the ~~first~~*last* patient ~~is~~ enrolled ~~(initiation of enrollment, Q3 2012; final OS cutoff, Q4 2018) (see Section 6.4).~~*has been followed for 2 years after Cycle 1, Day 1 of the study.*

SECTION 4.4.2: <u>Prohibited Therapy</u>

Follow-up for efficacy, exploratory outcomes, and new primary malignancies will continue until melanoma recurrence or an occurrence of a new primary melanoma ~~for up to 5 years after Cycle 1, Day 1~~*until end of study (see Section 3.2)* or loss to follow-up, withdrawal of consent, or death (whichever occurs first). Patients will be followed for survival ~~for up to 6 years after Cycle 1, Day 1.~~*until end of study (see Section 3.2).*

SECTION 4.5.1.3: Physical Examinations

During post-treatment follow-up, physical examinations will occur every 13 ± 2 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or ~~for 5 years after Cycle 1, Day 1~~*until end* of study ~~treatment~~ *(see Section 3.2)*, whichever occurs earlier.

SECTION 4.5.2.2: Assessments during Study

The following assessments will be done during the study:

[…]

- Physical examinations: Cycle 1 (Day 15 ± 3 days), Cycle 2 (Days 1 and 15, each ± 3 days), Day 1 (± 3 days) of every subsequent 4-week cycle, and at the end-of-treatment visit. Thereafter, physical examinations done by the investigator will be obtained every 13 ± 2 weeks from the last dose of study drug until recurrence of melanoma, occurrence of a new primary melanoma, or ~~for 5 years after Cycle 1, Day 1~~*until end* of study ~~treatment,~~*(see Section 3.2),* whichever occurs earlier. Height will be obtained at screening only.
- All patients will have a colonoscopy to the cecum, with adequate bowel preparation, by a gastroenterologist or his or her designee who is experienced in the colonoscopic diagnosis of colorectal polyps and colorectal cancer within 3 months of discontinuation of study drug. ~~Patients who have polyp(s) found at the colonoscopy will need a follow-up colonoscopy performed after an additional 3 years±3 months.~~ All polyps found at any of the colonoscopies will need to be adequately resected.

[…]

- Imaging studies (surveillance for melanoma recurrence): Contrast-enhanced CT or MRI of the chest, abdomen, and pelvis every 13±2 weeks until Week 104 and every 26±4 weeks thereafter until recurrence of melanoma, occurrence of a new primary melanoma, or ~~for 5 years after Cycle 1, Day 1~~*until end* of study ~~treatment,~~*(see Section 3.2),* whichever occurs earlier. In addition, all patients will undergo contrast-enhanced MRI of the brain (or CT if MRI is not available or is contraindicated) every 52±4 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or ~~for 5 years after Cycle 1, Day 1,~~*until end of study (see Section 3.2),* whichever occurs earlier. Patients who have had a DFS event do not need additional scans or physical exams for melanoma recurrence surveillance. However, these patients must still have a chest CT or MRI for SCC surveillance at 13±2 weeks and 26±2 weeks after last dose of study drug.

[…]

- Serum and plasma samples for exploratory biomarker assessments: Cycle 1 (Day 15±3 days), Cycle 2 (Day 1±3 days), Cycle 3 (Day 1±3 days). Serum and plasma samples should also be collected at the end-of-treatment visit and every 52±2 weeks after last dose of study drug until the recurrence of melanoma, occurrence of a new primary melanoma, or ~~for 5 years after Cycle 1, Day 1~~*until end* of study ~~treatment,~~*(see Section 3.2),* whichever occurs earlier.

[…]

- PROs will be assessed at Cycle 1 (Day 15±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle, at the end-of-treatment visit, and at each scheduled and unscheduled visit during the follow-up period, including the early termination visit. In post-treatment follow-up, the EORTC QLQ-C30 questionnaire will be completed every 13±2 weeks from last dose of study drug until recurrence of melanoma, occurrence of a new primary melanoma, or until ~~5 years after Cycle 1, Day 1,~~*end of study (see Section 3.2),* whichever occurs first.

SECTION 4.5.2.4: Post-Treatment Follow-Up Assessments

Patients who complete or discontinue study treatment without a recurrence or an occurrence of a new primary melanoma will continue to be followed with regular physical examinations (every 13±2 weeks) and imaging studies for a maximum of 5 years from Cycle 1, Day 1 or until a melanoma recurrence or an occurrence of a new primary melanoma *or until end of study (see Section 3.2),* whichever occurs first. All patients will be followed for the occurrence of new primary malignancies, regardless of melanoma recurrence or occurrence of a new primary melanoma, ~~for 5 years from Cycle 1, Day 1.~~*until end of study (see Section 3.2).*

SECTION 4.5.2.7: Survival and New Primary Malignancy Follow-Up Assessments

Survival follow-up information will be collected via telephone calls and/or clinic visits every 13±2 weeks until death, loss to follow-up, or study termination by Roche or ~~for a maximum~~*until end* of ~~6 years from Cycle 1, Day 1.~~*study (see Section 3.2).* Patients will be followed for new primary malignancies ~~for up to 5 years from Cycle 1, Day 1.~~*until end of study (see Section 3.2).*

SECTION 4.6.1.2: Withdrawal from Study

Patients who withdraw their consent to be followed for the primary study endpoint (DFS) will be asked to continue follow-up for OS until ~~a maximumof 6 years from Cycle 1, Day 1,~~ *end of study (see Section 3.2),* as well as for new primary malignancies ~~for up to 5 years from Cycle 1, Day 1.~~*until end of study (see Section 3.2).*

SECTION 5.1.2.3.4: Colorectal Polyps

All patients will be required to undergo a post-treatment colonoscopy within 3 months of discontinuation of study drug. ~~Patients who have polyp(s) found at the post-treatment colonoscopy will need a follow-up colonoscopy performed after an additional 3 years±3 months.~~

SECTION 5.1.2.3.5: New Primary Cancers

All new primary malignancies will be reported ~~for up to 5 years after Cycle 1, Day 1,~~*until end of study (see Section 3.2),* whether or not a patient has exhibited recurrence of melanoma in the study.

SECTION 5.3.1: Adverse Event Reporting Period

After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6). In addition, all new primary malignancies will be reported ~~for up to 5 years after Cycle 1, Day 1,~~*until end of study (see Section 3.2),* whether or not a patient has exhibited recurrence of melanoma while in the study.

SECTION 5.3.5.7: Deaths

~~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. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 5.3.5.9: Hospitalization or Prolonged Hospitalization

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:~~The following hospitalization scenarios are not considered to be serious adverse events:~~

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., complete regional lymphadenectomy)
- 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 adverse event.
- Hospitalization due solely to recurrence/progression of the underlying melanoma

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- *Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours*

SECTION 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 ~~within the 5 years starting from Cycle 1, Day 1.~~*until end of study (see Section 3.2).*

SECTION 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 ~~within the 5 years~~ *until end of study (see Section 3.2)* starting from Cycle 1, Day 1.

SECTION 5.5.1: New Primary Cancers

As noted in Section 5.1.2.3.5, all new primary cancers will be reported for ~~up to 5 years after Cycle 1, Day 1~~*until end of study*, whether or not a patient has experienced melanoma recurrence or an occurrence of a new primary melanoma.

SECTION 6.4.2.2: Overall Survival

The final OS analysis for Cohorts 1 and 2 will be performed ~~after~~*at* the ~~occurrence~~*end* of ~~approximately 107 and 118 deaths, respectively (projected to occur at approximately Month 72 in each cohort) or at Month 72, whichever occurs first. Additional details for interim analyses of OS are provided in Section 6.9 (Interim Analyses~~*study (see Section 3.2*).

SECTION 6.9: INTERIM ANALYSES

The final OS analysis for Cohorts 1 and 2 (see Table 5) will be performed ~~after~~*at* the ~~occurrence~~*end* of ~~approximately 107 and 118 deaths, respectively (projected to occur at approximately Month 72 in each cohort) or at Month 72, whichever occurs first~~*study (see Section 3.2)*.

TABLE 5: Assumptions and Characteristics for Overall Survival Analyses by Cohort

	Cohort 1 n = 300	Cohort 2 n = 175
HR targeted	0.70	0.70
Targeted median (control)	61 months	24.2 months
Targeted median (vemurafenib)	87.1 months	34.6 months
Interim OS (to be performed at time of final DFS analysis)		
Projected number of events (% of final events)	64 (60%)	59 (50%)
Final OS		
~~Number of events (% of final events)~~	~~107 (100%)~~	~~118 (100%)~~
Estimated cutoff date [a]	~~72~~*30* months after ~~FPI~~*LPI*	~~72~~*30* months after ~~FPI~~*LPI*
Alpha level (two sided)	0.05	0.05

DFS = disease-free survival; ~~FPI = first patient in;~~ HR = hazard ratio; *LPI = last patient in;* MDD = minimum detectable difference; OS = overall survival.

Note: 1% annual dropout rate is anticipated for OS analyses.

[a] ~~Estimated data cutoff time from study enrollment date.~~

SECTION 9.4: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

For more information, see the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~

APPENDIX 1: Schedule of Assessments

Appendix 1 has been updated to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VEMURAFENIB (RO5185426) ADJUVANT THERAPY IN PATIENTS WITH SURGICALLY RESECTED, CUTANEOUS BRAF-MUTANT MELANOMA AT HIGH RISK FOR RECURRENCE**
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MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature Date

Please return the signed original of this form to the Sponsor or its designee. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

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EUDRACT NUMBER:	2011-004011-24
IND NUMBER:	73620
TEST PRODUCT:	Vemurafenib (RO5185426)
PHASE:	III
INDICATION:	Melanoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary objective of this study is as follows:

- To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period in patients with completely resected *BRAF*^{V600} mutation–positive, cutaneous melanoma, as measured by disease-free survival (DFS)

The secondary objectives of this study are as follows:

- To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period, as measured by distant metastasis–free survival (DMFS)
- To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period, as measured by overall survival (OS)
- To evaluate the safety and tolerability of vemurafenib in the adjuvant setting
- To assess quality of life (QoL) as measured by EORTC 30-item Quality of Life Questionnaire (QLQ-C30)
- To describe the pharmacokinetics of vemurafenib in the adjuvant setting, assess between-patient variability of pharmacokinetic (PK) parameters, and explore and quantify potential covariates that may contribute to between-patient differences in PK parameters, with use of a population PK approach

Exploratory Objectives

The exploratory objectives of this study are as follows:

- To assess the efficacy outcomes and safety profile of vemurafenib adjuvant treatment in patients whose melanomas harbor non-E mutations of BRAF kinase at amino acid position 600, as detected by DNA sequencing methods
- To assess the relationship between vemurafenib exposure and the risk of melanoma recurrence or occurrence of new primary melanomas, the occurrence of serious adverse events, and abnormalities in safety laboratory parameters
- To assess the relationship between biomarkers and risk of melanoma recurrence or occurrence of new primary melanomas
- To characterize the biomarkers associated with acquisition of resistance to vemurafenib in the adjuvant setting
- To characterize the molecular phenotype of squamous cell carcinoma (SCC; cutaneous [including keratoacanthoma/KA] and non-cutaneous) or other new primary neoplasms that may be observed in patients treated with vemurafenib

Study Design

Description of Study

Study GO27826 is a Phase III, international, multicenter, double-blind, randomized, placebo-controlled study of patients with completely resected, *BRAF*^{V600} mutation–positive melanoma, as detected by the **cobas**® BRAF V600 Mutation Test, at high risk for recurrence.

A total of approximately 475 patients in two separate cohorts will be enrolled.

- Cohort 1 (approximately 300 patients) will include patients with completely resected Stage IIC, IIIA (patients with one or more nodal metastasis $>$ 1 mm in diameter), or IIIB cutaneous melanoma, as defined by the American Joint Committee on Cancer (AJCC) Classification, Version 7 (Balch et al. 2009).
- Cohort 2 (approximately 175 patients) will include patients with Stage IIIC cutaneous melanoma, as defined by this classification scheme.

The primary and secondary efficacy and safety objectives of this study will be evaluated separately for each cohort.

Eligible patients will be randomized (1:1 ratio) to receive placebo or vemurafenib over a 52-week period, with randomization stratified by pathologic stage (Stage IIC, Stage IIIA, Stage IIIB) and region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world) in Cohort 1 and by region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world) in Cohort 2.

Within each cohort, patients will receive study treatment according to one of the following treatment arms:

- Arm A: placebo orally, twice daily (BID) for 52 weeks (thirteen 28-day cycles)
- Arm B: vemurafenib 960 mg orally, BID for 52 weeks (thirteen 28-day cycles)

All eligible patients must have either newly diagnosed melanoma or, at most, one metachronous lymph node recurrence (in the absence of prior lymph node involvement) that has undergone gross total resection; no prior systemic treatment for melanoma is permitted. Full pathologic staging that incorporates the findings from sentinel lymph node biopsy and complete regional lymphadenectomy is required of all patients with lymph node involvement.

All patients will be required to provide a sample of tumor tissue for further *BRAF* mutation testing and exploratory biomarker and correlative science assessments at baseline.

Randomization will occur within 90 days after definitive surgery (i.e., the last surgery required for the treatment or the diagnosis of melanoma), and study drug administration will begin within 4 calendar days after randomization.

The final analysis of the primary endpoint of DFS will occur for each cohort after the targeted number of events for each cohort is reached (approximately 120 DFS events for Cohort 1 and

approximately 105 DFS events for Cohort 2). There will be no interim analyses of the primary endpoint of DFS.

For each cohort, patients without melanoma recurrence or an occurrence of a new primary melanoma and their physicians will remain blinded until the final DFS analysis for that cohort. Physicians may request unblinding for patients who have documented recurrence or an occurrence of a new primary melanoma for purposes of planning subsequent treatment. Unblinding requires prior approval of the Roche Medical Monitor or designee.

In this adjuvant trial, crossover to vemurafenib treatment will not be allowed for patients receiving placebo because this trial is designed to evaluate adjuvant vemurafenib therapy starting within 4 calendar days after randomization and no later than 94 calendar days after definitive melanoma surgery (i.e., the last surgery required for the treatment or the diagnosis of melanoma).

Number of Patients

A total of approximately 475 patients in two separate cohorts will be enrolled.

Target Population

Patients must meet all of the criteria listed below for study entry.

Inclusion Criteria

Disease-Specific Inclusion Criteria

- All patients should have histologically confirmed melanoma of cutaneous origin.
- All patients without clinical or radiologic evidence of regional lymph node involvement must undergo sentinel lymph node biopsy. Patients must undergo a complete regional lymphadenectomy if a sentinel lymph node biopsy procedure cannot be performed or a sentinel lymph node cannot be detected. All patients who have either clinical or radiographic evidence of regional lymph node involvement or evidence of melanoma involvement in the sentinel lymph node must undergo complete regional lymphadenectomy. Melanoma infiltration of lymph node(s) must be histologically confirmed.

  Note: Surgical management should comply with published guidelines for surgical standards of care.
- Patients with lymph node involvement either at initial presentation or a first metachronous nodal recurrence are eligible:

  $T_{any\ (including\ x)}\ N+$ at initial presentation

  $T_{any}N0$ followed by $N+$ recurrence (i.e., first metachronous nodal recurrence)
- Patients with *BRAF*^{V600} mutation–positive, cutaneous melanoma (either pathologic Stage IIC or Stage III according to AJCC Staging Criteria v7) that has been completely resected

  Note: Patients with Stage IIIA disease must have at least one lymph node metastasis measuring >1 mm in diameter (per the Rotterdam classification scheme) on pathologic staging.
- *BRAF*^{V600} mutation status of the current primary tumor or involved lymph node determined to be positive using the **cobas**® BRAF V600 Mutation Test
- The patient must have been surgically rendered free of disease within 90 days of randomization.
- Eastern Cooperative Oncology Group Performance Status of 0 or 1

General Inclusion Criteria

- Male or female patients aged ≥ 18 years
- Ability to participate and willingness to give signed informed consent prior to performance of any study-related procedures and to comply with the study protocol
- Life expectancy of at least 5 years
- Patients must have fully recovered from the effects of any major surgery (including complete regional lymphadenectomy) or significant traumatic injury prior to the first dose of study drug.

Note: All staging-related procedures, including complete regional lymphadenectomy, must be completed within 90 days prior to randomization.

- Negative stool occult blood

  Note: If stool occult blood is positive, the patient will need to be cleared for study inclusion by a gastroenterologist or appropriately trained designee.

- For select patients with known personal history of adenomatous colorectal polyps or colorectal cancer, family history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer at or after the age of 60 years, or signs or symptoms that could be related to colon cancer as determined by the site investigator or designee, a screening colonoscopy with adequate resection of all visualized polyps must be performed.

  Note: For select patients requiring a screening colonoscopy (described above), colonoscopy should be complete to the cecum, with adequate bowel preparation, and performed within the 90-day screening period. For select patients (described above), screening colonoscopy is not required if colonoscopy to the cecum with adequate bowel preparation and adequate resection of all visualized polyps was performed within 1 year of the start of the 90-day screening period, unless the site investigator deems it necessary.

  Note: A history of colon cancer greater than 5 years prior to randomization does not preclude patients from being eligible.

- Adequate hematologic, liver, and renal function, defined by the following laboratory results obtained within 28 days prior to randomization:

  Absolute neutrophil count $\geq 1.5 \times 10^9$/L

  Platelet count $\geq 100 \times 10^9$/L

  Hemoglobin ≥ 9 g/dL

  Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN)

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN

  Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockroft–Gault glomerular filtration rate estimation:

  $$[(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})]/[72 \times (\text{serum creatinine in mg/dL})]$$

  PT, INR, aPTT $\leq 1.5 \times$ ULN

- Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two effective forms of contraception beginning from the informed consent signature date until at least 6 months after completion of study therapy.

  In general, effective forms of contraception include surgical sterilization, a reliable barrier method with spermicide, birth control pills or patches, intrauterine contraceptive device, or contraceptive hormone implants. Please note that vemurafenib may decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including hormonal contraceptives; consider the use of alternative effective methods of contraception.

  Female patients of childbearing potential are defined as sexually mature women without prior hysterectomy who have had any evidence of menses within the past 12 months.

  In order to be considered NOT of childbearing potential, amenorrhea for a period of 12 months or longer must have occurred in the absence of chemotherapy, anti-estrogens, or ovarian suppression.

- Negative serum pregnancy test within 14 days prior to randomization in women of childbearing potential
- Women of non-childbearing potential need not undergo pregnancy testing.
- Absence of any psychological, familial, sociological, or geographical condition that has the potential to hamper compliance with the study protocol and follow-up schedule (such conditions should be discussed with the patient before trial entry)

Exclusion Criteria

Patients who meet any of the criteria listed below will be excluded from study entry.

Cancer-Related Exclusion Criteria

- History of any systemic or local therapy (e.g., chemotherapy, biologic or targeted therapy, hormonal therapy, or photodynamic therapy) for the treatment or prevention of melanoma, including interferon alpha-2b and pegylated interferon alpha-2b
- History of limb perfusion therapy
- History of radiotherapy for the treatment of melanoma including but not limited to radiation therapy to a resected nodal basin
- History of radiotherapy for the treatment of prostate, cervical, or rectal cancer
- Allergy or hypersensitivity to components of the vemurafenib formulation
- Invasive malignancy other than melanoma at the time of enrollment or within 5 years prior to first study drug administration, except for adequately treated (with curative intent) basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, in situ ductal adenocarcinoma of the breast, in situ prostate cancer, or limited stage bladder cancer

  Note: This requires that the pathology evaluation of the screening Papanicolaou smear and of any polyps resected at the screening colonoscopy does not show any invasive malignancy.
- Family history of inherited colon cancer syndromes (e.g., familial adenomatous polyposis, attenuated adenomatous polyposis, MUTYH-associated polyposis, hyperplastic polyposis syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Lynch syndrome, and Cowden syndrome) and/or history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer before the age of 60 years
- Known personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) >2 cm in size. This also applies to the screening colonoscopy for select patients.
- History of or current clinical, radiographic, or pathologic evidence of in-transit metastases, satellite, or microsatellite lesions

  Note: In-transit metastases are any skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin. Satellite lesions are skin or subcutaneous lesions within 2 cm of the primary tumor that are considered intralymphatic extensions of the primary mass. Microsatellite lesions are any discontinuous nest of metastatic cells more than 0.05 mm in diameter that are clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of melanoma by a distance of at least 0.3 mm (McCardle et al. 2011).
- History of or current clinical, radiographic, or pathologic evidence of recurrent lymph node involvement after resection of a primary melanoma with lymph node involvement at any time in the past
- History of local and/or regional and/or distant melanoma recurrence (excluding first metachronous nodal recurrence)

  Note: This does not include patients who have had a new primary melanoma.
- History or current radiographic or pathologic evidence of distant metastases as defined either by an abnormal contrast-enhanced brain magnetic resonance imaging (MRI; or brain computed tomography if MRI is not generally available or is contraindicated) or histologically proven, distant metastatic disease (visceral or cutaneous) in an extracranial site

  Note: This includes patients who have had their metastatic disease resected.

Cardiac Exclusion Criteria

- History of clinically significant cardiac or pulmonary dysfunction, including the following:
  - Current, uncontrolled Grade ≥2 hypertension
  - Unstable angina
  - Current Grade ≥2 dyspnea or hypoxia or need for supplemental oxygen
  - History of symptomatic congestive heart failure of Grade II–IV New York Heart Association Class (NYHA) (for the Criteria Committee of the NYHA 1994)
  - Serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia
  - History of myocardial infarction within 6 months prior to randomization
  - History of congenital long QT syndrome or QTc interval >450 ms at baseline
  - History of or current uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or magnesium

General Exclusion Criteria

- Major surgical procedure (other than wide local excision, sentinel lymph node biopsy, or complete regional lymphadenectomy) or significant traumatic injury within 4 weeks prior to the first dose of study drug.
- History of clinically significant liver disease (including cirrhosis), current alcohol abuse, or known infection with HIV, hepatitis B virus, or hepatitis C virus
- Active infection or chronic infection requiring chronic suppressive antibiotics
- Pregnancy or breastfeeding at the time of randomization
- Autoimmune disease (e.g., systemic lupus erythematosus, autoimmune vasculitis, inflammatory bowel disease [Crohn's disease and ulcerative colitis])
- Acromegaly
- History of malabsorption or other clinically significant metabolic dysfunction
- Any other serious concomitant medical condition that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to participate in the study
- Requirement for a concomitant medication or dietary supplement that is prohibited during the study
- Unwillingness or inability to comply with study and follow-up procedures
- Current, recent (within 28 days prior to randomization) or planned use of any investigational product outside of this study

Length of Study

All patients will be followed for melanoma recurrence or occurrence of new primary melanoma *and overall survival for at least 2 years after Cycle 1, Day 1 of study treatment. Patients may be followed for melanoma recurrence or occurrence of new primary melanoma* for up to 5 years and OS for up to 6 years after Cycle 1, Day 1 of study treatment. Patients who exhibit recurrence of melanoma or a new primary melanoma *during* the study will be followed for OS.

End of Study

The end of the *study is defined as the date of the last patient, last visit, which* is *expected* to occur approximately *6* months after the *last* patient enrolled *has been followed for 2 years after Cycle 1, Day 1 of the study. The final OS analysis will occur at the end of study.*

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are described below.

Primary Efficacy Outcome Measure

DFS will be defined as the time from randomization until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause. The DFS component of melanoma recurrence will be assessed by the investigator. The DFS component of an occurrence of a new primary melanoma will be based upon the diagnosis made by a Roche-designated central pathology laboratory.

Secondary Efficacy Outcome Measures

DMFS will be defined as the time from randomization until the date of diagnosis of distant (i.e., non-locoregional) metastases or death from any cause.

OS will be defined as the time from randomization to the date of death from any cause.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v4.0.
- Changes from baseline in ECG findings and targeted clinical laboratory analytes during the course of study treatment

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Plasma concentrations of vemurafenib at clinically relevant timepoints, including steady-state trough values as well as those associated with diagnosis of SCC, dose interruption, and/or reduction for toxicity, melanoma recurrence, and occurrence of a new primary melanoma

Patient-Reported Outcome Measures

The patient-reported outcome measure for this study is as follows:

- To assess patient-reported symptoms, functional interference, and health-related QoL in the vemurafenib and placebo treatment arms with use of EORTC QLQ-C30

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Retrospective identification of study patients whose tumors harbor non-E, activating mutations of BRAF kinase at amino acid position 600 (e.g., $BRAF^{V600K}$), with use of DNA sequencing methods as a means to assess clinical outcomes in this patient subgroup
- Levels of candidate tumor biomarkers in plasma and serum (e.g., circulating mutant *BRAF* DNA) at different timepoints during the study compared with baseline as a means to monitor for and predict melanoma recurrence or occurrence of a new primary melanoma
- Candidate tumor biomarkers at the protein, RNA, and DNA levels (including *RAS* mutations) that may characterize the molecular phenotype of tumors at melanoma recurrence or occurrence of a new primary melanoma as well as predict development of resistance to adjuvant vemurafenib treatment
- Molecular characterization of SCC (cutaneous [including KA] and non-cutaneous) or other new primary neoplasms that may be observed in patients treated with vemurafenib

Investigational Medicinal Products

Vemurafenib or placebo will be taken at home, orally, at a dose of 4 tablets BID for a maximum of 52 consecutive weeks (thirteen 28-day cycles).

Test Product

Study drug will be taken at home, orally, at a dose of 4 tablets BID for a maximum of 52 consecutive weeks (thirteen 28-day cycles).

The first dose is to be taken in the morning, and the second dose is to be taken approximately 12 hours later in the evening. Study drug tablets are to be swallowed whole with water. The tablets should not be chewed or crushed. If a dose is missed, it can be taken 4 or more hours prior to the next dose to maintain the BID regimen. Both doses should not be taken at the same time. Missed days or drug holidays will not be made up, thereby maintaining 52 weeks of treatment. A patient who has a break in dosing in excess of 28 consecutive days will be permanently discontinued from study treatment.

Patients will be asked to record the date and time of doses in a diary and to return all used and unused drug supply containers as a measure of compliance. All supplies, including partially used or empty containers of study drug, must be returned to the Roche study monitor at the end of the study, unless alternative destruction has been authorized by Roche/designee or is required by local or institutional regulations. Copies of all drug dispensing and inventory logs must be returned to the Roche study monitor at the end of the study.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Unless otherwise noted, all efficacy analyses will include all randomized patients (intent-to-treat analysis), and patients will be grouped according to the treatment assigned at randomization. The primary and all secondary objectives of this study will be evaluated separately for each cohort.

Primary Analysis

The primary endpoint, DFS, is defined as the time from randomization until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause. The DFS component of melanoma recurrence will be assessed by the investigator. The DFS component of an occurrence of a new primary melanoma will be based upon the diagnosis made by a Roche-designated central pathology laboratory. For patients without a DFS event at the time of data cutoff, data will be censored at the date of the last disease assessment. Details on censoring in the analysis of this endpoint are described in the Statistical Analysis Plan (SAP).

For patients whose recurrence has been proven histologically, the date of melanoma recurrence will be defined as the earliest date of the scan or clinical examination that prompted the biopsy. For patients whose suspicious lesions were deemed not amenable to biopsy or for patients who refuse a biopsy, the date of melanoma recurrence will be defined as the earliest date of the scan or clinical examination that would have prompted a biopsy. For patients with an occurrence of a new primary melanoma, the date of the new primary melanoma will be defined as the earliest date of the clinical examination or scan that prompted the biopsy.

The final analysis of the primary endpoint of DFS will take place when approximately 120 DFS events have occurred for Cohort 1 and approximately 105 DFS events have occurred for Cohort 2. The final DFS analyses for both cohorts will be conducted at the same time by using the dataset from the same data cutoff date for both cohorts. The primary efficacy analyses will be comparisons of the two treatment groups, using a two-sided, stratified log-rank test for Cohort 1 and Cohort 2 separately. To account for separate analysis for each cohort, the statistical significance of the comparison of DFS between treatment arms will be based an alpha level of 0.05 (two sided) of the family-wise Type I error rate for two tests of two cohorts. Detailed testing procedures will be provided in the SAP.

Median DFS time will be estimated using the Kaplan-Meier method, and the two-sided 95% CI will be calculated using the method of Brookmeyer and Crowley (1982) for each cohort.

The HR of DFS (recurrence, new primary melanoma, or death) and the associated two-sided 95% CI will be estimated by using a stratified Cox proportional hazards model.

The stratification factors in the stratified analyses are the stratification factors used in randomization of patients in each cohort. For Cohort 1, stratified analyses will incorporate two stratification factors: pathologic stage (Stage IIC; Stage IIIA; Stage IIIB) and region (North

America, Australia/New Zealand/South Africa/Latin America, rest of the world). For Cohort 2, stratified analyses will incorporate one stratification factor, region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world).

In addition, Kaplan-Meier methodology will be used to estimate landmark (e.g., 1-year, 2-year, and 3-year) DFS rates and the associated two-sided 95% CIs for each treatment arm, and the Kaplan-Meier curves will be provided.

Subgroup analyses for the primary efficacy outcome, DFS, will be performed to assess the robustness of the results across patient subgroups in each cohort separately. The subgroups will include but are not limited to the categories of demographic (age, sex), baseline disease characteristics, *BRAF* mutation status such as V600E versus non-V600E, and stratification variables.

Secondary Analysis

DMFS and OS are the secondary efficacy endpoints.

DMFS is defined as the time from randomization until the date of diagnosis of distant (i.e., non-locoregional) metastasis or death from any cause. Details on censoring in the analysis of this endpoint are described in the SAP. DMFS will be analyzed at the time of the final DFS analysis in each cohort. The analysis methods to be employed for DMFS are the same as those described for the primary endpoint of DFS.

OS is defined as the time from randomization until the date of death from any cause. For patients still alive at the time of analysis, the data will be censored at the date the patient was last known to be alive. The study is not powered for OS, so adequate power statistical testing for this endpoint is not possible. However, some standard OS estimates will be provided by using the same analysis methods as those described for the primary endpoint of DFS.

Two OS analyses are planned for each cohort. The OS interim analysis in each cohort will be performed at the time of the final DFS analysis for both cohorts. The final OS analysis for Cohorts 1 and 2 will be performed *at the end of study*.

Determination of Sample Size

Cohort 1

The final analysis of the primary endpoint of DFS for Cohort 1 will take place when approximately 120 DFS events have occurred, on the basis of the following assumptions:

- Two-sided, stratified log-rank test at the 0.05 significance level
- 80% power
- Median DFS for the control arm of 24 months and estimated median DFS in the vemurafenib treatment arm of 40 months (which corresponds to an HR of 0.60)
- 5% annual loss to follow-up for DFS
- No interim analysis

Assuming an accrual rate of 8 patients per month in Cohort 1 and a 17-month ramp-up period to reach steady-state enrollment, approximately 300 patients will be required to be enrolled in Cohort 1 during 43 months and followed for an additional 7 months in order to observe 120 DFS events.

On the basis of the assumptions above, 120 DFS events are projected to occur in Cohort 1 approximately 50 months after the first patient is randomized in this study. At that time, it is projected that median follow-up time will be 21 months in Cohort 1, and the minimum follow-up time (e.g., for the last patient randomized) is projected to be 7 months. Also on the basis of the assumptions of 120 DFS events required and a target HR of 0.60, it is projected that an observed HR of 0.70 or better in the DFS analysis will result in a statistically significant difference between treatment arms (i.e., HR of 0.70 is the minimally detectable difference for that analysis).

For Cohort 1, on the basis of the assumptions of a target HR of 0.60, 120 DFS events would also provide 80% power to detect a 16% absolute increase in the 2-year DFS rate (50% vs. 66%, corresponding to a 40% risk reduction; i.e., HR of 0.60).

Cohort 2

The final analysis of the primary endpoint of DFS for Cohort 2 will take place when approximately 105 DFS events have occurred, on the basis of the following assumptions:

- Two-sided, stratified log-rank test at the 0.05 significance level
- 80% power
- Median DFS for the control arm of 7.7 months and estimated median DFS in the vemurafenib treatment arm of 13.3 months (which corresponds to an HR of 0.58)
- 5% annual loss to follow-up for DFS
- No interim analysis

Assuming an accrual rate of 5 patients per month in Cohort 2 and a 27-month ramp-up period to reach steady-state enrollment, approximately 175 patients will be required to be enrolled in Cohort 2 over 40 months in order to observe 105 DFS events.

For Cohort 2, on the basis of the assumptions of a target HR of 0.58, 105 DFS events would provide 80% power to detect a 17% absolute increase in the 2-year DFS rate (12% vs. 29%, corresponding to a 42% risk reduction; i.e., HR of 0.58).

Interim Analyses

No interim analyses of the primary endpoint, DFS, will be performed.

As stated in the protocol, two OS analyses (one interim analysis and one final analysis) are planned for each cohort. The OS interim analysis will be performed at the time of the final DFS analysis for each cohort. The final OS analysis for Cohorts 1 and 2 will be performed *at the end of study*. The Lan-DeMets implementation (Lan and DeMets 1983) of the O'Brien-Fleming use function will be used to control the overall Type I error for the OS comparison in each cohort at a two-sided 0.05 significance level.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AJCC	American Joint Committee on Cancer
anti-HBc	hepatitis B core antibody
AUC	area under the concentration-time curve
AUC_{0-last}	area under the concentration-time curve from Time 0 to last measurable concentration
BID	twice daily
BORR	best overall response rate
CRO	contract research organization
CT	computed tomography (scan)
cuSCC	cutaneous squamous cell carcinoma
CYP	cytochrome P450
DFS	disease-free survival
DILI	drug-induced liver injury
DMFS	distant metastasis–free survival
DSMB	Data Safety Monitoring Board
DTIC	dacarbazine
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire
ERK	extracellular-signal-regulated kinase
FDA	U.S. Food and Drug Administration
FDG-PET	fluorodeoxyglucose–positron emission tomography
FF	fresh frozen
FFPE	formalin-fixed paraffin-embedded
GGT	gamma glutamyl transferase
GM-CSF	granulocyte macrophage colony–stimulating factor
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papilloma virus
HR	hazard ratio

Abbreviation	Definition
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
IxRS	interactive voice or Web response system
KA	keratoacanthoma
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association Class
OS	overall survival
Pap	Papanicolaou
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PRO	patient-reported outcome
QoL	quality of life
QTc	corrected QT
RCR	Roche Clinical Repository
RFS	relapse-free survival
SAP	Statistical Analysis Plan
SCC	squamous cell carcinoma
TMA	tissue microarray
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON MELANOMA

Melanoma is one of the most deadly skin cancers. In the United States, a total of 68,130 new cases of and 8700 deaths from melanoma are estimated to have occurred in 2010 (Jemal et al. 2010). In Europe, approximately 26,100 males and 33,300 females are diagnosed annually with melanoma, and approximately 8300 males and 7600 females die from the disease every year (de Vries et al. 2003). Australia has the highest incidence of melanoma in the world (Whiteman et al. 1997), and in the Australian state of Victoria, melanoma is the fourth most common cancer in males and the third most common in females (Victorian Cancer Registry 2011). Worldwide, the incidence of melanoma has been increasing at a rapid rate (Linos et al. 2009; Rigel et al 2010). Ultraviolet light exposure is a well-known environmental risk factor for melanoma (Erdei and Torres 2010).

Detection and surgical treatment of early-stage disease seem to prevent progression in most cases. However, patients with deep primary tumors or tumors that metastasize to regional lymph nodes frequently develop distant metastases. Median survival after the onset of distant metastases is only 6–9 months, and the 5-year survival rate is $<5\%$ (Balch et al. 2009).

The primary treatment modality for localized cutaneous melanoma is surgery. Wide local excision and sentinel lymph node biopsy are considered the standard of care for patients with localized cutaneous melanoma (Garbe et al. 2012; National Comprehensive Cancer Network 2013). Regional lymphadenectomy is indicated if the results of the sentinel lymph node biopsy reveal the presence of micrometastatic melanoma or if enlarged lymph nodes are present upon physical examination or radiographic imaging studies.

Staging of localized, cutaneous melanoma is based on clinical and pathologic criteria (Balch et al. 2009) and relies on characteristics of the primary tumor (i.e., tumor thickness and the presence or absence of ulceration), the extent of involvement of regional lymph nodes, and the presence or absence of satellite or “in-transit” metastases. Appendix 10 describes the current staging algorithm promulgated by the American Joint Committee on Cancer (AJCC) for cutaneous melanoma (Balch et al. 2009).

Data from cooperative group and surveillance epidemiology studies reveal a high risk of recurrence in patients with locally advanced, resectable melanomas. Specifically, patients with Stage IIC and Stage III disease (patients with Stage IIIA disease having at least one nodal metastasis >1 mm in diameter) exhibit a $>50\%$ risk of melanoma recurrence and a 40%–60% mortality rate at 5 years after surgical resection of their primary malignancy (see Table 1).

Table 1 Risks Associated with Melanoma on the Basis of AJCC Stage

Stage	5-Year Risk of Recurrence	RFS (median, months)	OS at 5 years[a]	Incidence per 1×10^5 Population[b]
IIC	>50%	22.2[c]	54%	0.5 (2.2%)
IIIA[d]	>50%	NA	50%[e]	—
IIIB	>50%	18.7[f]	59%	0.5 (2.2%)
IIIC	>50%	7.7[f]	40%	0.3 (1.32%)

AJCC = American Joint Committee on Cancer; NA = not available; OS = overall survival; RFS = relapse-free survival.

[a] Balch et al. 2009.

[b] National Cancer Institute 2007.

[c] Kirkwood et al. 2004.

[d] At least one nodal metastasis > 1 mm in diameter.

[e] Eggermont AM, "Update on staging, tumor burden and adjuvant therapy," presented at Perspectives in Melanoma XIV Conference, Sept 17–18, 2010.

[f] Eggermont et al. 2008.

The only widely approved adjuvant therapy for melanoma patients at high risk for recurrence is interferon alpha-2b with a high-dose regimen (PDR Network 2011). Interferon alpha-2b is administered intravenously at a dose of 20 million IU/m^2 daily for 5 days per week for a 4-week period followed by 10 million IU/m^2 administered subcutaneously 3 days a week (every other day) for 48 weeks.

A pooled analysis of results derived from Eastern Cooperative Oncology Group (ECOG) and Intergroup trials showed that high-dose interferon alpha-2b is associated with a relapse-free survival (RFS) but not an overall survival (OS) advantage (Kirkwood et al. 2004). A recent meta-analysis in patients with high-risk melanoma (Mocellin et al. 2010) concluded that adjuvant interferon therapy improved both disease-free survival (DFS) and OS in patients with high-risk cutaneous melanoma; however, the randomized studies that were included in this meta-analysis were widely disparate with regard to dose, duration of therapy, and comparator arm.

A large, randomized adjuvant therapy trial in Stage III melanoma patients treated with pegylated interferon alpha-2b was conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Study Group (Eggermont et al. 2008). Patients were stratified by the presence of microscopically versus macroscopically involved lymph nodes. The dose of pegylated interferon alpha-2b was 6 μg/kg of body weight for the first 8 weeks followed by 3 μg/kg for 5 years. The results indicate a statistically significant prolongation of RFS for all patients and a significant benefit in distant metastasis–free survival (DMFS) in patients with microscopic lymph node involvement. There was no significant benefit in terms of OS for pegylated interferon–treated patients. Although this regimen was recently approved

in the United States, pegylated interferon is not currently approved in Europe for adjuvant melanoma therapy.

High-dose and pegylated interferon have significant toxicities that affect the tolerability, compliance, and effectiveness of this agent in the adjuvant setting (Hauschild et al. 2008). The most common toxicities include flu-like symptoms (fever, myalgia and fatigue, nausea, vomiting, headache), myelosuppression, liver function abnormalities, and depression (Hauschild et al. 2008; PDR Network 2011). Kirkwood et al. (1996) reported a 76% incidence of at least one severe or life-threatening adverse event as well as two lethal adverse events from hepatic toxicity in patients treated with high-dose interferon alpha-2b. In this study (ECOG 1684), approximately one-third of interferon-treated patients required at least one reduction in dose for toxicity. In the recent EORTC 18991 trial that evaluated the adjuvant administration of pegylated interferon alpha-2b for up to 5 years, 31% of 608 pegylated interferon–treated patients discontinued study treatment for toxicity, and the median duration of treatment was only 12 months (Eggermont et al. 2008).

A number of studies have focused on the safety and efficacy of low-dose interferon alpha-2b in the adjuvant treatment of resected cutaneous melanoma. Patients in these studies have received 3 million IU three times per week for 6–24 months (Grob et al.1998; Pehamberger et al. 1998; Hancock et al. 2004; Richtig et al. 2005). These studies have either demonstrated no benefit on RFS or OS in association with low-dose interferon therapy (Hancock et al. 2004; Richtig et al. 2005) or enrolled only Stage II patients who did not have the benefit of sentinel lymph node biopsy (Grob et al. 1998; Pehamberger et al. 1998). Thus, there are no studies that demonstrate durable effects of low-dose interferon on RFS in adequately staged patients with Stage IIC or Stage III disease.

Prospective randomized studies using various non-specific immunostimulatory agents (such as bacille Calmette-Guérin, Corynebacterium parvum, levamisole, and mistletoe extract), cytokines (such as interferon gamma, interleukin-2, and granulocyte macrophage colony-stimulating factor [GM-CSF]), and melanoma-specific vaccines have not shown any therapeutic efficacy in the adjuvant setting (Garbe et al. 2008).

In summary, there is currently no international consensus regarding the dose, duration, or use of interferon alpha-2b for the treatment of melanoma in the adjuvant setting (Hauschild et al. 2008). There is no generally accepted standard of care for adjuvant therapy in patients with resected cutaneous melanoma at high risk for recurrence that is both effective and well tolerated (Balch et al. 2009; Dummer et al. 2010). Consequently, patients are very often offered participation in clinical trials of investigational adjuvant therapies (Marsden et al. 2010).

1.2 BACKGROUND ON VEMURAFENIB

1.2.1 Role of BRAF Kinase in Melanoma

Recent advances in the understanding of the biology of melanoma have identified the role of BRAF kinase, a serine-threonine kinase downstream of RAS within the mitogen-activated protein kinase (MAPK) pathway. Mutated BRAF dimers constitutively activate the MAPK pathway leading to the generation of transcriptional signaling that promotes tumor growth. *BRAF* mutations 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) (Maldonado et al. 2003; Beeram et al. 2005; Curtin et al. 2005; Lang and MacKie 2005). *BRAF* mutations are uncommon in acral, mucosal, and uveal melanomas. At the same time, *BRAF* mutations are common in benign nevi, suggesting that they are an early event in melanoma oncogenesis. Approximately 90% of the *BRAF* mutations seen in metastatic melanoma occur in codon V600, and over 90% of the V600 mutations involve the substitution of valine for glutamate at amino acid 600 of the BRAF kinase (i.e., V600E; 1799 T→A) (Sanger Institute 2011). 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, similar to V600E, result in constitutive activation of the BRAF kinase. Most of the transforming activity of $BRAF^{V600}$ is thought to occur through the constitutive activation of the MAPK pathway (Gray-Schopfer et al. 2007). Depletion of mRNA that codes for oncogenic BRAF by small interfering RNA leads to growth inhibition of melanoma cell lines in vitro (Sumimoto et al. 2004), thus leading to the development of agents that can inhibit mutated BRAF kinase and to tests that can identify V600 mutations (Ascierto et al. 2010; Flaherty et al. 2010; Vultur et al. 2011).

The **cobas**® BRAF V600 Mutation Test and Sanger sequencing techniques have been used to identify $BRAF^{V600E}$ mutation status in clinical trials.

1.2.2 Vemurafenib BRAF Inhibitor

Vemurafenib (formerly RO5185426) is a low–molecular weight, orally available inhibitor of the oncogenic form of the BRAF kinase commonly found in melanoma. It is a potent and highly selective inhibitor of V600-mutant BRAF.

1.2.3 Clinical Pharmacokinetics of Vemurafenib

The clinical pharmacokinetics of vemurafenib are based on data available from five studies in patients who received the commercial (microprecipitated bulk powder) formulation: Study NP22676, a cytochrome P450 (CYP) metabolism study in patients with $BRAF^{V600}$ mutation–positive Stage IV melanoma; Study NP25158, a mass balance study in patients with $BRAF^{V600}$ mutation–positive Stage IV melanoma; Study NP25163, a dose-escalation study in patients with $BRAF^{V600}$ mutation–positive unresectable Stage IIIC or Stage IV melanoma; Study NP22657, a Phase II, open-label study in patients with $BRAF^{V600}$ mutation–positive Stage IV melanoma, in which the effects of

vemurafenib on the QT interval were evaluated; and Study NO25026, a Phase III, randomized, controlled study in patients with *BRAF*^{V600} mutation–positive unresectable Stage IIIC or Stage IV melanoma. Detailed descriptions of the design and pharmacokinetic (PK) results for each of these studies are provided in the Vemurafenib Investigator's Brochure (IB).

On the basis of dose-limiting toxicities reported at the 1120-mg twice daily (BID) dose level, the 960-mg BID dose was considered the maximum tolerated dose (MTD) and selected for use in all subsequent clinical trials, including the Phase I (Study PLX06-02) treatment extension cohorts, the aforementioned clinical pharmacology studies, and the Phase II (Study NP22657) and Phase III (Study NO25026) studies in patients with unresectable Stage IIIC or metastatic melanoma.

Population PK analysis using pooled data from 458 patients estimated the median of the steady-state maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), and area under the concentration–time curve (AUC) from 0 to 12 hours (AUC_{0-12hr}) to be 62 μg/mL, 59 μg/mL, and 734 μg/mL × hour, respectively. The pharmacokinetics of vemurafenib are shown to be dose proportional between 240 and 960 mg BID, and a population PK analysis also confirmed that the pharmacokinetics of vemurafenib are linear.

Vemurafenib at a dose of 960 mg BID (240-mg film-coated tablets) is absorbed with a median time to maximum concentration (t_{max}) of approximately 4 hours. Vemurafenib exhibits marked accumulation after repeat dosing at 960 mg BID, with high inter-patient variability. The median accumulation ratio estimate for a BID regimen is 7.36. In the Phase II study, mean vemurafenib plasma concentration 4 hours after dose increased from 3.6 μg/mL on Day 1 to 49.0 μg/mL on Day 15 (range: 5.4–118 μg/mL).

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

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

The apparent volume of distribution for vemurafenib in patients with metastatic melanoma on the basis of population PK analysis is estimated to be 91 L (with 64.8% between-patient variability). It is highly bound to human plasma proteins in vitro (> 99%).

The relative proportions of vemurafenib and its metabolites recovered in blood, urine, and feces were characterized in a human mass balance study at Genentech.
On average, 95% of the dose was recovered within 18 days, the majority (94%) in feces,

with $<1\%$ recovered in urine. The parent compound was the predominant component (95%) in plasma.

The commercial dosage form of vemurafenib is the 240-mg film-coated tablet.

1.2.4 Efficacy of Vemurafenib in Patients with *BRAF*^{V600} Mutation–Positive Metastatic Melanoma

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

Results of the Phase II, open-label, single-arm study (Study NP22657) of vemurafenib in 132 patients with progression of metastatic melanoma after first-line treatment showed a confirmed BORR of 53% on the basis of independent review committee assessments. The median duration of response and PFS were 6.7 and 6.1 months, respectively (Vemurafenib IB).

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

A total of 675 patients were randomized to vemurafenib ($n=337$) or DTIC ($n=338$). Randomization was stratified according to disease stage, LDH, ECOG Performance Status, and geographic region. Baseline characteristics were well balanced between treatment groups. Of the patients randomized to vemurafenib, most were male (59%) and White (99%), median age was 56 years (28% were ≥ 65 years), all patients had ECOG Performance Status of 0 or 1, and the majority of patients had Stage M1c disease (66%). The co-primary efficacy endpoints of the study were OS and PFS.

At the preplanned interim analysis for OS, the Data Safety Monitoring Board (DSMB) recommended a release of the study results because of the compelling efficacy findings. Statistically significant and clinically meaningful improvements were observed in the co-primary endpoints of OS ($p<0.0001$) and PFS ($p<0.0001$) (unstratified log-rank test). Statistical analyses used a clinical cutoff date of 31 March 2011. After a median 6.21 months of follow-up in the vemurafenib arm, the Kaplan-Meier estimate of median survival of patients randomized to vemurafenib was not reached (expected 95% CI: 9.59 months). For patients randomized to receive DTIC, after a median

4.46 months of follow-up, the Kaplan-Meier estimate of median survival was 7.89 months (95% CI: 7.26, 9.63). The Kaplan-Meier estimate of the 6-month survival rate for patients randomized to vemurafenib was 83% (95% CI: 79%, 87%) and 63% (95% CI: 57%, 69%) for 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 resulted in a clinically meaningful and statistically significant improvement in PFS compared with DTIC treatment ($p < 0.0001$). There was a statistically significant improvement in BORR (confirmed) with vemurafenib (48.4%; 95% CI: 41.6%, 55.2%) compared with DTIC (5.5%; 95% CI: 2.8%, 9.3%; $p < 0.0001$), as assessed by the investigator.

Detailed descriptions of the design and results for each of these studies are provided in the Vemurafenib IB.

1.2.5 Safety of Vemurafenib

The safety evaluation of vemurafenib is based on results in patients from three Genentech clinical pharmacology studies (Study NP22676, n=25; Study NP25163, n=52; and Study NP25158, n=7), a Phase I study, (Study PLX06-02, n=108; Vemurafenib IB), a single-arm, Phase II study in previously treated patients with *BRAF*^{V600} mutation–positive Stage IV melanoma (Study NP22657, n=132; Vemurafenib IB; Sosman et al. 2012), and a Phase III, randomized, open-label, multicenter, global study in patients with unresectable Stage IIIC or Stage IV *BRAF*^{V600} mutation–positive melanoma (Study NO25026, n=675; Vemurafenib IB; Chapman et al. 2011). The type and incidence of adverse events observed across all studies in patients with *BRAF*^{V600} mutation–positive unresectable or metastatic melanoma patients were consistent.

In the clinical pharmacology Study NP25163, all 52 patients (100%) had at least one adverse event. Nearly all patients (96%) had at least one treatment-related adverse event. The majority of adverse events were of mild or moderate intensity. The most common adverse events (reported in ≥30% of patients) in the vemurafenib group were fatigue (58%), arthralgia (58%), nausea (50%), rash (38%), and diarrhea (33%). Fifty-four percent of patients had at least one Grade ≥3 adverse event; 40% of patients had at least one treatment-related adverse event. The most commonly reported treatment-related adverse events (incidence ≥5%) were squamous cell carcinoma (SCC) of skin (23%), increased gamma glutamyl transferase (GGT; 9%), basal cell carcinoma (7%), rash (7%), maculopapular rash (6%), and arthralgia (6%). Twelve patients (23%) experienced at least one Grade 4 adverse event, including 2 patients who experienced two Grade 4 adverse events. Five of the 12 patients had Grade 4 adverse events that were assessed by the investigator as treatment related. The most frequent Grade 4 adverse event was increased GGT (n=5 patients, assessed as related to treatment in 4 patients). The other Grade 4 adverse events were hyperuricemia (assessed as related to treatment) and pneumonia, sepsis, convulsion, pseudomonas infection,

staphylococcal infection, multi-organ failure, and pulmonary embolism (all of which were assessed as unrelated to study treatment).

Study PLX06-02 (Flaherty et al. 2010; Vemurafenib IB) assessed the safety of escalating doses of vemurafenib. At the highest dose administered (1120 mg BID), dose-limiting rash (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Grade 3) and fatigue (Grade 3) were observed in multiple patients. Vemurafenib doses of up to 960 mg BID (the MTD) were generally well tolerated.

In the Phase II clinical trial (Study NP22657) (Sosman et al. 2012), all patients experienced at least one adverse event, the most common of which were arthralgia (68%), fatigue (57%), rash (54%), photosensitivity (52%), nausea (42%), alopecia (38%), pruritus (32%), diarrhea (32%), skin papilloma (31%), and hyperkeratosis (30%). Seventy-three percent of patients experienced at least one Grade ≥3 adverse event. Sixty-one percent of patients had at least one Grade ≥3 treatment-related adverse event. The most commonly reported, treatment-related adverse events (incidence ≥5%) were SCC of skin (23%), increased serum GGT (9%), basal cell carcinoma (7%), rash (7%), maculopapular rash (6%), and arthralgia (6%). The Vemurafenib IB contains detailed descriptions of study drug-related adverse events observed in Study NP22657.

In the Phase III randomized study of vemurafenib versus DTIC (BRIM-3, Study NO25026, clinical cutoff: 1 March 2011) (Chapman et al. 2011; Vemurafenib IB), the safety results showed that vemurafenib was generally tolerable and toxicity was manageable with dose modifications. Ninety-nine percent and ninety-one percent of patients in the vemurafenib and DTIC treatment groups, respectively, experienced at least one adverse event. The majority of adverse events were of mild or moderate intensity. The most common adverse events (reported in ≥30% of patients) in the vemurafenib group were in the system organ class of skin and subcutaneous tissue disorders; the most common of which were alopecia, rash, and photosensitivity. Other adverse events that occurred in ≥10% of vemurafenib-treated patients and at an incidence of more than twice that observed in the DTIC group included SCC of skin, skin papilloma, arthralgia, headache, dysgeusia, pyrexia, peripheral edema, pain in extremity, myalgia, decreased appetite, diarrhea, hyperkeratosis, seborrheic keratosis, and dry skin. Of the 37 patients who switched from DTIC to vemurafenib, 32 patients (86%) had at least one adverse event and 26 patients (70%) reported at least one treatment-related adverse event. The majority of adverse events were of mild or moderate intensity.

Fifty-nine percent of patients in the vemurafenib arm and thirty-three percent of patients in the DTIC arm experienced one or more adverse events of Grade ≥3 in intensity. Treatment-related adverse events of Grade ≥3 occurred in 49% of patients in the vemurafenib arm and 20% in the DTIC arm. Sixteen percent and nine percent of vemurafenib-treated patients had cutaneous SCC (cuSCC) and keratoacanthoma (KA), respectively, compared with <1% and 0% for DTIC-treated patients. For reporting purposes, all cases of cuSCC and KA were considered to be treatment related, Grade 3,

and serious. Other common Grade ≥3 adverse events in the vemurafenib group included photosensitivity reaction (9%), rash (8%), maculopapular rash (8%), and arthralgia (4%); the corresponding frequency of these adverse events in the DTIC group were 0%, 0%, 0%, and <1%. The most common Grade≥3 adverse event in the DTIC group was neutropenia, occurring in 9% of patients; ≤1% of patients in the vemurafenib group experienced neutropenia. Of the 37 patients who crossed over from DTIC to vemurafenib, 11 (30%) experienced one or more Grade ≥3 adverse event after crossover. These consisted of fatigue (2 patients), muscle weakness, pyrexia, anemia, hyperkeratosis, basal cell carcinoma, maculopapular rash, rash, cellulitis, palmar–plantar erythrodysesthesia syndrome, and decreased neutrophil counts (all 1 patient each). Of these, eight events were considered by the investigator to be treatment related.

The percentage of patients who experienced one or more Grade 4 adverse events was lower in the vemurafenib group (13 patients [4%]) than in the DTIC group (22 patients [8%]). Grade 4 adverse events in the vemurafenib group included pulmonary embolism (3 patients), increased GGT (2 patients), increased blood creatine phosphokinase (CPK), increased blood bilirubin, increased lipase, ageusia, intraventricular hemorrhage, pneumonia, pneumothorax, respiratory distress, and neutropenia (1 patient each). Five patients treated with vemurafenib had a total of six Grade 4 adverse events that were assessed as related to treatment (increased blood bilirubin, GGT increased [2 patients], ageusia, increased CPK, and neutropenia). One of the 37 patients who crossed over experienced a Grade 4 decreased neutrophil count after crossover. It was assessed as unrelated to treatment and non-serious.

Grade 5 adverse events were reported in 6 patients (2%) in the vemurafenib group. Only one adverse event (intracranial tumor hemorrhage) was assessed as treatment related. Each of the other 5 patients experienced the following Grade 5 adverse events (all unrelated to study treatment): general physical health deterioration, cerebrovascular accident, pneumonia, aortic aneurysm rupture, and cardiac failure. Grade 5 adverse events were reported in 8 DTIC-treated patients (3%). Fatigue and mucosal inflammation, initially classified as Grade 5 adverse events in 1 patient, were subsequently considered to be symptoms of disease progression and downgraded to Grade 1, resulting in a total of 7 patients with Grade 5 adverse events. Only one adverse event (shock) was assessed as treatment related. Dyspnea, lung infection, cardiac arrest, and cardiac tamponade were reported in 1 patient each, and cardiopulmonary failure was reported in 2 patients. No Grade 5 adverse events were reported in the 37 patients who crossed over from DTIC to vemurafenib.

The incidence of cuSCC in vemurafenib-treated patients was approximately 20% across studies. The majority of the excised lesions reviewed by an independent central dermatopathology laboratory were classified as SCC-KA subtype or with mixed KA features (52%), both of which are less invasive types of cuSCC. Most lesions classified as “other” (43%) were benign skin lesions (e.g., verruca vulgaris, actinic keratosis, benign keratosis, cyst/benign cyst). cuSCC usually occurred early in the course of

treatment, with a median time to the first appearance of 7–8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced more than one occurrence, with a median time between occurrences of 6 weeks. Cases of cuSCC (including KA) were typically managed with simple excision, and patients generally continued on treatment without dose modification. A risk mitigation plan, 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 5.1.2.3).

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 patients treated with DTIC. Cases were managed with excision and without sequelae, and patients continued treatment without dose adjustment. Surveillance measures to monitor for the occurrence of new primary melanomas as well as cuSCC are outlined in Section 4.5.1.5, Section 4.5.2.2, and Section 5.1.2.3. Details for Study NO25026 are summarized in the Vemurafenib IB.

The effects of vemurafenib on the QT interval were investigated as part of the Phase II Study NP22657. This was not a “thorough” QT study as defined by health authorities because vemurafenib cannot be administered to healthy volunteers and it was not feasible to administer a positive or negative control to patients with metastatic melanoma. However, the centrally read ECG data obtained in triplicate at serial, time-matched points before and after dosing met the regulatory expectations for robust assessment of oncology therapeutics on the QT interval. The maximum absolute corrected QT (QTc) values at any point after dosing were as follows: >450 milliseconds (ms), 49 patients (37.1%); >480 ms, 6 patients (4.5%); >500 ms (Grade 3), 2 patients (1.5%). One patient (0.8%) had a maximal QTc increment >60 ms (Grade 2) compared with baseline. The upper boundary of the one-sided 95% CI for mean QTc prolongation reached a maximum of 17.7 ms on Day 105 of study treatment, on the basis of measurements in 90 patients. Mean QTc interval prolongation closely tracked with the mean vemurafenib steady-state concentration over time. 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. Additional information on the relationship between vemurafenib exposure and QT interval prolongation may be found in the Vemurafenib IB.

Two cases of SCC of the head and neck have been reported in two patients treated with vemurafenib in excess of 300 days while enrolled in a clinical trial. Pathology examination 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 did 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 Vemurafenib IB.

Five cases of adenomatous colonic polyps have been reported in patients treated with vemurafenib for 2 or more 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 5 colonic polyps (3 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 7 colonic polyps (5 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 (7 of which were adenomatous). This patient had a previous colonoscopy 7 years prior to starting vemurafenib. The fourth patient had, on elective colonoscopy, 1 adenomatous colonic polyp. The fifth patient had, on elective colonoscopy, 3 adenomatous colonic polyps. The latter two patients had histories of no prior colonoscopy. In addition, a patient on the Expanded Access Program had 1 colonic adenoma discovered after being on vemurafenib for 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.

One case of progression of *NRAS*-mutated chronic myelomonocytic leukemia occurred in a male patient with metastatic melanoma treated with vemurafenib for less than 2weeks (Callahan et al. 2012). After the first dose of vemurafenib, laboratory results showed a marked leukocytosis 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 extracellular-signal-regulated kinase (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 Vemurafenib IB.

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 7–25 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 Vemurafenib IB.

In a Phase I trial (Study CA 184161, sponsored by Bristol-Myers Squibb), asymptomatic Grade 3 increases in transaminases and bilirubin occurred with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID) (Ribas et al. 2012). All liver laboratory abnormalities were asymptomatic and reversible with permanent discontinuation of the study drugs or, in some cases, administration of corticosteroids. On the basis of these data, concurrent administration of ipilimumab and vemurafenib is not recommended outside of a clinical trial. Full details are provided in the Vemurafenib IB.

An assessment of liver-related adverse events reported with vemurafenib use showed that 63 cases of medically confirmed serious adverse events were drug-induced liver injury (DILI) on the basis of clinical chemistry criteria from the DILI Expert Working Group (Aithal et al. 2011). Of the 63 cases, two were assessed as severe; both were reported as hepatic failure. The outcome of both cases of hepatic failure have been reported to be completely resolved following vemurafenib discontinuation. There were no reported deaths among the 63 cases of liver injury. The median time to onset of the adverse events was 44 days after initial dose. The median ALT to alkaline phosphatase ratio was 1.5, suggesting a trend toward cholestatic pattern of liver injury. There were no risk factors or populations at risk identified.

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, often occurring during the first 6–12 weeks of treatment. It appears to be reversible—usually within 2 weeks—with temporary interruption, dose reduction, or discontinuation and, in some cases, was managed with GM-CSF.

A safety review completed in 2014 identified pancreatitis as an adverse drug reaction in patients treated with vemurafenib. Seventeen cases of pancreatitis with no strong risk factors or alternative explanations were reported. Eight of the seventeen cases were assessed as likely associated with vemurafenib use on the basis of event onset latency and rechallenge/dechallenge information. The clinical presentation in terms of severity, mild to moderate, was consistent with the clinical picture of drug-induced pancreatitis (Lankisch et al. 1995).

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 twenty cases of radiation injuries, adjudicated as radiation recall (n = 8) and radiation sensitization (n = 12). The nature and severity of

the events in all 20 cases were evaluated as worse than expected for the normal tissue tolerance to therapeutic radiation with fatal outcome in 3 cases. The reaction was seen in the skin, esophagus, lung, liver, rectum, and urinary bladder. Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Full details are provided in the Vemurafenib IB.

For a review of serious adverse events and adverse events that led to discontinuation of study treatment, please consult the Vemurafenib IB.

See the Vemurafenib IB and/or prescribing information for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

To date, clinical studies of vemurafenib in $BRAF^{V600}$ locally advanced/unresectable or metastatic melanoma have demonstrated a highly favorable ratio of benefit versus risk, most compellingly revealed by the meaningful clinical benefit observed in the Phase III, randomized, comparative study (BRIM-3, Study NO25026) of vemurafenib versus DTIC. The clearly demonstrated benefit of vemurafenib in metastatic melanoma suggests that it might also be beneficial to patients with resected cutaneous melanoma who are at high risk for recurrence—that is, patients with Stage IIC and Stage III disease. As noted above, interferon alpha-2b is the only widely approved adjuvant therapy for resected, cutaneous melanoma but its use is limited by the high incidence of debilitating side effects leading to treatment discontinuation in up to one-third of patients (Eggermont et al. 2008).

Because the mutation of BRAF kinase appears to be an early event in the natural history of melanoma oncogenesis (Pollock et al. 2003; Kumar et al. 2004), it is likely that the prevalence of patients with resected cutaneous melanoma whose tumors harbor V600 mutations of BRAF kinase will approximate that observed in the metastatic disease setting.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is as follows:

- To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period in patients with completely resected *$BRAF^{V600}$* mutation–positive, cutaneous melanoma, as measured by DFS

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

- To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period, as measured by DMFS
- To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period, as measured by OS
- To evaluate the safety and tolerability of vemurafenib in the adjuvant setting
- To assess quality of life (QoL) as measured by EORTC 30-item Quality of Life Questionnaire (QLQ-C30)
- To describe the pharmacokinetics of vemurafenib in the adjuvant setting, assess between-patient variability of PK parameters, and explore and quantify potential covariates that may contribute to between-patient differences in PK parameters, with use of a population PK approach

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- To assess the efficacy outcomes and safety profile of vemurafenib adjuvant treatment in patients whose melanomas harbor non-E mutations of BRAF kinase at amino acid position 600, as detected by DNA sequencing methods
- To assess the relationship between vemurafenib exposure and the risk of melanoma recurrence or occurrence of new primary melanomas, the occurrence of serious adverse events, and abnormalities in safety laboratory parameters
- To assess the relationship between biomarkers and risk of melanoma recurrence or occurrence of new primary melanomas
- To characterize the biomarkers associated with acquisition of resistance to vemurafenib in the adjuvant setting
- To characterize the molecular phenotype of SCC (cutaneous [including KA] and non-cutaneous) or other new primary neoplasms that may be observed in patients treated with vemurafenib

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

Study GO27826 is a Phase III, international, multicenter, double-blind, randomized, placebo-controlled study of patients with completely resected, *BRAF*^{V600} mutation–positive melanoma, as detected by the **cobas**® BRAF V600 Mutation Test, at high risk for recurrence.

A total of approximately 475 patients in two separate cohorts will be enrolled.

- Cohort 1 (approximately 300 patients) will include patients with completely resected Stage IIC, IIIA (patients with one or more nodal metastasis >1 mm in diameter), or IIIB cutaneous melanoma, as defined by the AJCC Classification, Version 7 (Balch et al. 2009).
- Cohort 2 (approximately 175 patients) will include patients with Stage IIIC cutaneous melanoma, as defined by this classification scheme.

The primary and secondary efficacy and safety objectives of this study will be evaluated separately for each cohort.

Eligible patients will be randomized (1:1 ratio) to receive placebo or vemurafenib over a 52-week period, with randomization stratified by pathologic stage (Stage IIC, Stage IIIA, Stage IIIB) and region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world) in Cohort 1 and by region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world) in Cohort 2.

Within each cohort, patients will receive study treatment according to one of the following treatment arms:

- Arm A: placebo orally, BID for 52 weeks (thirteen 28-day cycles)
- Arm B: vemurafenib 960 mg orally, BID for 52 weeks (thirteen 28-day cycles)

All eligible patients must have either newly diagnosed melanoma or, at most, one metachronous lymph node recurrence (in the absence of prior lymph node involvement) that has undergone gross total resection; no prior systemic treatment for melanoma is permitted. Full pathologic staging that incorporates the findings from sentinel lymph node biopsy and complete regional lymphadenectomy is required of all patients with lymph node involvement.

All patients will be required to provide a sample of tumor tissue for further *BRAF* mutation testing and exploratory biomarker and correlative science assessments at baseline.

Randomization will occur within 90 days after definitive surgery (i.e., the last surgery required for the treatment or the diagnosis of melanoma), and study drug administration will begin within 4 calendar days after randomization.

After signing informed consent, all eligible patients will undergo screening procedures that include a contrast-enhanced magnetic resonance imaging (MRI) of the brain (or contrast-enhanced CT of the brain if an MRI is not generally available or is contraindicated) and contrast-enhanced CT or MRI of the chest, abdomen, and pelvis. While participating in the study, patients will undergo regular, periodic safety evaluations. Surveillance for tumor recurrence (including physical examination and contrast-enhanced CT or MRI of the chest, abdomen, and pelvis) will be performed

every 13±2 weeks until Week 104. During Years 3, 4, and 5 of the study, physical examination will be performed every 13±2 weeks, and the aforementioned imaging studies will be performed every 26±4 weeks until recurrence of melanoma or an occurrence of a new primary melanoma or *until end* of study *(see Section 3.2)*, whichever occurs earlier.

In addition, all patients will undergo contrast-enhanced MRI of the brain (or CT if MRI is generally not available or is contraindicated) every 52±4 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or *until end* of study *(see Section 3.2)*, whichever occurs earlier. Results of fluorodeoxyglucose–positron emission tomography (FDG-PET) scans alone will not be sufficient for purposes of documenting disease recurrence. Evidence of recurrence must be documented by biopsy of a suspect lesion, except in patients whose suspicious lesions are deemed by the investigator not amenable to biopsy. For patients with an isolated, suspected intracranial recurrence, histologic documentation of recurrence of surgically accessible lesions is highly recommended but not required; for these patients, MRI (or CT if MRI is not generally available or is contraindicated) documentation of recurrent disease is sufficient. Surveillance studies to monitor for melanoma recurrence should use the same imaging modality that was used at screening.

Patients who have had a DFS event do not need additional scans or physical exams for surveillance of melanoma recurrence. These patients are also required to discontinue study drug if it was being administered at the time of final diagnosis of the DFS event. However, these patients must still have a chest CT or MRI for SCC surveillance at 13±2 weeks and 26±2 weeks after the last dose of study drug.

A schedule of assessments is provided in Appendix 1.

Details about the first anti-cancer therapy given after melanoma recurrence or an occurrence of a new primary melanoma will be captured for all patients in the study.

The final analysis of the primary endpoint of DFS will occur for each cohort after the targeted number of events for each cohort is reached (approximately 120 DFS events for Cohort 1 and approximately 105 DFS events for Cohort 2). There will be no interim analyses of the primary endpoint of DFS.

For each cohort, patients without melanoma recurrence or an occurrence of a new primary melanoma and their physicians will remain blinded until the final DFS analysis for that cohort. Physicians may request unblinding for patients who have documented recurrence or an occurrence of a new primary melanoma for purposes of planning subsequent treatment. Unblinding requires prior approval of the Roche Medical Monitor or designee.

In this adjuvant trial, crossover to vemurafenib treatment will not be allowed for patients receiving placebo because this trial is designed to evaluate adjuvant vemurafenib therapy starting within 4 calendar days after randomization and no later than 94 calendar days after definitive melanoma surgery (i.e., the last surgery required for the treatment or the diagnosis of melanoma).

3.1.1 Independent Review Committee

An independent review committee will not be employed for this study.

3.1.2 Data Safety Monitoring Board

An independent DSMB that has been involved in the review of safety data from prior and current vemurafenib studies will be employed for this study. This committee will conduct periodic reviews of selected safety data according to procedures outlined in a DSMB charter.

3.2 END OF STUDY

All patients will be followed for melanoma recurrence or occurrence of new primary melanoma *and overall survival for at least 2 years after Cycle 1, Day 1 of study treatment. Patients may be followed for melanoma recurrence or occurrence of new primary melanoma* for up to 5 years and OS for up to 6 years after Cycle 1, Day 1 of study treatment. Patients who exhibit recurrence of melanoma or a new primary melanoma *during* the study will be followed for OS.

The end of the study is defined as the date of the last patient, last visit, which is expected to occur approximately *6* months after the *last* patient enrolled *has been followed for 2 years after Cycle 1, Day 1 of the study.*

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Test Product Dosage

The vemurafenib dose selected for the current study was based on clinical efficacy and safety initially observed in Study PLX06-02 (Phase I) at the MTD of 960 mg BID and further characterized in Studies NP22657 (Phase II) and NO25026 (Phase III) of vemurafenib in locally advanced/unresectable or metastatic melanoma. This regimen is associated with suppression of pERK in tumor biopsy specimens and consistent with exposures in nonclinical models that were associated with anti-tumor activity.

A 52-week period of adjuvant therapy has been selected because this is believed to balance the risks and tolerability of therapy with the expected benefit in the adjuvant setting, on the basis of an assessment of benefit versus risk observed in the metastatic setting.

3.3.2 Rationale for Patient Population

This study includes patients with AJCC v7 Stages IIC, IIIA (patients with at least one nodal metastasis >1 mm in diameter), IIIB, and IIIC melanoma, primarily because the risk of melanoma recurrence is in excess of 50% over the 5-year period after primary surgical resection and 5-year OS estimates vary from 40% to 60% in these patients (Balch et al. 2009). This segment of the melanoma patient population has a high unmet medical need for effective adjuvant treatment.

On the basis of historical data, the median recurrence-free interval in patients with Stages IIC–IIIB disease is expected to be approximately 24 months, on average. In contrast, the median recurrence-free interval for Stage IIIC patients is expected to be a much shorter 7.7 months (Eggermont et al. 2008; Eggermont AM, "Update on staging, tumor burden and adjuvant therapy," presented at Perspectives in Melanoma XIV Conference, Sept 17–18, 2010). Because of the disparate distributions of time to melanoma recurrence for the different substages and in order to ensure adequate power to detect the hypothesized treatment effect across a broad spectrum of patients at high risk for recurrence, eligible patients will be grouped into two independently powered cohorts: Stage IIC–IIIB patients will be in Cohort 1 and Stage IIIC patients will be in Cohort 2.

3.3.3 Rationale for Control Group

This will be a placebo-controlled study. Whereas the unique toxicity profile for vemurafenib may pose difficulty in effectively masking the proposed study, a placebo control will help to minimize bias in reporting of key assessments of safety, efficacy, and QoL.

Although high-dose interferon alpha-2b is widely approved as an adjuvant treatment for resected cutaneous melanoma, a placebo control group will be used for the following reasons:

- There is no clear international consensus on the utility of adjuvant interferon alpha-2b in the management of resected, cutaneous melanoma.
- The treatment effect of adjuvant interferon alpha-2b as measured by recurrence-free survival is relatively modest (only about an 18% reduction in the risk of melanoma recurrence [Mocellin et al. 2010]).
- The considerable toxicity of interferon alpha-2b appears to be associated with substantial deterioration in QoL among recipients (Bottomley et al. 2009).
- A substantial proportion of interferon alpha-2b–treated patients discontinue study treatment prematurely because of toxicity (Eggermont et al. 2008).
- Recent studies of other anti-melanoma therapies (e.g., ipilimumab) have demonstrated the feasibility of conducting a placebo-controlled study in the adjuvant setting.

3.3.4 Rationale for Biomarker Assessments

Roche is committed to the collection of biomarker samples in all clinical study protocols. The objective of biomarker profiling is to enable development of treatments specifically targeted for optimal patient benefit. The rationale for the planned biomarker analyses is explained below. However, because the body of knowledge of potential new biomarkers is evolving, the definitive list of analyses may be modified on the basis of new information.

3.3.4.1 Biomarkers Associated with Recurrence of Melanoma or Occurrence of New Primary Melanomas

Despite high rates of objective response observed with vemurafenib monotherapy in locally advanced or metastatic melanoma, advanced disease is still not curable. Preliminary results suggest that resistance to BRAF kinase inhibition is driven by multiple mechanisms including alternate signaling via the MAPK pathway (as a result of NRAS mutations, CRAF activation, and MEK activation via COT kinase), signaling through the PI3K/AKT pathway (as a result of either AKT3 amplification or PTEN loss), or signaling via activation of cell surface receptors PDGFRβ or IFG-1R (Vultur et al. 2011). Some or all of these biomarkers (and others that may be of interest as a result of further progress in the field) will be investigated in paired tumor specimens obtained at baseline and at melanoma recurrence or occurrence of a new primary melanoma in order to help researchers understand the molecular phenotype of tumors at the time of melanoma recurrence or occurrence of a new primary melanoma as well as potential mechanisms of resistance to adjuvant vemurafenib.

3.3.4.2 Cutaneous Squamous Cell Carcinoma or Other New Primary Neoplasms

Cases of cuSCC (which include those classified as KA or mixed KA subtype) have been reported in patients treated with vemurafenib. CuSCC (including the events of SCC of the skin and KA) is an adverse event of special interest. In addition, other neoplastic lesions (SCC of the head and neck and adenomatous colonic polyps) have been observed in patients who received long-term vemurafenib therapy. Biomarkers will be evaluated in a biopsy of cuSCC/KA (and compared with normal skin) and the other new primary neoplasms. The objective of additional molecular analyses of cuSCC/KA lesions or other suspicious neoplasms that develop during the study is to explore their potential relationship to study treatment, to further understand the molecular profile of these lesions, and to identify factors that may be associated with development of these lesions. Candidate mutations that have been implicated in the development of cuSCC/KA—such as *HRAS*, *NRAS*, *KRAS*, and p53—will be investigated. Furthermore, expression levels of MAPK pathway proteins such as ERK phosphorylation may be investigated if further evidence develops, implicating these effector molecules in the development of cuSCC/KA or other suspicious neoplasms.

3.3.4.3 Disease Monitoring and Prediction of Early Relapse

One of the most critical challenges in adjuvant therapy has been the effective monitoring of the presence of minimal residual disease and the identification in an early and timely fashion of those patients with an increased risk for relapse. Common serum markers such as LDH, MIA, and S100B have been shown to predict a poor prognosis in advanced melanoma (Perrotta et al. 2010). However, LDH and S100B do not reliably identify the presence of low tumor burden or locoregional metastases in melanoma patients at high risk for recurrence (Egberts et al. 2009). Longitudinal monitoring for the presence of or changes in the *BRAF*^{V600} mutation in blood (by measuring the level of circulating *BRAF*-mutant DNA) could potentially be an important marker to monitor for melanoma recurrence or the occurrence of new primary melanomas.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are described below.

3.4.1.1 Primary Efficacy Outcome Measure

DFS will be defined as the time from randomization until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause. The DFS component of melanoma recurrence will be assessed by the investigator. The DFS component of an occurrence of a new primary melanoma will be based upon the diagnosis made by a Roche-designated central pathology laboratory. See Section 4.5.1.4 for histopathologic and imaging requirements for documentation of recurrence.

3.4.1.2 Secondary Efficacy Outcome Measures

DMFS will be defined as the time from randomization until the date of diagnosis of distant (i.e., non-locoregional) metastases or death from any cause.

OS will be defined as the time from randomization to the date of death from any cause.

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest. Severity will be graded according to NCI CTCAE, Version 4.0.
- Changes from baseline in ECG findings and targeted clinical laboratory analytes during the course of study treatment

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Plasma concentrations of vemurafenib at clinically relevant timepoints, including steady-state trough values as well as those associated with diagnosis of SCC,dose interruption, and/or reduction for toxicity, melanoma recurrence, and occurrence of a new primary melanoma

3.4.4 Patient-Reported Outcome Measure

The patient-reported outcome (PRO) measure for this study is as follows:

- To assess patient-reported symptoms, functional interference, and health-related QoL in the vemurafenib and placebo treatment arms with use of EORTC QLQ-C30 (see Appendix 4)

3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Retrospective identification of study patients whose tumors harbor non-E, activating mutations of BRAF kinase at amino acid position 600 (e.g., $BRAF^{V600K}$), with use of DNA sequencing methods as a means to assess clinical outcomes in this patient subgroup
- Levels of candidate tumor biomarkers in plasma and serum (e.g., circulating mutant *BRAF* DNA) at different timepoints during the study compared with baseline as a means to monitor for and predict melanoma recurrence or occurrence of a new primary melanoma
- Candidate tumor biomarkers at the protein, RNA, and DNA levels (including *RAS* mutations) that may characterize the molecular phenotype of tumors at melanoma recurrence or occurrence of a new primary melanoma as well as predict development of resistance to adjuvant vemurafenib treatment
- Molecular characterization of SCC (cutaneous [including KA] and non-cutaneous) or other new primary neoplasms that may be observed in patients treated with vemurafenib

3.5 MINIMIZATION OF BIAS

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

A DSMB will be employed to conduct periodic evaluations of safety data. All analyses for the DSMB's review will be prepared by an independent data coordinating center. Sponsor's personnel will not have access to by-arm efficacy and safety summaries or listings prior to the formal reporting of study results.

Patients who are free from melanoma recurrence and occurrence of a new primary melanoma will be blinded to treatment assignment until completion of the final DFS analysis for each cohort. Only when knowledge of the investigational product is essential for a treatment decision (e.g., planning follow-on therapy in a patient who exhibits melanoma recurrence or an occurrence of a new primary melanoma prior to the final DFS analysis), clinical management, or the welfare of the patient, the investigator may request to unblind a patient's treatment assignment. In such cases, the IxRS system will be used to allow disclosure of an individual patient's treatment assignment to the treating investigator without unblinding the study Sponsor. Unblinding requires prior approval of the Roche Medical Monitor or designee.

In this adjuvant trial, crossover to vemurafenib treatment will not be allowed for patients receiving placebo because this trial is designed to evaluate adjuvant vemurafenib therapy starting within 4 calendar days after randomization and no later than 94 calendar days after definitive melanoma surgery (i.e., the last surgery required for the treatment or the diagnosis of melanoma).

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria listed below for study entry.

Disease-Specific Inclusion Criteria

- All patients should have histologically confirmed melanoma of cutaneous origin.
- All patients without clinical or radiologic evidence of regional lymph node involvement must undergo sentinel lymph node biopsy. Patients must undergo a complete regional lymphadenectomy if a sentinel lymph node biopsy procedure cannot be performed or a sentinel lymph node cannot be detected. All patients who have either clinical or radiographic evidence of regional lymph node involvement or evidence of melanoma involvement in the sentinel lymph node must undergo complete regional lymphadenectomy. Melanoma infiltration of lymph node(s) must be histologically confirmed.

  Note: Surgical management should comply with published guidelines for surgical standards of care (see Appendix 5).
- Patients with lymph node involvement either at initial presentation or a first metachronous nodal recurrence are eligible:

  $T_{any\ (including\ x)}\ N+$ at initial presentation

  $T_{any}N0$ followed by $N+$ recurrence (i.e., first metachronous nodal recurrence)
- Patients with *BRAF*^{V600} mutation–positive, cutaneous melanoma (either pathologic Stage IIC or Stage III according to AJCC Staging Criteria v7 [see Appendix 10]) that has been completely resected

Note: Patients with Stage IIIA disease must have at least one lymph node metastasis measuring >1 mm in diameter (per the Rotterdam classification scheme) on pathologic staging.

- *BRAF*^{V600} mutation status of the current primary tumor or involved lymph node determined to be positive using the **cobas**® BRAF V600 Mutation Test
- The patient must have been surgically rendered free of disease within 90 days of randomization.
- ECOG Performance Status of 0 or 1 (see Appendix 6)

General Inclusion Criteria

- Male or female patients aged ≥ 18 years
- Ability to participate and willingness to give signed informed consent prior to performance of any study-related procedures and to comply with the study protocol
- Life expectancy of at least 5 years
- Patients must have fully recovered from the effects of any major surgery (including complete regional lymphadenectomy) or significant traumatic injury prior to the first dose of study drug.

  Note: All staging-related procedures, including complete regional lymphadenectomy, must be completed within 90 days prior to randomization.
- Negative stool occult blood

  Note: If stool occult blood is positive, the patient will need to be cleared for study inclusion by a gastroenterologist or appropriately trained designee.
- For select patients with known personal history of adenomatous colorectal polyps or colorectal cancer, family history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer at or after the age of 60 years, or signs or symptoms that could be related to colon cancer as determined by the site investigator or designee, a screening colonoscopy with adequate resection of all visualized polyps must be performed.

  Note: For select patients requiring a screening colonoscopy (described above), colonoscopy should be complete to the cecum, with adequate bowel preparation, and performed within the 90-day screening period. For select patients (described above), screening colonoscopy is not required if colonoscopy to the cecum with adequate bowel preparation and adequate resection of all visualized polyps was performed within 1 year of the start of the 90-day screening period, unless the site investigator deems it necessary.

  Note: A history of colon cancer greater than 5 years prior to randomization does not preclude patients from being eligible.
- Adequate hematologic, liver, and renal function, defined by the following laboratory results obtained within 28 days prior to randomization:

  Absolute neutrophil count $\geq 1.5 \times 10^9$/L

  Platelet count $\geq 100 \times 10^9$/L

Hemoglobin ≥ 9 g/dL

Bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN)

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN

Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockroft–Gault glomerular filtration rate estimation:

$[(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})]/[72 \times (\text{serum creatinine in mg/dL})]$

PT, INR, aPTT $\leq 1.5 \times$ ULN

- Female patients of childbearing potential and male patients with partners of childbearing potential must agree to always use two effective forms of contraception beginning from the informed consent signature date until at least 6 months after completion of study therapy.

  In general, effective forms of contraception include surgical sterilization, a reliable barrier method with spermicide, birth control pills or patches, intrauterine contraceptive device, or contraceptive hormone implants. Please note that vemurafenib may decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including hormonal contraceptives; consider the use of alternative effective methods of contraception.

  Female patients of childbearing potential are defined as sexually mature women without prior hysterectomy who have had any evidence of menses within the past 12 months.

  In order to be considered NOT of childbearing potential, amenorrhea for a period of 12 months or longer must have occurred in the absence of chemotherapy, anti-estrogens, or ovarian suppression.
- Negative serum pregnancy test within 14 days prior to randomization in women of childbearing potential
- Women of non-childbearing potential need not undergo pregnancy testing.
- Absence of any psychological, familial, sociological, or geographical condition that has the potential to hamper compliance with the study protocol and follow-up schedule (such conditions should be discussed with the patient before trial entry)

4.1.2 Exclusion Criteria

Patients who meet any of the criteria listed below will be excluded from study entry.

Cancer-Related Exclusion Criteria

- History of any systemic or local therapy (e.g., chemotherapy, biologic or targeted therapy, hormonal therapy, or photodynamic therapy) for the treatment or prevention of melanoma, including interferon alpha-2b and pegylated interferon alpha-2b
- History of limb perfusion therapy
- History of radiotherapy for the treatment of melanoma including but not limited to radiation therapy to a resected nodal basin
- History of radiotherapy for the treatment of prostate, cervical, or rectal cancer

- Allergy or hypersensitivity to components of the vemurafenib formulation (see Section 4.3.1.1)
- Invasive malignancy other than melanoma at the time of enrollment or within 5 years prior to first study drug administration, except for adequately treated (with curative intent) basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, in situ ductal adenocarcinoma of the breast, in situ prostate cancer, or limited stage bladder cancer

  Note: This requires that the pathology evaluation of the screening Papanicolaou (Pap) smear and of any polyps resected at the screening colonoscopy does not show any invasive malignancy.
- Family history of inherited colon cancer syndromes (e.g., familial adenomatous polyposis, attenuated adenomatous polyposis, MUTYH-associated polyposis, hyperplastic polyposis syndrome, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Lynch syndrome, and Cowden syndrome) and/or history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer before the age of 60 years
- Known personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) >2 cm in size. This also applies to the screening colonoscopy for select patients.
- History of or current clinical, radiographic, or pathologic evidence of in-transit metastases, satellite, or microsatellite lesions

  Note: In-transit metastases are any skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin. Satellite lesions are skin or subcutaneous lesions within 2 cm of the primary tumor that are considered intralymphatic extensions of the primary mass. Microsatellite lesions are any discontinuous nest of metastatic cells more than 0.05 mm in diameter that are clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of melanoma by a distance of at least 0.3 mm (McCardle et al. 2011).
- History of or current clinical, radiographic, or pathologic evidence of recurrent lymph node involvement after resection of a primary melanoma with lymph node involvement at any time in the past
- History of local and/or regional and/or distant melanoma recurrence (excluding first metachronous nodal recurrence)

  Note: This does not include patients who have had a new primary melanoma.
- History or current radiographic or pathologic evidence of distant metastases as defined either by an abnormal contrast-enhanced brain MRI (or brain CT if MRI is not generally available or is contraindicated) or histologically proven, distant metastatic disease (visceral or cutaneous) in an extracranial site

  Note: This includes patients who have had their metastatic disease resected.

Cardiac Exclusion Criteria

- History of clinically significant cardiac or pulmonary dysfunction, including the following:

  Current, uncontrolled Grade ≥2 hypertension

  Unstable angina

  Current Grade ≥2 dyspnea or hypoxia or need for supplemental oxygen

  History of symptomatic congestive heart failure of Grade II–IV New York Heart Association Class (NYHA) (for the Criteria Committee of the NYHA 1994, see Appendix 3)

  Serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia

  History of myocardial infarction within 6 months prior to randomization

  History of congenital long QT syndrome or QTc interval >450 ms at baseline

  History of or current uncorrectable electrolyte disorder affecting serum levels of potassium, calcium, or magnesium

General Exclusion Criteria

- Major surgical procedure (other than wide local excision, sentinel lymph node biopsy, or complete regional lymphadenectomy) or significant traumatic injury within 4 weeks prior to the first dose of study drug
- History of clinically significant liver disease (including cirrhosis), current alcohol abuse, or known infection with HIV, hepatitis B virus, or hepatitis C virus (HCV)
- Active infection or chronic infection requiring chronic suppressive antibiotics
- Pregnancy or breastfeeding at the time of randomization
- Autoimmune disease (e.g., systemic lupus erythematosus, autoimmune vasculitis, inflammatory bowel disease [Crohn's disease and ulcerative colitis])
- Acromegaly
- History of malabsorption or other clinically significant metabolic dysfunction
- Any other serious concomitant medical condition that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to participate in the study
- Requirement for a concomitant medication or dietary supplement that is prohibited during the study (see Section 4.4.2)
- Unwillingness or inability to comply with study and follow-up procedures
- Current, recent (within 28 days prior to randomization), or planned use of any investigational product outside of this study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established, each patient will be assigned an identification number and randomized to one of the

two treatment arms with the use of an IxRS. Randomization will be stratified by pathologic stage (Stage IIC, Stage IIIA, Stage IIIB) and region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world) in Cohort 1 and by region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world) in Cohort 2. A stratified, permuted, block randomization scheme will be used to obtain approximately a 1:1 ratio between the two treatment groups.

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

As noted in Section 3.5, patients who are free from melanoma recurrence or an occurrence of a new primary melanoma will be blinded to treatment assignment until completion of the final DFS analysis for each cohort. Only when knowledge of the investigational product is essential for a treatment decision (e.g., planning follow-on therapy in a patient who exhibits melanoma recurrence or an occurrence of a new primary melanoma prior to the final DFS analysis), clinical management, or the welfare of the patient, the investigator may request to unblind a patient's treatment assignment. In such cases, the IxRS system will be used to allow disclosure of an individual patient's treatment assignment to the treating investigator without unblinding the study Sponsor.

Any site requests for unblinding (whether for safety reasons or planning follow-on therapy in the setting of melanoma recurrence or an occurrence of a new primary melanoma) require prior approval of the Roche Medical Monitor or designee.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Study drug packaging will be overseen by the Roche Clinical Trial Supplies department and bear a label with the identification required by local law as well as the protocol number. The packaging and labeling of the study medication will be in accordance with Roche standards and local regulations.

Local packaging and labeling requirements may differ in some countries.

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

Study drug will be stored at the clinical site under the recommended storage conditions: Do not store above 25°C (77°F) as indicated on the study drug label. Patients will be requested to store study drug at the recommended storage conditions noted on the label, out of the reach of children or other co-inhabitants.

4.3.1.1 Active Study Drug (Vemurafenib) and Placebo

The active study drug (RO5185426/F17) is a pinkish white to orange white, oval, biconvex film-coated tablet with “ROCHE” engraved on one side. It contains 240 mg of vemurafenib. The inactive ingredients in the active study drug tablets are as follows:

- Kernel: croscarmellose sodium, colloidal anhydrous silica, hydroxypropylcellulose, and magnesium stearate
- Film coat: poly(vinyl alcohol), titanium dioxide, macrogol 3350, talc, and iron oxide red

The placebo (RO5185426/F18) is a pinkish white to orange white, oval, biconvex film-coated tablet with “ROCHE” engraved on one side, matching the active study drug (RO5185426/F17). It contains no drug substance. The placebo tablet contains:

- Kernel: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate
- Film coat: Poly(vinyl alcohol), titanium dioxide, macrogol 3350, talc, and iron oxide red

Each placebo tablet contains 796 mg of lactose (3.2 g lactose per 4-tablet dose). The effect of lactose on individuals varies from person to person dependent upon the lactose exposure, lactase deficiency, and lactose malabsorption. A study (Suarez et al. 1995) found that individuals who self-reported severe lactose intolerance could drink one 240 mL glass of milk with minimal, if any, symptoms. There are approximately 12 g of lactose in 240 mL (8 oz) of milk. In light of this, it is unlikely that most patients who are lactose intolerant will suffer any gastrointestinal discomfort from the 3.2 g BID of lactose in the placebo tablet.

For further details, see the local prescribing information for vemurafenib or the Vemurafenib IB.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Study Drug (Vemurafenib/Placebo)

Study drug will be taken at home, orally, at a dose of 4 tablets BID for a maximum of 52 consecutive weeks (thirteen 28-day cycles).

The first dose is to be taken in the morning, and the second dose is to be taken approximately 12 hours later in the evening. Study drug tablets are to be swallowed whole with water. The tablets should not be chewed or crushed. If a dose is missed, it can be taken 4 or more hours prior to the next dose to maintain the BID regimen. Both doses should not be taken at the same time. Missed days or drug holidays will not be made up, thereby maintaining 52 weeks of treatment. A patient who has a break in dosing in excess of 28 consecutive days will be permanently discontinued from study treatment.

Patients will be asked to record the date and time of doses in a diary and to return all used and unused drug supply containers as a measure of compliance. All supplies, including partially used or empty containers of study drug, must be returned to the Roche study monitor at the end of the study, unless alternative destruction has been authorized by Roche/designee or is required by local or institutional regulations. Copies of all drug dispensing and inventory logs must be returned to the Roche study monitor at the end of the study.

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

4.3.3 Investigational Medicinal Product Accountability

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

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

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

4.3.4 Post-Study Access to Vemurafenib

Because this is an adjuvant study, Roche does not intend to provide vemurafenib or other study interventions to patients after conclusion of the protocol-specified treatment period (i.e., 52 weeks) or after 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 the date of informed consent until the end-of-treatment visit. Patients who use oral contraceptives or hormone replacement or maintenance therapies should continue their use as outlined in the eligibility criteria. Please note that vemurafenib may decrease the plasma exposure of medicines predominantly metabolized by CYP3A4, including hormonal contraceptives; consider the use of an effective alternative method of contraception. Refer to Section 4.1.1 for information on contraception. Patients who experience toxicities may be treated symptomatically as clinically indicated. All

concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

At study initiation, patients should continue with their permitted concomitant therapies as directed by their physician. Additionally, any diagnostic, therapeutic, or surgical procedure performed during the study period should be recorded, including the date, indication, description of the procedure(s), and any clinical findings.

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

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study treatment period (i.e., from the time of informed consent through the end-of-treatment visit):

- St. John's wort or hyperforin, rifampicin/rifampin, rifabutin, rifapentine, carbamazepine, phenytoin, and phenobarbital
- Anti-platelet agents (except for low-dose aspirin)

Use of the following therapies is prohibited during the study (i.e., from the time of informed consent through the study completion visit):

- Any concomitant therapy intended for the treatment of melanoma, either approved by health authorities or experimental, including chemotherapy, radiotherapy, immunotherapy, hormonal therapy, biologic therapy, investigational agents, or herbal therapy
- Chronic systemic corticosteroid use other than the management of toxicity related to study drug ($>$10 mg of prednisone or equivalent dose of other anti-inflammatory corticosteroids for $>$7 days) or use of immunosuppressants

Institution of corticosteroids during the study for the management of toxicity related to study drug is allowed as long as the minimum effective dose is utilized for the shortest period of time needed to adequately treat the patient and that a quick taper is instituted as soon as possible.

Patients who require the use of any of these agents will be discontinued from study treatment and followed for safety outcomes for 4 weeks after the last dose of study drug or until initiation of another anti-cancer therapy, whichever comes first. Follow-up for efficacy, exploratory outcomes, and new primary malignancies will continue until melanoma recurrence or an occurrence of a new primary melanoma *until end of study*

(see Section 3.2) or loss to follow-up, withdrawal of consent, or death (whichever occurs first). Patients will be followed for survival *until end of study (see Section 3.2).*

4.4.2.1 Medication Precautions to Prevent Drug Interactions

Results from a drug–drug interaction study in patients with metastatic melanoma demonstrated no interaction of vemurafenib with CYP2C19 and CYP2C9. However, drug interactions were observed with CYP1A2 and CYP3A4.

CYP1A2 inhibition was observed when a single dose of caffeine (a CYP1A2 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, resulting in a 2.6-fold increase in the mean AUC of caffeine.

CYP3A4 induction was observed when a single dose of midazolam (a CYP3A4 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, resulting in a 39% decrease in the mean AUC of midazolam.

An interaction between vemurafenib and dextromethorphan (a CYP2D6 substrate) was suggested by a mean increase in dextromethorphan area under the concentration-time curve from Time 0 to last measurable concentration (AUC_{0-last}) of 47% based on the no-effect 90% CI boundary. However, this interaction is not likely to be because of the inhibition of CYP2D6 by vemurafenib because the AUC_{0-last} of the dextromethorphan metabolite dextrorphan also increased by 46%.

In nonclinical studies, inhibition of CYP2C9 inhibition by vemurafenib was observed in vitro (i.e., IC_{50} of 5.9 μM). When a single dose of warfarin (a CYP2C9 substrate) was co-administered after repeat dosing with vemurafenib for 15 days, some patients exhibited increased warfarin exposure (mean, 18%).

In another in vitro CYP inhibition study, the effect of vemurafenib on CYPs 2A6, 2B6, 2C8, and 2E1 was studied at concentrations up to 100 μM. The determined IC_{50} values were >100, >100, 12, and >100 μM, respectively. Therefore, vemurafenib could potentially impact exposure of concomitant drugs which major clearance route relies on the CYP2C8 enzymatic pathway.

In summary, vemurafenib may increase the plasma exposure of drugs predominantly metabolized by CYP1A2 and decrease the plasma exposure of drugs predominantly metabolized by CYP3A4. In addition, vemurafenib could potentially impact exposure of concomitant drugs which major clearance route relies on the CYP2C8 enzymatic pathway.

If CYP1A2 substrates must be co-administered with vemurafenib, investigators should assess the safety risk associated with a potential increase in plasma concentrations of CYP1A2-metabolized drugs. If CYP3A4 substrates must be co-administered with vemurafenib, investigators should monitor for signs of reduced benefit of

CYP3A4-metabolized drugs due to a potential decrease in their plasma concentration. Dose adjustments for medications predominantly metabolized via CYP1A2 or CYP3A4 should be considered on the basis of their therapeutic windows before concomitantly treating with vemurafenib. Doses of concomitant CYP1A2- and CYP3A4-metabolized drugs, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Caution should be exercised when vemurafenib is co-administered with warfarin (CYP2C9) in patients with melanoma.

No dose adjustment is recommended for drugs metabolized by CYP2D6 or CYP2C19.

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

In vitro studies have demonstrated that vemurafenib is both a substrate and an inhibitor of the efflux transporter P-glycoprotein (P-gp). In the clinical setting, the effects of vemurafenib on drugs that are substrates of P-gp and the effects of P-gp inducers and inhibitors on vemurafenib exposure are unknown.

Refer to Appendix 8 for a list of typical examples of CYP1A2, CYP3A4, and CYP2C9 substrates and CYP3A4 inducers and inhibitors. A more extensive list of medications can be found online at the following link: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

4.4.2.2 Medications Affecting the QT Interval

Certain medications could affect the QT interval in 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 because 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 9. 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 within the previous 5 years, major surgeries, cancer history (including prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the date of informed consent.

Demographic data will include age, sex, and self-reported race/ethnicity (where applicable/permissible).

4.5.1.2 Vital Signs

For all patients, systolic and diastolic blood pressure, heart rate, and temperature (°C) will be recorded. Systolic and diastolic blood pressure and heart rate will be recorded with the patient in the seated position after a 5-minute rest period.

4.5.1.3 Physical Examinations

A complete physical examination should include measurement of height and weight; head, eyes, ears, nose, and throat; neck; and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Visual and digital evaluation of the anus and anal canal is required as part of a physical examination at screening, at Cycle 6, Day 1 (±2 weeks), and at the end-of-treatment visit (±2 weeks). In addition, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Pap smear, at screening, at Cycle 6, Day 1 (±2 weeks), and at the end-of-treatment visit (±2 weeks). Pelvic examinations, including Pap smear, that were conducted up to 3 months prior to the start of the 90-day screening period and found to be normal, need not be repeated at screening.

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

Physical examinations will occur at regular intervals during study drug administration period as outlined in Appendix 1. A physical examination is required at the end-of-treatment visit. During post-treatment follow-up, physical examinations will occur every 13 ± 2 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or *until end* of study *(see Section 3.2)*, whichever occurs earlier. Patients who have had recurrence of melanoma or occurrence of new primary melanoma will not be required to continue to have physical examinations.

4.5.1.4 Surveillance for Melanoma Recurrence: Imaging Studies

All eligible patients will undergo a contrast-enhanced MRI of the brain (or contrast-enhanced CT if MRI is not generally available or is contraindicated) and contrast-enhanced CT or MRI of the chest, abdomen, and pelvis at screening (post-definitive surgery; i.e., the last surgery required for the treatment or the diagnosis of melanoma). Surveillance imaging studies should use the same imaging modality that was used at screening.

Results of FDG-PET scans alone will not be sufficient for purposes of documenting melanoma recurrence.

If recurrent disease or occurrence of a new primary melanoma is suspected on clinical grounds, imaging studies (chest, abdomen, pelvis, and brain) must be performed expeditiously, even if not mandated in the schedule of assessments.

All patients who present with findings suspicious for melanoma recurrence must undergo a biopsy for histopathologic confirmation, except patients whose suspicious lesions are deemed by the investigator not to be amenable to biopsy. For patients with an isolated, suspected intracranial recurrence, histologic documentation of recurrence of surgically accessible lesions is highly recommended but not required. For such patients, MRI (or CT if MRI is not generally available or is contraindicated) documentation of recurrent disease is sufficient.

4.5.1.5 Dermatologic Examination

A complete history of dermatologic interventions and medications, cuSCC risk factors (i.e., Fitzpatrick skin type, radiotherapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, and precursor lesions), and prior HPV vaccination must be collected at baseline. Refer to Appendix 7 for a list of Fitzpatrick skin phototypes.

Complete evaluation of the skin will be conducted at baseline and specified timepoints during the study by a dermatologist or his or her designee who is experienced in the diagnosis and management of melanoma, non-melanoma skin cancer, cuSCC/KA, and actinic keratosis.

Any suspicious lesions identified from the screening period to the examination at 26 ± 2 weeks after last dose of study drug must be biopsied and excised and sent for pathologic examination. The available specimen block/sections should be sent to the Roche-designated central pathology laboratory for confirmation of diagnosis. Instruction manuals and supply kits will be provided for all central laboratory assessments. Actinic keratosis, KA, or other skin conditions identified by the dermatologist should be treated per local standards of care.

4.5.1.6 Head and Neck Evaluation

For all patients, a thorough evaluation of the head and neck will be performed as part of the physical examination by the site investigator at screening and every 13±2 weeks during the study drug treatment period. Once a patient completes the treatment period or discontinues study drug early, a thorough evaluation of the head and neck by the site investigator will be performed at the end-of-treatment visit as part of the physical examination. Once a patient completes the treatment period or discontinues study drug early, a thorough head and neck exam to monitor for non-cuSCC will occur (as part of the physical examination for patients who continue to have physical examinations) at 13±2 weeks and 26±2 weeks from the last dose of study drug. For patients who no longer require physical examinations, the head and neck examination will occur independently at 13±2 weeks and 26±2 weeks from the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up). Evaluation will consist of at least a visual inspection of the oral mucosa and palpation of the tonsils, base of tongue, and lymph nodes.

If, at any time, a head and neck cancer is suspected (e.g., on the basis of signs or symptoms), the patient will be referred to a head and neck surgeon/otorhinolaryngologist or his or her designee who is experienced in the diagnosis and management of SCC of the head and neck. The head and neck surgeon/otorhinolaryngologist or designee will perform a complete evaluation of the head and neck including visual inspection of the oral mucosa, palpation of the tonsils, base of tongue, and lymph nodes and flexible fiberoptic laryngoscopy in order to evaluate at least the sinonasal cavity, the nasopharynx, the base of tongue, larynx, and hypopharynx. For patients who have been referred to a head and neck surgeon/otorhinolaryngologist or designee, this complete evaluation of the head and neck by a head and neck surgeon/otorhinolaryngologist or designee who is experienced in the diagnosis and management of SCC of the head and neck will continue to be conducted every 26±2 weeks during the study drug administration period. Once a patient completes the treatment period or discontinues study drug early, a complete evaluation of the head and neck by a head and neck surgeon/otorhinolaryngologist will be performed at 26±2 weeks after the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).

An unscheduled examination may be performed for investigation of any new head and neck lesions that are suspected of being non-cuSCC.

Any suspicious lesions identified must be biopsied and excised and sent for pathological examination with appropriate follow-up instituted. Instruction manuals and supply kits will be provided for all central laboratory assessments.

4.5.1.7 Colonoscopy by Gastroenterologist

For select patients with known personal history of adenomatous colorectal polyps or colorectal cancer, family history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer at or after the age of 60 years, or

signs or symptoms that could be related to colon cancer as determined by the site investigator or designee, a screening colonoscopy will be conducted. Patients with family history of inherited colon cancer syndromes and/or history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer before the age of 60 years will be excluded from this study.

Colonoscopy must be complete to the cecum, with adequate bowel preparation, and must be performed within the 90-day screening period by a gastroenterologist or his or her designee who is experienced in the colonoscopic diagnosis of colorectal polyps and colorectal cancer. All visualized polyps found at the screening or subsequent colonoscopies will need to be adequately resected.

For select patients (described above), the screening colonoscopy is not required if colonoscopy to the cecum with adequate bowel preparation and adequate resection of all visualized polyps was performed within 1 year of the start of the 90-day screening period, unless the site investigator deems it necessary. Please note that patients with a known personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) >2 cm in size will be excluded from this study. This also applies to the polyps visualized during the screening colonoscopy for select patients described above (see also Section 4.1.2).

All patients will be required to undergo a post-treatment colonoscopy within 3 months of discontinuation of study drug. Patients who have polyp(s) found at the post-treatment colonoscopy will need a follow-up colonoscopy performed after an additional 3 years $\pm$ 3 months.

4.5.1.8 Laboratory Assessments

Blood samples for hematology, coagulation screening studies, liver function tests, serum chemistry, pregnancy test, and hepatitis B and C serology will be analyzed at the study site's local laboratory. Stool for occult blood will be analyzed at the local site. Blood and tumor tissue samples for biomarker and PK studies will be sent to one or several Roche-designated central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. All screening laboratory assessments should be obtained prior to initiation of study drug at Cycle 1, Day 1.

Laboratory assessments will include the following:

- Hematology: Hemoglobin, hematocrit, platelet count, WBC, WBC differential (absolute neutrophil count, lymphocyte, monocyte, eosinophil, and basophil counts and other cells)
- Coagulation: PT, INR, and aPTT
- Serum chemistry: urea (BUN), creatinine, sodium, potassium, chloride, bicarbonate, glucose, phosphorus, magnesium, total calcium, serum albumin, LDH, and uric acid

- Liver function tests: ALT, AST, total bilirubin, and alkaline phosphatase
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and every 3 cycles (i.e., Cycles 3, 6, 9, and 12 or every 12±2 weeks), starting from Cycle 1, Day 1, and at 12±2 weeks and 26±2 weeks after the last dose of study drug. Urine pregnancy tests will be performed as needed. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Viral serology/detection: Hepatitis B (hepatitis B surface antigen [HBsAg] and total hepatitis B core antibody [anti-HBc]) and HCV antibody
- Stool for occult blood

4.5.1.9 *BRAF*^{V600} Mutation Testing

Assessment of *BRAF*^{V600} mutation status of primary tumor tissue will be investigated using the **cobas**® BRAF V600 Mutation Test. A formalin-fixed paraffin-embedded (FFPE) tumor block or at least five serially cut, unstained tumor tissue slides (5 μm–thick sections) from one block will be collected at screening from consented patients. Patients whose tumors test positively for the *BRAF*^{V600} mutation will be eligible for enrollment in the clinical study if they meet other eligibility criteria.

For patients whose tumors undergo **cobas**® testing at a Roche-designated central testing facility, tumor blocks from the patients who are not eligible for the study will be returned after screening has been completed. For patients eligible for the study, additional testing will be performed at Roche or a centralized specialty laboratory (see Section 4.5.1.12, Exploratory Biomarker Assessments). These additional investigations will be performed retrospectively and will not influence patient's eligibility for this study.

4.5.1.10 Pharmacokinetic Assessments

Plasma concentrations of vemurafenib will be measured in a central laboratory using a validated assay. Venous blood samples (2 mL) will be collected in sodium heparin according to the Schedule of Pharmacokinetic Assessments (Section 4.5.2.2 and Appendix 2).

For all scheduled and unscheduled PK samples, the date and time of the last dose of study drug should be specified on the eCRF along with the actual time of the PK blood draw. The procedures for the collection, handling, and shipping of PK samples can be found in the laboratory manual.

The total volume of blood collected for PK assessments will be approximately 16 mL for Cycle 1 and an additional approximately 26 mL for patients who complete the full 52-week treatment regimen. Unscheduled PK samples are not considered in this calculation (see Section 4.5.2.2).

4.5.1.11 Electrocardiograms

All patients will undergo longitudinal ECG monitoring for surveillance of study drug–mediated prolongation of the QT interval.

Triplicate digital ECG recordings will be obtained within approximately 2–5 minutes of each other at timepoints specified below and in Appendix 1 (Schedule of Assessments). An average of the three readings will be used to determine ECG intervals (e.g., PR, QT). ECGs for each patient should be obtained using the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to administration of the first daily dose of study drug and any scheduled vital sign measurements and blood draws.

This study will employ a central ECG reading facility.

For safety monitoring purposes, the investigator or his or her designee must review, sign, and date all ECG tracings. Patient management decisions should be based on ECG results obtained at the investigative site. Overall ECG interpretations based on ECG results obtained at the investigative site will be documented on the eCRF. In addition, ECG characteristics including heart rate, QRS duration, RR, PR, and QT intervals, and changes in T-wave and U-wave morphology will be electronically obtained from a central ECG reading facility. One set of all ECG tracings should be printed and kept with the patient's permanent study file at the site.

4.5.1.12 Exploratory Biomarker Assessments

Patient specimens for dynamic (non-inherited) biomarker discovery and validation will be collected from all patients participating in the trial. These specimens will be used for research purposes to identify biomarkers that correlate with response/resistance to adjuvant vemurafenib therapy and will help researchers to better understand the pathogenesis, course, and outcome of cutaneous melanoma and related diseases. The biomarker analyses are listed below each objective (but may be amended if further scientific evidence justifies additional or modified areas of scientific inquiry):

- Identify potential biomarkers in blood to monitor for melanoma recurrence or occurrence of a new primary melanoma

  Circulating DNA that harbors the V600 mutation of *BRAF*

- Characterize the molecular phenotype of recurrent melanomas or occurrence of new primary melanomas and explore potential biomarkers in primary tumor tissue that may predict development of resistance to vemurafenib treatment

BRAF mutation analysis by DNA sequencing to identify *BRAF* non-E mutations

RAS and *MEK* mutations (other mutations in oncogenes and tumor suppressor genes)

Expression of BRAF, PDGFR, IGF1R, PTEN, COT kinase, and other components of melanoma signaling pathways

- Characterize SCC (cutaneous [including KA] and non-cutaneous) or other new primary neoplasms and normal skin

  HRAS/*KRAS*/*NRAS*, *BRAF*, *TP53* mutations as well as other tumor-specific mutations

  ERK phosphorylation and Ki-67 expression

  Additional markers dependent on the type of lesion or if new scientific evidence warrants

Patients will be asked to provide the following samples:

- Melanoma tumor tissue

  Mandatory archival FFPE melanoma tumor tissue (collected prior to initiation of study drug). Note: 10–20 unstained FFPE slides will be accepted only if the tumor block cannot be provided.

  If additional consent is obtained, archival tumor tissue blocks will be used to create a tissue microarray (TMA) for immunohistochemistry analysis and potentially for the extraction of RNA and DNA.

  The tumor blocks will be used to set up a TMA: Tissue cores from tumor and normal tissues will be taken out using a puncher and then rearranged as an array into a block of wax. A single array may include tissue cores from different patients.

  Melanoma tumor tissue at the time of disease recurrence: If the patient has a lesion accessible for biopsy, the lesion must be a progressing lesion. If the patient is receiving study drug, the specimen should be obtained while the patient is still receiving drug (or at maximum, 7 days after last study dose).

  First priority should be given to the collection of a fresh frozen tumor sample (FF tumor block).

  Second priority (or if a FF tumor block cannot be obtained) should be given to the collection of a FFPE tissue block or 10–20 slides.

- Serum and plasma samples

  One 6-mL blood sample anticoagulated in EDTA and one 6-mL blood sample in a serum separator tube at repeated timepoints (see Schedule of Assessments; Appendix 1)

  The total blood loss for plasma and serum biomarker assessments will be approximately 12 mL per study visit.

- Presumed or suspected SCC (cutaneous [including KA] and non-cutaneous), new primary melanoma, other suspicious lesions, and normal skin

  FFPE tissue or 6–10 unstained FFPE slides from a presumed or suspected SCC (cutaneous [including KA] and non-cutaneous), new primary melanoma, or other suspicious lesion. Blocks will be returned after analyses are complete.

  An FFPE specimen containing normal skin (sun exposed, if possible) from patients who develop cuSCC/KA or new primary melanoma (only one specimen of normal skin is required from patients who develop multiple cuSCCs/KAs during study treatment). Note: Normal skin biopsies should be collected at the time the cuSCC/KA lesion, new primary melanoma, or other suspicious lesion is excised in an area of skin with hair follicles present to the level of subcutaneous tissue. These samples may be obtained by using a 3- to 4-mm punch biopsy device, which should not require suturing.

  Biopsies of suspicious malignant lesions not thought to represent SCC (including KA) or new primary melanoma (e.g., basal cell carcinoma) may be submitted at the discretion of the investigator.

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

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

Storage of Patient Specimens

Exploratory biomarker samples (with the exception of the original archival tissue block) will be stored for up to 5 years after completion of the study. Archival tissue blocks will be returned at the latest within 3–6 months. Patients will have the option to consent to the storage of samples remaining after protocol-defined analyses for up to 15 years in the Roche Clinical Repository (RCR; see Section 4.5.1.15). If no consent has been given for long-term storage, all samples will be destroyed no later than 5 years after the final close of the respective clinical database, unless regulatory authorities require that specimens be maintained for a longer period.

4.5.1.13 Unscheduled Assessments

For the purposes of this study, unscheduled assessments may occur coincident with early discontinuation of study treatment, early study termination, suspected melanoma recurrence, or suspected occurrence of a new primary melanoma between protocol-specified study visits (see Section 4.5.2.2 and Section 4.5.2.4).

4.5.1.14 Patient-Reported Outcomes

PRO data will be elicited from all patients in this study to more fully characterize the clinical profile of vemurafenib with use of the EORTC QLQ-C30. The EORTC QLQ-C30 is a validated and reliable self-report measure of QoL for patients with cancer. The EORTC QLQ-C30 consists of 30 questions that are incorporated into five functional

domains (i.e., physical, role, cognitive, emotional, and social), a global health status/global QoL, three symptom scales (i.e., fatigue, pain, and nausea and vomiting), and six single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and the perceived financial burden of treatment experienced by cancer patients). The PRO instrument, EORTC QLQ-C30, will be supplied in the local language of each participating country. Paper-based instruments will be distributed by the investigative staff and completed in their entirety by the patient at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigative site prior to the completion of other study assessments and the administration of study drug.

4.5.1.15 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

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

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

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

Approval by the Institutional Review Board or Ethics Committee

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

For all patients, date of consent should be recorded on the associated page of the eCRF.

RCR specimens will be stored until completely depleted for up to 15 years after the final freeze of the respective clinical database, unless regulatory authorities require that specimens be maintained for a longer period. The RCR storage period will be in

accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Optional Samples for the Roche Clinical Repository

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

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

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

- One 6-mL whole blood sample (anticoagulated in K3EDTA) at Cycle 1, Day 1 (or at the first visit following the RCR consent if this occurs after Cycle 1, Day 1).

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

Confidentiality

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

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

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

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators, unless a request for research use is granted. The

aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Consent to Participate in the Roche Clinical Repository

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

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

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

Withdrawal from the Roche Clinical Repository

Patients who give consent to long-term storage of exploratory biomarker specimens for further research in the RCR have the right to withdraw their consent to long-term storage of their specimens at any time for any reason. If a patient wishes to withdraw consent to the long-term storage of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO27826 does not, by itself, constitute withdrawal of specimens from long-term storage in the RCR. Similarly, a patient's withdrawal from long-term storage in the RCR does not constitute withdrawal from Study GO27826.

Monitoring and Oversight

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

review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

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

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the patient is randomized to study treatment. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 14 days prior to randomization may be used, and such tests do not need to be repeated for screening.

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

The following assessments will be performed at screening:

- Within 90 days prior to randomization:

  Pathologic stage of melanoma according to the AJCC v7 classification, on the basis of the following:

  Physical examination

  Post-surgery imaging studies (contrast-enhanced CT or MRI of the chest, abdomen, and pelvis; contrast-enhanced MRI of the brain [or CT if MRI is not generally available or is contraindicated])

  Sentinel lymph node biopsy and, if applicable, complete regional lymphadenectomy

  BRAF^{V600} mutation status of the primary tumor or involved lymph node confirmed using the **cobas**® BRAF V600 Mutation Test

  A locally obtained **cobas**® BRAF V600 Mutation Test using current primary or involved lymph node tissue can be used for screening purposes even if performed outside of the 90-day screening window.

  Melanoma tumor tissue for exploratory biomarker assessments

  Current primary or involved lymph node tissue can be submitted even if obtained outside of the 90-day screening window.

  Baseline dermatologic examination for cuSCC/KA surveillance

Pelvic examination, including visual inspection of the uterine cervix and Pap smear, unless this was done and found to be normal within the 3 months prior to the start of the 90-day screening period (women only)

Anal examination

Stool for occult blood

For select patients described in Section 4.5.1.7, colonoscopy to the cecum, with adequate bowel preparation, by a gastroenterologist or his or her designee (unless colonoscopy to the cecum with adequate bowel preparation and adequate resection of all visualized polyps was performed within 1 year of the start of the 90-day screening period)

Note: All polyps found at the screening colonoscopy will need to be adequately resected.

Please note that a patient with a known personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) >2 cm in size will be excluded from this study; this also applies to the screening colonoscopy for select patients (see Section 4.1.2).

Concomitant medications

- Within 28 days prior to randomization:

  Medical history, complete physical examination (including height and weight), and vital signs

  Thorough head and neck examination by the investigator

  Hematology, coagulation screening studies, serum chemistry, and liver function tests

  Hepatitis B virus (HBsAg and total anti-HBc) and HCV serology

  Triplicate ECGs

- Within 14 days prior to randomization:

  Serum pregnancy test

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

- Baseline PRO assessment (i.e., EORTC QLQ-C30 questionnaire)
- Triplicate ECG

  Note: If the screening ECG was performed within 7 days of the Cycle 1, Day 1 visit, it does not have to be repeated at Day 1.

- Vital signs, physical examination

  Note: If vital signs and physical examination are assessed within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.

- Hematology, serum chemistry, and liver function tests

  Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
- Blood samples for PK assessments (pre-dose, 1–4 hours after dose)
- Serum and plasma samples for exploratory biomarker assessments (6 mL in EDTA; 6 mL in serum separator tube)
- An optional whole blood sample (6 mL in EDTA) will be collected from patients consenting to provide a sample for the RCR.

  Note: This specimen can be collected at the first visit following the RCR consent if this occurs after Cycle 1, Day 1.

See Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Study

All assessments must be performed on the day of the specified visit, unless a time window is specified in the Schedule of Assessments (see Appendix 1). Assessments scheduled on the day of study drug administration should be performed prior to administration of study drug, unless otherwise noted in the Schedule of Assessments. The PRO assessment (EORTC QLQ-C30) should be performed prior to the completion of other study assessments. The timing of interval assessments (such as the head and neck examination and imaging studies) should be calculated from the Cycle 1, Day 1 visit. The frequency of the dermatological examination should be calculated from the date of the first dermatological examination, which should occur after 4 weeks of study drug administration.

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

The following assessments will be done during the study:

- Interval medical history, including documentation of new or worsening adverse events: Cycle 1 (Days 8, 15, and 22, each ±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle, and at the end-of-treatment visit
- Vital signs: Cycle 1 (Day 15±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle, and at the end-of-treatment visit
- Physical examinations: Cycle 1 (Day 15±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle, and at the end-of-treatment visit. Thereafter, physical examinations done by the investigator will be obtained every 13±2 weeks from the last dose of study drug until recurrence of melanoma, occurrence of a new primary melanoma, or *until end* of study *(see Section 3.2*), whichever occurs earlier. Height will be obtained at screening only.

Note: For all patients, as part of the physical examination, a thorough head and neck evaluation to monitor for non-cuSCC, consisting of at least a visual inspection of the oral mucosa and lymph node palpation, must be performed by the site investigator every 13±2 weeks during the study drug treatment period. Once a patient completes the treatment period or discontinues study drug early, a thorough evaluation of the head and neck by the study investigator will be performed at the end-of-treatment visit as part of the physical examination. Once a patient completes the treatment period or discontinues study drug early, a thorough head and neck evaluation to monitor for non-cuSCC will occur (as part of the physical examination for patients who continue to have physical examinations) at 13±2 weeks and 26±2 weeks from the last dose of study drug. For patients who no longer require physical examinations, the head and neck examination will occur independently at 13±2 weeks and 26±2 weeks from the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).

Patients with signs or symptoms consistent with head and neck cancer as determined by the site investigator will have a complete evaluation of the head and neck by a head and neck surgeon/otorhinolaryngologist or his or her designee who is experienced in the diagnosis and management of SCC of the head and neck: every 26±2 weeks during the study drug administration period. Once a patient completes the treatment period or discontinues study drug early, a complete evaluation of the head and neck by a head and neck surgeon/otorhinolaryngologist will be performed at 26±2 weeks after the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).

- All patients will have a colonoscopy to the cecum, with adequate bowel preparation, by a gastroenterologist or his or her designee who is experienced in the colonoscopic diagnosis of colorectal polyps and colorectal cancer within 3 months of discontinuation of study drug. All polyps found at any of the colonoscopies will need to be adequately resected.
- Hematology: Day 1 (±3 days) of each cycle and the end-of-treatment visit
- Serum chemistry and liver function tests: Cycle 1 (Days 8, 15, and 22, each ±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle and at the end-of-treatment visit
- Serum pregnancy test for all women of childbearing potential (including those who have had a tubal ligation): every three cycles (i.e., Cycles 3, 6, 9, and 12 or every 12±2 weeks), starting from Cycle 1, Day 1. If a patient discontinues study drug early, a serum pregnancy test will be performed at 12±2 weeks and 26±2 weeks after the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).
- Stool for occult blood: Cycle 6, Day 1 (±2 weeks) and end-of-treatment visit (±2 weeks)

- An anal examination and pelvic examination (including visual inspection of the uterine cervix and Pap smear): Cycle 6, Day 1 (±2 weeks) and end-of-treatment visit (±2 weeks)
- Triplicate ECGs: Cycle 1 (Day 15±3 days), Cycle 2 (Days 1 and 15, each±3 days), Cycle 3, Day 1 (±3 days), Day 1 (±3 days) of every subsequent third cycle, and at the end-of-treatment visit
- Imaging studies (surveillance for melanoma recurrence): Contrast-enhanced CT or MRI of the chest, abdomen, and pelvis every 13±2 weeks until Week 104 and every 26±4 weeks thereafter until recurrence of melanoma, occurrence of a new primary melanoma, or *until end* of study *(see Section 3.2)*, whichever occurs earlier. In addition, all patients will undergo contrast-enhanced MRI of the brain (or CT if MRI is not available or is contraindicated) every 52±4 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study (see Section 3.2)*, whichever occurs earlier. Patients who have had a DFS event do not need additional scans or physical exams for melanoma recurrence surveillance. However, these patients must still have a chest CT or MRI for SCC surveillance at 13±2 weeks and 26±2 weeks after last dose of study drug.
- Dermatologic examination performed by a dermatologist or his or her designee who is experienced in the diagnosis and management of cuSCC (surveillance for cuSCC/KA, new primary melanoma, or other suspicious lesions): end of Cycle 1±1 week and then every 13±2 weeks during the study drug treatment period. Once a patient completes the treatment period or discontinues study drug early, dermatologic examinations (including a complete evaluation of the skin) will occur at the end-of-treatment visit, at 13±2 weeks, and at 26±2 weeks from the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).
- An unscheduled dermatologic examination may be performed for investigation of any new skin lesions that are suspected of being cuSCC/KA or a new primary melanoma.
- Biopsy of suspected SCC (cutaneous [including KA] and non-cutaneous), new primary neoplasms (FFPE tissue blocks or 6–10 unstained tissue slides): one sample of normal skin from patients who develop cuSCC/KA or new primary melanoma
- PK assessments (2 mL of whole blood per sample): prior to and 1–4 hours after the morning dose in Cycle 1 (Days 8, 15, and 22, each±3 days), prior to the morning dose in Cycle 2 (Days 1 and 15, each±3 days), and prior to the morning dose on Day 1 (±3 days) of each subsequent cycle until the end-of-treatment visit. During Cycle 1, if drug is not administered on a visit day (Days 1, 8, 15, or 22), only one PK sample should be collected on that day. In addition, an unscheduled PK sample will be collected (when feasible) at the following timepoints:

  End-of-treatment visit

  As soon as possible after the diagnosis of melanoma recurrence or occurrence of a new primary melanoma while on study treatment (i.e., in conjunction with the tumor biopsy for biomarker assessments)

Note: In the event of melanoma recurrence or occurrence of a new primary melanoma during study treatment or if the patient discontinues study treatment because of other reasons, a PK sample should be taken upon drug discontinuation as well as at the study visit most proximate after study treatment discontinuation.

Coincident with the diagnosis of SCC (cutaneous [including KA] and non-cutaneous)

Coincident with any dose interruption and/or reduction for toxicity

Note: In the event of dose reduction or drug holiday, another unscheduled PK sample should be taken immediately before the patient resumes treatment at the modified dose as well as at Day 1 of the next cycle of treatment.

- Serum and plasma samples for exploratory biomarker assessments: Cycle 1 (Day 15±3 days), Cycle 2 (Day 1±3 days), Cycle 3 (Day 1±3 days). Serum and plasma samples should also be collected at the end-of-treatment visit and every 52±2 weeks after last dose of study drug until the recurrence of melanoma, occurrence of a new primary melanoma, or *until end* of study *(see Section 3.2)*, whichever occurs earlier.

  Note: In the event of melanoma recurrence or occurrence of a new primary melanoma during study treatment or if the patient discontinues study treatment because of other reasons, a sample should be taken upon drug discontinuation
- Melanoma tumor tissue: at recurrence of melanoma, as pathologically documented, (FF tissue and FFPE tissue) or occurrence of a new primary melanoma (FFPE tissue)
- PROs will be assessed at Cycle 1 (Day 15±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle, at the end-of-treatment visit, and at each scheduled and unscheduled visit during the follow-up period, including the early termination visit. In post-treatment follow-up, the EORTC QLQ-C30 questionnaire will be completed every 13±2 weeks from last dose of study drug until recurrence of melanoma, occurrence of a new primary melanoma, or until *end of study (see Section 3.2)*, whichever occurs first.

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

4.5.2.3 End-of-Treatment Visit

Patients who complete study drug treatment or discontinue study drug treatment early will be asked to return to the clinic 28±3 days after the last dose of study drug for an end-of-treatment visit. If the patient withdraws study consent prior to 28±3 days after the last dose of study drug, then the end-of-treatment visit can occur earlier. Refer to Section 4.5.2.2 and Appendix 1 for the Schedule of Assessments required at the end-of-treatment visit.

4.5.2.4 Post-Treatment Follow-Up Assessments

Patients who complete or discontinue study treatment without a recurrence or an occurrence of a new primary melanoma will continue to be followed with regular physical examinations (every 13±2 weeks) and imaging studies for a maximum of 5 years from Cycle 1, Day 1 or until a melanoma recurrence or an occurrence of a new primary melanoma *or until end of study (see Section 3.2),* whichever occurs first. All patients will be followed for the occurrence of new primary malignancies, regardless of melanoma recurrence or occurrence of a new primary melanoma, *until end of study (see Section 3.2).*

See Appendix 1 for the Schedule of Assessments performed during follow-up.

4.5.2.5 Melanoma Recurrence or New Primary Melanoma Occurrence

See Appendix 1 for the assessments required for patients who develop a melanoma recurrence or have an occurrence of a new primary melanoma. These patients will then continue in the study for post-recurrence follow-up.

4.5.2.6 Early Study Termination Visit (during Post-Treatment Follow-Up)

Patients who discontinue post-treatment follow-up will be asked to return to the clinic for a final visit to complete study assessments within 28 days. Assessments completed at melanoma recurrence or occurrence of a new primary melanoma do not need to be repeated at the early study termination visit. See Appendix 1 for the assessments required at the early study termination visit. Patients will continue to be followed for survival and new primary malignancy as outlined in Section 4.5.2.7.

4.5.2.7 Survival and New Primary Malignancy Follow-Up Assessments

Survival follow-up information will be collected via telephone calls and/or clinic visits every 13±2 weeks until death, loss to follow-up, or study termination by Roche or *until end* of *study (see Section 3.2).* Patients will be followed for new primary malignancies *until end of study (see Section 3.2).* All patients will be followed for survival information and new primary malignancy unless the patient requests to be withdrawn from follow-up; this request must be documented in the patient's medical record and signed by the investigator. If the patient withdraws from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only.

4.5.2.8 Adverse Event Follow-Up

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

After completion of study drug administration, adverse events should be followed as outlined in Section 5.5 and Section 5.6.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study protocol

4.6.1.1 Discontinuation from Study Drug

Patients are to receive study drug for up to 52 weeks. Patients must discontinue study drug if they experience any of the following:

- Pregnancy
- Histopathologic confirmation of occurrence of a new primary melanoma (diagnosed by Roche-designated central pathology laboratory). Refer to Section 5.1.2.3 for a discussion on new primary melanoma
- Histopathologic confirmation of recurrent melanoma
- Radiographic and/or histopathologic findings consistent with recurrence of melanoma in brain
- Radiographic findings consistent with recurrence when suspicious lesions are deemed not amenable to biopsy by the investigator or the patient refuses biopsy confirmation

Patients who discontinue study drug prematurely will be asked to return to the clinic for an end-of-treatment visit (see Section 4.5.2.2, Section 4.5.2.3 and Appendix 1) and may undergo follow-up assessments (see Section 4.5.2.2, Section 4.5.2.3, Section 4.5.2.4, and Appendix 1). 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

The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If patient is lost to follow-up, the investigator should make every effort to contact the patient by telephone or by sending a registered letter to establish as completely as possible the reason for the withdrawal and survival status. These steps for contacting patients (who prematurely withdraw or who are lost to follow-up) will be documented in the patient informed consent form.

Patients who withdraw their consent to be followed for the primary study endpoint (DFS) will be asked to continue follow-up for OS until *end* of *study (see Section 3.2),* as well as for new primary malignancies *until end of study (see Section 3.2).* Patients will not be followed for any reason after full consent, for DFS, OS, and new primary malignancies, has been withdrawn. Patients who withdraw from the study will not be replaced.

An excessive rate of withdrawals can potentially render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

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 International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial, in particular, the use of stringent inclusion and exclusion criteria and close monitoring of patients.

5.1.1 Background: Vemurafenib Risks

The toxicity profile for vemurafenib has been documented from safety data derived from seven studies of over 600 treated patients with locally advanced unresectable or metastatic melanoma. The most common toxicities observed were rash, fatigue, arthralgia, myalgia, headache, nausea, photosensitivity, alopecia, and pruritus. The most common laboratory abnormalities reported as adverse events included elevations of liver function tests (i.e., GGT, alkaline phosphatase, ALT, AST, and bilirubin). The majority of adverse events reported in conjunction with Phase I–III clinical trials were of mild or moderate severity. Approximately one-half of all patients treated with vemurafenib required interruption and/or reduction of dose on at least one occasion, although treatment discontinuation because adverse events has been rare.

Approximately 20% of vemurafenib recipients developed one or more localized cuSCCs (mainly KA type). The majority of these was observed within the first 7–8 weeks of vemurafenib exposure and was not treatment limiting. As with all clinical studies of vemurafenib to date, the risk for cuSCC will be mitigated through the use of a Risk Management Plan as outlined in Section 5.1.2.3.

Analysis of ECG data from the Phase II Study NP22657 of vemurafenib in patients with metastatic melanoma revealed a risk of QT interval prolongation without associated clinical symptomatology (as noted in Section 5.1.2.3.7).

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. In addition, five cases of adenomatous colonic polyps have been reported in patients who received vemurafenib for 2 or more years on a clinical trial. One patient who was participating in the Expanded Access Program was found to have a colonic adenoma after being on vemurafenib for 0.57 years (see Section 1.2.5 and the Vemurafenib IB for additional details).

5.1.2 General Plan to Manage Safety Concerns

5.1.2.1 Eligibility Criteria

Eligibility criteria promulgated for this study will guard the safety of patients in this trial. The exclusion criteria for safety shall include (but are not limited to) the following: major surgical procedure (other than sentinel lymph node biopsy or complete regional lymphadenectomy) or significant traumatic injury within 4 weeks prior to first dose of study drug; pregnancy or breastfeeding; clinically significant cardiovascular disease;

history of congenital long QT syndrome or QTc interval $>$450 ms at baseline; inadequate bone marrow, hepatic, or renal function; and history of malabsorption or other clinically significant metabolic dysfunction.

5.1.2.2 Monitoring

Safety will be evaluated in this study through the monitoring of all adverse events and targeted laboratory assessments. Adverse event severity will be graded according to NCI CTCAE v4.0. Patients will be monitored weekly during Cycle 1, every 2 weeks during Cycle 2, Day 1 of every subsequent cycle, and as needed until 4 weeks after the last dose of study treatment or initiation of other anti-melanoma therapy, whichever occurs first. All treatment-emergent adverse events and serious adverse events whether or not deemed treatment related will be followed until they resolve or become stabilized, new anti-tumor treatment is initiated, the patient is lost to follow-up or withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event or serious adverse event. General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies including serum chemistry, liver function tests, and blood counts. All serious adverse events and protocol-defined adverse event of special interest will be reported in an expedited fashion.

In addition to the oversight provided by the Medical Monitor and Drug Safety personnel for this trial, an independent DSMB that has been tasked with monitoring safety data from vemurafenib studies will be employed to evaluate safety data from this study. The DSMB will review safety data every 3 months starting 3 months after the data become available and continuing until the study is unblinded coincident with the final DFS analysis for each cohort. The quarterly safety review will include summary tables of subject disposition, all adverse events, serious adverse events, deaths, adverse events leading to treatment discontinuations, adverse events of special interest, and treatment exposure.

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

5.1.2.3 Monitoring and Management of Specific Toxicities and Conditions That May Arise with Vemurafenib Treatment

5.1.2.3.1 Non–Squamous Cell Carcinoma Skin Toxicity

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

Mild to severe photosensitivity has been reported in patients who received vemurafenib in clinical studies. All patients should be advised to avoid sun exposure while taking study drug. Patients should be advised to wear protective clothing and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF ≥30) when outdoors to help protect against sunburn. For photosensitivity Grade ≥2 (intolerable) adverse reactions, dose modifications will be required.

5.1.2.3.2 Non–Cutaneous Squamous Cell Carcinoma

For all patients, a thorough examination of the head and neck to monitor for non-cuSCC, consisting of at least a visual inspection of the oral mucosa and lymph node palpation, must be performed by the site investigator or designee according to Section 4.5.1.6 and Appendix 1. In the case of a suspected head and neck cancer (e.g., on the basis of signs or symptoms), a flexible fiberoptic laryngoscopy will be performed by a head and neck surgeon/otorhinolaryngologist or his or her designee who is experienced in the diagnosis and management of SCC of the head and neck. Assessment will consist of at least a visual inspection of the oral mucosa and palpation of the tonsils, base of tongue, and lymph nodes in order to evaluate the sinonasal cavity, the nasopharynx, the base of tongue, larynx, and hypopharynx.

The routinely scheduled chest CT (or MRI) scan performed as part of the assessment for tumor recurrence will be used for SCC surveillance during study drug treatment and post-treatment follow-up at 13±2 weeks and 26±2 weeks after last dose of study drug. If intravenous contrast is contraindicated, then a non-contrasted CT (or MRI) scan of the chest is to be performed. Patients who have had a DFS event do not need additional scans or physical examinations for melanoma recurrence surveillance; however, chest CT is required at 13±2 weeks and 26±2 weeks after last dose of study drug for SCC surveillance.

Visual and digital evaluation of the anus and anal canal will be performed according to Section 4.5.2 and Appendix 1. For female patients, a pelvic examination including visual inspection of the uterine cervix and Pap smear will occur according to Section 4.5.2 and Appendix 1.

For patients who have been referred to a head and neck surgeon/otorhinolaryngologist because of suspected head and neck cancer, this assessment will occur at screening and every 26±2 weeks during the study drug administration period. Patients who complete the treatment period or discontinue study drug early will have this assessment at 26±2 weeks after the last dose of study drug.

An unscheduled examination may be performed for investigation of any new head and neck lesions that are suspected of being SCC. Any suspicious lesions identified must be biopsied or excised, and a specimen (tissue block/sections) is sent to a Roche-designated central laboratory for pathological examination and further molecular characterization. In addition, appropriate follow-up must be instituted.

5.1.2.3.3 Cutaneous Squamous Cell Carcinoma (including Keratoacanthoma) and New Primary Melanoma

For all patients, a complete evaluation of the skin by a designated dermatologist or his or her designee who is experienced in the diagnosis and management of cuSCC/KA will be conducted at baseline (up to 90 days prior to randomization), during study drug treatment period, and post-treatment follow-up according to Section 4.5.2 and Appendix 1. An unscheduled dermatology examination may be performed for investigation of any new skin lesions that are suspected of being cuSCC (including those classified as KA) or new primary melanomas. If a patient develops cuSCC/KA either during or after the study drug administration period, this information must be collected and reported as a non-serious adverse event of special interest to the Sponsor, whether it is deemed related or unrelated to study drug. If a patient develops a new primary melanoma either during or after the study drug administration period, this information must be collected and reported to the Sponsor, whether it is deemed related or unrelated to study drug. The following bullet points detail the required monitoring/management of skin-associated vemurafenib risks:

- A dermatologist or his or her designee who is experienced in the diagnosis and management of cutaneous neoplasms will perform skin evaluations to monitor for cuSCC/KA, new primary melanoma, BCC, and actinic keratosis.
- A complete history of prior dermatologic interventions and medications, cuSCC risk factors (i.e., Fitzpatrick skin type, radiotherapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, and precursor lesions), and prior HPV vaccination must be collected. Refer to Appendix 7 for a list of Fitzpatrick skin phototypes.
- Any suspicious lesions identified at baseline and while on study drug and 26 ± 2 weeks after last dose of study drug must be biopsied and excised and sent for pathological examination.
- Available specimen block/sections should be sent to a Roche-designated central pathology laboratory for confirmation of diagnosis and further molecular characterization.
- Tissue from lesions that are suspicious for a new primary melanoma must be evaluated by both the local pathology laboratory and the Roche-designated central pathology laboratory. For study purposes, a new primary melanoma will be diagnosed based on central pathology review. Patients should remain on study drug until central pathology confirmation of new primary melanoma, unless the investigator determines that treatment should be discontinued for clinical reasons. Should this be the case, the investigator should contact the Medical Monitor.
- Actinic keratosis or other skin conditions identified by the dermatologist should be treated per local standards of care.
- The occurrence of any skin changes, including rash and photosensitivity, should be reported to the study investigator, and patients will be referred to the dermatologist as required.

5.1.2.3.4 Colorectal Polyps

For select patients with known personal history of adenomatous colorectal polyps or colorectal cancer, family history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer at or after the age of 60 years, or signs or symptoms that could be related to colon cancer as determined by the site investigator or designee, a screening colonoscopy will be conducted. Patients with family history of inherited colon cancer syndromes and/or history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer before the age of 60 years will be excluded from this study.

Colonoscopy must be complete to the cecum, with adequate bowel preparation, and must be performed within the 90-day screening period by a gastroenterologist or his or her designee who is experienced in the colonoscopic diagnosis of colorectal polyps and colorectal cancer. All visualized polyps found at the screening or subsequent colonoscopies will need to be adequately resected. For select patients (described above), the screening colonoscopy is not required if colonoscopy to the cecum with adequate bowel preparation and adequate resection of all visualized polyps was performed within 1 year of the start of the 90-day screening period, unless the site investigator deems it necessary. Please note that patients with a personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) >2 cm in size will be excluded from this study; this also applies to the screening colonoscopy for the select patients described above (see also Section 4.1.2).

All patients will be required to undergo a post-treatment colonoscopy within 3 months of discontinuation of study drug.

5.1.2.3.5 New Primary Cancers

All new primary malignancies will be reported *until end of study (see Section 3.2),* whether or not a patient has exhibited recurrence of melanoma in the study.

Visual and digital evaluation of the anus and anal canal will be performed according to Section 4.5.2 and Appendix 1. For female patients, a pelvic examination, including visual inspection of the uterine cervix and Pap smear, will occur according to Section 4.5.2 and Appendix 1.

For all patients, a thorough evaluation of the head and neck will be performed as part of the physical examination by the site investigator according to Section 4.5.2 and Appendix 1. Evaluation will consist of at least a visual inspection of the oral mucosa and palpation of the tonsils, base of tongue, and lymph nodes.

If, at any time, head and neck cancer is suspected (e.g., on the basis of signs or symptoms), the patient will be referred to a head and neck surgeon/otorhinolaryngologist or designee who is experienced in the diagnosis and management of SCC of the head

and neck. The head and neck surgeon/otorhinolaryngologist or designee will perform an assessment including at least a visual inspection of the oral mucosa, palpation of the tonsils, base of tongue, and lymph nodes and flexible fiberoptic laryngoscopy in order to evaluate at least the sinonasal cavity, the nasopharynx, the base of tongue, the larynx, and the hypopharynx. For patients who have been referred to a head and neck surgeon/otorhinolaryngologist or designee who is experienced in the diagnosis and management of SCC of the head and neck, this assessment will occur at screening and every 26 ± 2 weeks during the study drug administration period. Patients who complete the treatment period or discontinue study drug early will have this assessment at 26 ± 2 weeks after the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).

If a patient develops a new primary malignancy (other than cuSCC/KA or melanoma) either during or after study treatment, this information must be collected and reported as a serious adverse event to the Sponsor, whether it is deemed related or unrelated to study drug. If the patient is still receiving study drug, the investigator should contact the Medical Monitor to discuss study drug administration. For cuSCC/KA or new primary melanoma, refer to Section 5.1.2.3.3.

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

5.1.2.3.6 Hepatic Toxicity

Liver injury (ALT $\geq 5 \times$ ULN, ALT $\geq 3 \times$ ULN with bilirubin $\geq 2 \times$ ULN, or alkaline phosphatase $\geq 2 \times$ ULN with GGT elevation), including severe cases of liver injury (described as hepatic failure), has been reported in patients treated with vemurafenib. All patients will undergo liver function testing (i.e., AST, ALT, total bilirubin, and alkaline phosphatase) at periodic intervals while receiving study treatment (see Appendix 1). In addition, Grade 4 elevations of AST, ALT, serum bilirubin OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, (as defined in Section 5.3.5.6) qualifies as a non-serious adverse event of special interest and must be reported to the Sponsor within 24 hours after learning of the event.

Guidelines for interruption/dose reduction of study drug in the setting of liver function abnormality are provided in Table 2. Please note that all Grade 2 liver function test abnormalities will be defined as “intolerable” for the purposes of interruption/dose reduction of study drug.

5.1.2.3.7 Cardiac Toxicity

QT interval prolongation was observed in the ECG substudy of Study NP22657, the Phase II clinical trial of vemurafenib in patients with previously treated, metastatic melanoma ($n = 132$). Vemurafenib treatment at a dose of 960 mg BID was associated with a prolongation of the QTc interval in some adult patients with metastatic melanoma,

and the largest mean QTc interval change from baseline noted was 15.1 ms (upper bound of the one-sided 95% CI, 17.7 ms). The extent of change in the QTc interval from baseline was related to the vemurafenib steady-state concentration in plasma. One patient (0.8%) had a QTc interval prolongation >60 ms (Grade 2) compared with baseline, and 2 patients (1.5%) had an absolute QTc interval >500 ms (Grade 3) on at least one occasion. The mean QTc interval prolongation in the study population appeared to remain stable between 12 and 15 ms at all assessment timepoints after Cycle 1, Day 15. To date, there have been no clinical adverse events, manifest cardiac arrhythmias, or other clinically significant cardiac events in clinical trials that are linked to QTc interval prolongation.

As a result of these findings, the following guidelines will be implemented in this study to minimize the risk of ventricular arrhythmia in patients with melanoma treated with vemurafenib in this study:

- Patients with a baseline QTc interval >450 ms or a history of congenital long QT syndrome will not be eligible to participate in this study.
- Triplicate ECG monitoring will occur at baseline and at regular intervals during study treatment (see Appendix 1).
- Combination therapy with other medications known to lead to prolongation of QTc interval should be avoided, if possible.

Dose Interruption and Permanent Discontinuation for QTc Prolongation

If QTc exceeds 500 ms (measured in triplicate ECG) but is less than or equal to a 60-ms increment compared with baseline OR the change from baseline is greater than 60 ms without QTc >500 ms, study drug treatment should be temporarily interrupted.

If QTc increases to 500 ms AND the change from baseline exceeds 60 ms, study drug treatment should be permanently discontinued. Such patients will NOT be able to restart the study.

Assessment and Management of QTc Prolongation

Immediate action upon observation of QTc >500 ms:

- Both the QTc interval and serum electrolytes with appropriate correction should be monitored regularly until there is clear evidence that the QTc is <500 ms. Patients should remain under close observation until the QTc returns to <500 ms and/or discharge is considered appropriate by consulting cardiologist.
- Serum electrolytes (particularly potassium, magnesium, and corrected calcium) must be evaluated, and any and all electrolyte abnormalities, with particular attention to hypokalemia, hypomagnesemia, and hypocalcemia, must be corrected.
- Patients must be closely monitored and, in particular, re-evaluated for other cardiac risk factors (e.g., hypertension, congestive heart failure, cardiac ischemia, bradyarrhythmias, diabetes). Any other treatable risk factors (e.g., hypothyroidism) should be corrected per standard of care.

- All concomitant medications must be re-evaluated, and consideration should be given to discontinuing those that could prolong the QTc interval and, if appropriate, substituting them with an alternative medication that does not affect the QTc interval.
- Patients must have ECG re-evaluated within 48 hours to ensure QTc interval is improving after interruption of study medication and correction of aforementioned potential concomitant factors.
- Study treatment will not be resumed until the QTc is clearly $<$500 ms. Upon resumption of study drug treatment, the study drug dose should be reduced. Refer to Table 2.
- Upon resumption of study drug treatment, ECG (measured in triplicate) and electrolytes should be monitored at Day 1 (i.e., day when study drug is resumed) pre-dose, then every 2 weeks ($\pm$3 days) for at least two cycles, then Day 1 ($\pm$3 days) of the following cycle, and then Day 1 ($\pm$3 days) of every subsequent third cycle. This replaces the protocol-mandated ECG monitoring that is outlined in Appendix 1.
- A cardiologist must be consulted if any of the following occurs:

  The QTc does not return to baseline upon temporary or permanent interruption of study drug or upon correction of secondary causes (e.g., electrolyte abnormalities, concomitant medications known to prolong QT, cardiac ischemia, severe bradycardia).

  There are concomitant signs or symptoms of potential pro-arrhythmia (e.g., premature ventricular contractions [PVCs], persistent bradycardia, syncope, palpitations, etc.).

  The physician is not comfortable managing prolonged QTc according to the guidelines outlined above.

For all patients with QTc change from baseline $>$60 ms, without QTc $>$500 ms:

- Serum electrolytes (particularly potassium, magnesium, and corrected calcium) should be evaluated, and any and all electrolyte abnormalities, with particular attention to hypokalemia, hypomagnesemia, and hypocalcemia, must be corrected.
- Patients should be closely monitored and in, particular, re-evaluated for other cardiac risk factors (e.g., hypertension, congestive heart failure, cardiac ischemia, bradyarrhythmias, diabetes). Any other treatable risk factors (e.g., hypothyroidism) should be corrected per standard of care.
- All concomitant medications should be re-evaluated, and consideration should be given to discontinuing those that could prolong the QTc interval and, if appropriate, substituting them with an alternative medication that does not affect the QTc interval.
- Both the QTc interval and serum electrolytes (with appropriate correction) should be monitored weekly until the QTc change from baseline is less than 60 ms before resuming therapy.

- Upon resumption of study drug treatment, the study drug dose should be reduced. Refer to Table 2.

  Upon resumption of study drug treatment, the ECG (measured in triplicate) and electrolytes should be monitored at Day 1 (i.e., day when study drug is resumed) pre-dose, then every 2 weeks (±3 days) for at least two cycles, then Day 1 (±3 days) of the following cycle, and then Day 1 (± 3 days) of every subsequent third cycle. This replaces the protocol-mandated ECG monitoring that is outlined in Appendix 1.

- A cardiologist must be consulted if any of the following occurs:

  The QTc does not return to baseline upon temporary or permanent interruption of study drug or upon correction of secondary causes (e.g., electrolyte abnormalities, concomitant medications known to prolong QT, cardiac ischemia, severe bradycardia).

  There are concomitant signs or symptoms of potential pro-arrhythmia (e.g., PVCs, persistent bradycardia, syncope, palpitations, etc.).

  The physician is not comfortable managing prolonged QTc according to the guidelines outlined above.

5.1.3 Management of Specific Adverse Events

Management of symptomatic adverse events or QTc prolongation may require temporary interruption, dose reduction, or treatment discontinuation of study drug (see Table 2). Dose modifications or interruptions are not recommended for cuSCC/KA adverse events. Dose modifications or interruptions should occur in accordance with the schedule below, regardless of causality determination.

Table 2 Dose Modification Schedule

Grade [a]	Recommended Dose Modification [b]
Grade 1 or Grade 2 (tolerable) [c]	Maintain study drug at a dose of 4 tablets twice daily
Grade 2 (intolerable) [c] or Grade 3	
First appearance	Interrupt treatment until Grade 0 or 1. Resume dosing at 3 tablets twice daily
Second appearance	Interrupt treatment until Grade 0 or 1. Resume dosing at 2 tablets twice daily
Third appearance	Discontinue permanently
Grade 4	
First appearance	Discontinue permanently or interrupt study drug treatment until Grade 0 or 1. Resume dosing at 2 tablets twice daily
Second appearance	Discontinue permanently

[a] The intensity of clinical adverse events graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

[b] No dose modification is required in the setting of an isolated increase in gamma glutamyl transferase in the absence of a transaminitis, elevated serum bilirubin, or other hepatic symptoms.

[c] All Grade 2 liver function test abnormalities will be defined as "intolerable."

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to Roche)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.9)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

Recurrence of melanoma is not reported as an adverse event if it is clearly consistent with the suspected recurrence of the disease under study. Clinical signs or symptoms of recurrence may be reported as adverse events only if the symptom cannot be determined as exclusively due to the recurrence of the underlying malignancy or does not fit the expected pattern of recurrence for the disease under study. If there is any uncertainty about an adverse event being due only to the extent of the disease under study, it should be reported as an adverse event or a serious adverse event.

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

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

Serious adverse events are required to be reported by the investigator to the Sponsor 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 Roche)

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

- Grade ≥3 photosensitivity
- Grade 4 elevations of AST, ALT, serum bilirubin OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
- cuSCC (including KA)
- Grade ≥3 QT interval prolongation
- Gastrointestinal polyps
- Suspected transmission of an infectious agent by study drug

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events as defined in Section 5.2.1 are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 through Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2), severity (Section 5.3.3), and causality (Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported up to and including 28 days after the last dose of study drug. After

this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6). In addition, all new primary malignancies will be reported *until end of study (see Section 3.2),* whether or not a patient has exhibited recurrence of melanoma while in the study.

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 adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe 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 adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

- Is 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

- Is clinically significant in the investigator's judgment

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

If a clinically significant laboratory abnormality is a manifestation of a disease or syndrome (e.g., 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 manifestation of a clearly discernible disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

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

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ the baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ the baseline value in combination with clinical jaundice

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

5.3.5.7 Deaths

For this protocol, mortality is a secondary efficacy endpoint. All deaths must be recorded on the Study Completion/Discontinuation eCRF.

Deaths that are attributed by the investigator solely to recurrence of melanoma are not considered an adverse event and should not be recorded on the Adverse Event eCRF. Rather, these deaths should be recorded on the Study Completion/Discontinuation eCRF.

All other deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent DSMB will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. 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. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

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 Hospitalization or Prolonged Hospitalization

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

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., complete regional lymphadenectomy)
- 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 adverse event.
- Hospitalization due solely to recurrence/progression of the underlying melanoma

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- *Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours*

5.3.5.10 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 adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

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

5.3.5.11 Patient-Reported Outcome Data

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse event of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor 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 serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Contacts

5.4.1.1 Non–Medical Emergency Medical Contacts

Contact the medical monitor or designee for your respective region. Please refer to a Medical Contact List for the name and contact information. Should you be unable to reach your regional medical monitor or designee, you can contact the global medical monitor (or back up) also listed in the Medical Contact List located in your Investigator Site file.

5.4.1.2 Medical Emergency Medical Contacts

24-HOUR MEDICAL COVERAGE (Roche Emergency Medical Call Center Help Desk):

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. Please refer to the Emergency Medical Call Center Country Specific Toll-Free Number Details for your country, located in your Investigator Site File.

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

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

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee 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 *until end of study (see Section 3.2)*. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening (within 14 days prior to randomization) and every three cycles (e.g., Cycles 3, 6, 9, and 12 or every 12 $\pm$ 2 weeks), starting from Cycle 1, Day 1 during study drug administration and at 12 $\pm$ 2 weeks and 26 $\pm$ 2 weeks after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator 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 within 24 hours after learning of the pregnancy, using the

fax numbers provided to investigators (see “Protocol Administrative and Contact Information and List of Investigators”).

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant *until end of study (see Section 3.2)* starting from Cycle 1, Day 1. A Pregnancy Report eCRF should be completed by the investigator 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 a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor 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 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 New Primary Cancers

In fulfillment of a post-marketing requirement as a condition of vemurafenib approval in the United States (for the treatment of unresectable or metastatic melanoma), all new primary cancers will be reported to the U.S. Food and Drug Administration (FDA) every 12 months after the first patient enrolls and for 1 year after the last patient has completed study treatment. As noted in Section 5.1.2.3.5, all new primary cancers will be reported for *until end of study*, whether or not a patient has experienced melanoma recurrence or an occurrence of a new primary melanoma.

5.5.2 Investigator Follow-Up

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

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

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

5.5.3 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

At the study treatment completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, serious adverse event (including new primary malignancies), or other adverse event of 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 survival follow-up, deaths attributed to recurrence of melanoma should be recorded on the Study Completion/Discontinuation eCRF.

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

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

- Vemurafenib IB
- Local prescribing information for vemurafenib
- 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

Descriptive summaries of continuous data for each cohort will include the mean, standard deviation, median, minimum, and maximum, and number of patients. Descriptive summaries of discrete data for each cohort will include the number of patients and incidence as a frequency and percentage.

6.1 DETERMINATION OF SAMPLE SIZE

The overall Type I error (alpha) for this study is 0.05 (two sided). The primary objective of the protocol to assess efficacy as measured by DFS will be evaluated separately for each of the two cohorts. The sample size determination was evaluated separately for each cohort. The final primary efficacy endpoint (DFS) analyses for the two cohorts will be conducted according to the procedure specified in Section 6.4.1. The detailed analysis plan will be specified in Statistical Analysis Plan (SAP).

6.1.1 Cohort 1

The final analysis of the primary endpoint of DFS for Cohort 1 will take place when approximately 120 DFS events have occurred, on the basis of the following assumptions:

- Two-sided, stratified log-rank test at the 0.05 significance level
- 80% power
- Median DFS for the control arm of 24 months and estimated median DFS in the vemurafenib treatment arm of 40 months (which corresponds to an HR of 0.60)
- 5% annual loss to follow-up for DFS
- No interim analysis

Assuming an accrual rate of 8 patients per month in Cohort 1 and a 17-month ramp-up period to reach steady-state enrollment, approximately 300 patients will be required to be enrolled in Cohort 1 during 43 months and followed for an additional 7 months in order to observe 120 DFS events.

On the basis of the assumptions above, 120 DFS events are projected to occur in Cohort 1 approximately 50 months after the first patient is randomized in this study. At that time, it is projected that median follow-up time will be 21 months in Cohort 1, and the minimum follow-up time (e.g., for the last patient randomized) is projected to be 7 months. Also on the basis of the assumptions of 120 DFS events required and a target HR of 0.60, it is projected that an observed HR of 0.70 or better in the DFS analysis will result in a statistically significant difference between treatment arms (i.e., HR of 0.70 is the minimally detectable difference for that analysis).

A summary of the assumptions and characteristics of the DFS analysis for Cohort 1 is shown in Table 4.

For Cohort 1, on the basis of the assumptions of a target HR of 0.60, 120 DFS events would also provide 80% power to detect a 16% absolute increase in the 2-year DFS rate (50% vs. 66%, corresponding to a 40% risk reduction; i.e., HR of 0.60).

6.1.2 Cohort 2

The final analysis of the primary endpoint of DFS for Cohort 2 will take place when approximately 105 DFS events have occurred, on the basis of the following assumptions:

- Two-sided, stratified log-rank test at the 0.05 significance level
- 80% power
- Median DFS for the control arm of 7.7 months and estimated median DFS in the vemurafenib treatment arm of 13.3 months (which corresponds to an HR of 0.58)
- 5% annual loss to follow-up for DFS
- No interim analysis

Assuming an accrual rate of 5 patients per month in Cohort 2 and a 27-month ramp-up period to reach steady-state enrollment, approximately 175 patients will be required to be enrolled in Cohort 2 over 40 months in order to observe 105 DFS events.

A summary of the assumptions and characteristics of the DFS analysis for Cohort 2 is shown in Table 4.

For Cohort 2, on the basis of the assumptions of a target HR of 0.58, 105 DFS events would provide 80% power to detect a 17% absolute increase in the 2-year DFS rate (12% vs. 29%, corresponding to a 42% risk reduction; i.e., HR of 0.58).

Table 4 Assumptions and Characteristics for Disease-Free Survival Analyses by Cohort

	Cohort 1	Cohort 2
Patients enrolled	300	175
Hazard ratio targeted	0.60	0.58
Target median (control)	24 months	7.7 months
Target median (vemurafenib)	40 months	13.3 months
Final DFS analysis		
Number of DFS events	120	105
MDD hazard ratio [a]	0.70	0.68
Alpha level (two sided)	0.05	0.05
Power	80%	80%

DFS = disease-free survival; FPI = first patient in; MDD = minimum detectable difference.

Note: A 5% annual dropout rate is anticipated for DFS analyses.

[a] Minimally detectable difference; the largest observed hazard ratio that is projected to be statistically significant.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, eligibility violations, and patient disposition will be summarized for randomized patients by treatment arm. The summary of patient disposition will include whether treatment was completed or discontinued prematurely and the reason for premature treatment discontinuation. Study treatment administration will be summarized by treatment arm for all treated patients.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables, stratification factors, and other baseline characteristics will be summarized.

6.4 EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will include all randomized patients (intent-to-treat analysis), and patients will be grouped according to the treatment assigned at randomization. The primary and all secondary objectives of this study will be evaluated separately for each cohort.

6.4.1 Primary Efficacy Endpoint

The primary endpoint, DFS, is defined as the time from randomization until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause. The DFS component of melanoma recurrence will be assessed by the investigator. The DFS component of an occurrence of a new primary melanoma will be based upon the diagnosis made by a Roche-designated central pathology laboratory. For patients without a DFS event at the time of data cutoff,

data will be censored at the date of the last disease assessment. Details on censoring in the analysis of this endpoint are described in the SAP.

For patients whose recurrence has been proven histologically, the date of melanoma recurrence will be defined as the earliest date of the scan or clinical examination that prompted the biopsy. For patients whose suspicious lesions were deemed not amenable to biopsy (see Section 4.5.1.4) or for patients who refuse a biopsy, the date of melanoma recurrence will be defined as the earliest date of the scan or clinical examination that would have prompted a biopsy. For patients with an occurrence of a new primary melanoma, the date of the new primary melanoma will be defined as the earliest date of the clinical examination or scan that prompted the biopsy.

The final analysis of the primary endpoint of DFS will take place when approximately 120 DFS events have occurred for Cohort 1 and approximately 105 DFS events have occurred for Cohort 2 (see Section 6.1). The final DFS analyses for both cohorts will be conducted at the same time by using the dataset from the same data cutoff date for both cohorts. The primary efficacy analyses will be comparisons of the two treatment groups, using a two-sided, stratified log-rank test for Cohort 1 and Cohort 2 separately. To account for separate analysis for each cohort, the statistical significance of the comparison of DFS between treatment arms will be based an alpha level of 0.05 (two sided) of the family-wise Type I error rate for two tests of two cohorts. Detailed testing procedures will be provided in the SAP.

Median DFS time will be estimated using the Kaplan-Meier method, and the two-sided 95% CI will be calculated using the method of Brookmeyer and Crowley (1982) for each cohort.

The HR of DFS (recurrence, new primary melanoma, or death) and the associated two-sided 95% CI will be estimated by using a stratified Cox proportional hazards model.

The stratification factors in the stratified analyses are the stratification factors used in randomization of patients in each cohort. For Cohort 1, stratified analyses will incorporate two stratification factors: pathologic stage (Stage IIC; Stage IIIA; Stage IIIB) and region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world). For Cohort 2, stratified analyses will incorporate one stratification factor, region (North America, Australia/New Zealand/South Africa/Latin America, rest of the world).

In addition, Kaplan-Meier methodology will be used to estimate landmark (e.g., 1-year, 2-year, and 3-year) DFS rates and the associated two-sided 95% CIs for each treatment arm, and the Kaplan-Meier curves will be provided.

Subgroup analyses for the primary efficacy outcome, DFS, will be performed to assess the robustness of the results across patient subgroups in each cohort separately. The

subgroups will include but are not limited to the categories of demographic (age, sex), baseline disease characteristics, *BRAF* mutation status such as V600E versus non-V600E, and stratification variables.

The following sensitivity analyses will be performed for DFS by study cohort. Details are provided in the SAP:

- Unstratified log-rank test and HR
- DFS analysis accounting for missing disease assessments for patients later diagnosed with a DFS event
- DFS analysis accounting for DFS events reported at an off-schedule disease assessment

As an exploratory analysis, DFS analyses based on the pooled data from both cohorts will also be performed for descriptive purposes to characterize the benefit of vemurafenib in the total study population. This exploratory analysis will be stratified by region.

6.4.2 Secondary Efficacy Endpoints

DMFS and OS are the secondary efficacy endpoints. The Type I error management for secondary endpoints is described in the SAP.

6.4.2.1 Distant Metastasis–Free Survival

DMFS is defined as the time from randomization until the date of diagnosis of distant (i.e., non-locoregional) metastasis or death from any cause. Details on censoring in the analysis of this endpoint are described in the SAP. DMFS will be analyzed at the time of the final DFS analysis in each cohort. The analysis methods to be employed for DMFS are the same as those described for the primary endpoint of DFS.

6.4.2.2 Overall Survival

OS is defined as the time from randomization until the date of death from any cause. For patients still alive at the time of analysis, the data will be censored at the date the patient was last known to be alive. The study is not powered for OS, so adequate power statistical testing for this endpoint is not possible. However, some standard OS estimates will be provided by using the same analysis methods as those described for the primary endpoint of DFS.

Two OS analyses are planned for each cohort. The OS interim analysis in each cohort will be performed at the time of the final DFS analysis for both cohorts. The final OS analysis for Cohorts 1 and 2 will be performed *at the end of study (see Section 3.2)*.

6.5 SAFETY ANALYSES

Safety analyses will include all patients who receive any amount of study treatment (vemurafenib or placebo), with patients grouped according to the patients' safety group.

Patients who receive at least one dose of vemurafenib will be included in the vemurafenib safety population. Safety will be assessed through summaries of all adverse events, including serious adverse events, adverse events of special interest, and adverse events leading to discontinuation of vemurafenib or placebo. All verbatim descriptions of treatment-emergent adverse events will be summarized by MedDRA preferred terms. Adverse events will be graded by the investigator according to NCI CTCAE v4.0.

The following safety parameters will be summarized by treatment arm for patients in Cohort 1 and Cohort 2 separately as well as for all study patients pooled:

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

In addition, treatment exposure, including cumulative dose and treatment duration, will be summarized by treatment arm.

Selected laboratory data will be summarized by treatment arm and toxicity grade (NCI CTCAE v4.0). Further details on safety analyses, including descriptions of the analyses of ECGs, are provided in the SAP.

6.6 PHARMACOKINETIC ANALYSES

The PK-evaluable population will include all patients who have received at least one dose of vemurafenib and have provided valid PK assessments. Summary statistics will be used as appropriate to perform the descriptive analysis of the plasma concentrations of vemurafenib at clinically relevant timepoints. These timepoints will include all available Cycle 1 data and predose values from all available cycles. In addition, summary statistics may be provided for PK data from patients after the diagnosis of melanoma recurrence or occurrence of a new primary melanoma during study treatment, at the time of diagnosis of SCC (cutaneous [including KA] and non-cutaneous), and at the occurrence of a dose-limiting toxicity and concomitant decision to reduce the dose or interrupt or discontinue treatment. All PK parameters will be presented descriptively including arithmetic means, standard deviations, geometric means, coefficients of variation, medians, and ranges.

In the scenario, in which major discrepancies are observed in the exposure levels and in the PK characteristics, nonlinear mixed-effects modeling (with software NONMEM [Beal and Sheiner 1998]) will be used to analyze the sparse PK concentration–time data for vemurafenib, and the results of these analyses will be reported in a document separate from the Clinical Study Report.

Graphical analyses will be conducted to explore the possible relationship between vemurafenib exposure and the following parameters:

- The risk of melanoma recurrence or the occurrence of a new primary melanoma
- The occurrence of serious adverse events
- The abnormalities in selected safety laboratory parameters

6.7 PATIENT-REPORTED OUTCOMES

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual. For all questionnaire subscales, if $>50\%$ of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with $<50\%$ of the items completed, the subscale will be considered as missing. All PRO data analyses will be performed on patients with baseline assessments and at least one post-baseline PRO assessment by treatment arm.

QoL, as measured by EORTC QLQ-C30, will be evaluated for patients with a baseline assessment and at least one post-baseline QLQ-C30 assessment that generate a score. Total QLQ-C30, each domain score (i.e., physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), symptom scales, and their changes from baseline will be examined for each timepoint with use of descriptive statistics, including mean, median, standard deviation, and range.

Compliance rates for patients who complete QoL assessments will be assessed over time (i.e., QoL "drop out") and by treatment arm.

6.8 OTHER ANALYSES

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

6.9 INTERIM ANALYSES

No interim analyses of the primary endpoint, DFS, will be performed.

As stated in Section 6.4.2.2, two OS analyses (one interim analysis and one final analysis) are planned for each cohort. The OS interim analysis will be performed at the time of the final DFS analysis for each cohort. The final OS analysis for Cohorts 1 and 2 (see Table 5) will be performed *at the end of study (see Section 3.2)*. The Lan-DeMets implementation (Lan and DeMets 1983) of the O'Brien-Fleming use function will be used to control the overall Type I error for the OS comparison in each cohort at a two-sided 0.05 significance level.

Table 5 Assumptions and Characteristics for Overall Survival Analyses by Cohort

	Cohort 1 n = 300	Cohort 2 n = 175
HR targeted	0.70	0.70
Targeted median (control)	61 months	24.2 months
Targeted median (vemurafenib)	87.1 months	34.6 months
Interim OS (to be performed at time of final DFS analysis)		
Projected number of events (% of final events)	64 (60%)	59 (50%)
Final OS		
Estimated cutoff date	30 months after LPI	30 months after LPI
Alpha level (two sided)	0.05	0.05

DFS = disease-free survival; HR = hazard ratio; $LPI = last\ patient\ in;$ MDD = minimum detectable difference; OS = overall survival.

Note: 1% annual dropout rate is anticipated for OS analyses.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the 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 CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Roche will perform oversight of the data management of this study. Roche will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Other electronic data will be sent directly to Roche, using Roche'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 at Roche and records retention for the study data will be consistent with Roche's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and a have access to a manual for appropriate eCRF completion. eCRFs will be

submitted electronically to Roche and should be handled in accordance with instructions from Roche.

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, PROs, 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 IRB/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 lead investigator at each study site 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 Roche. Written notification should be provided to Roche prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the 15-year storage

period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will check a "no" box in the appropriate section and will not provide a separate signature.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The lead study site investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are

also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

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

8.4 CONFIDENTIALITY

Roche 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 Roche location.

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the final DFS analysis for Cohorts 1 and 2.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and

governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

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

9.3 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operational procedures.

This study will be sponsored by F. Hoffmann-La Roche and managed with the support of a CRO, which will provide clinical monitoring, sample management, and project management support. Approximately 200 centers globally may participate in the study and will enroll approximately 475 patients.

Randomization will occur through an IxRS (see Section 4.2). Central facilities will be used for study assessments (i.e., ECG, specified laboratory tests, pharmacokinetics, dermatology). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Data for this study will be recorded via an EDC system using eCRF. It will be transcribed by the site from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial (see Section 7.2).

A DSMB will be utilized to ensure patient safety and will consist of external clinicians who are experts in the disease area and one external statistician. Details of the DSMB's responsibilities and logistics are outlined in the DSMB Charter. The DSMB, which will review safety data from vemurafenib trials, will review available safety data from this trial at regularly scheduled intervals specified in the DSMB Charter.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific meetings. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to Roche prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche 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 Roche, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the IRB/EC of any amendments to the protocol. Approval must be obtained from the IRB/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).

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Appendix 1
Schedule of Assessments

	Screening (Days prior to Randomization)			Treatment Period, 28-Day Cycles									Melanoma Recurrence /NPM	End of Tx Visit [b,c]	Post Tx FU [d]	Early Study Term Visit [b,e] (Post-Treatment)	Post-Recurrence FU/*End of Study*
				Cycle 1				Cycle 2		Cycle 3–13	Every 13 Wk [a]	Every 26 Wk					
Day(s)	–90	–28	–14	1	8	15	22	1	15	1							
Sign informed consent	x [f]																
Tumor tissue for $BRAF^{V600}$ mutation testing and exploratory analyses [g]	x [h]												x [h]				
Medical history, baseline conditions, and demographics		x															
Interval medical history					x	x	x	x	x	x				x			
Vital signs [i]		x		x [j]		x		x	x	x				x			
Physical exam [k]	x			x [j]		x		x	x	x			x	x	x [l]	x	
Dermatology evaluation [m]	x							x [m]			x [m]			x	x [m]	x	
Complete head and neck evaluation [n]		x										x			x		

Appendix 1
Schedule of Assessments (cont.)

	Screening (Days prior to Randomization)			Treatment Period, 28-Day Cycles								Melanoma Recurrence /NPM	End of Tx Visit [b,c]	Post Tx FU [d]	Early Study Term Visit [b,e] (Post-Treatment)	Post-Recurrence FU/*End of Study*
				Cycle 1				Cycle 2		Cycle 3–13	Every 13 Wk [a]	Every 26 Wk					
Day(s)	–90	–28	–14	1	8	15	22	1	15	1							
Anal exam and pelvic exam with Pap smear [o]	x									x				x			
Colonoscopy [p]	x [p]														x		
Stool for occult blood [q]	x									x				x			
Hematology [r]		x		x [j]				x		x				x			
Serum chemistry [s], LFTs		x		x [j]	x	x	x	x	x	x				x			
PT/INR and aPTT		x															
Serum pregnancy test [t]			x [u]							x [v]					x [v]	x [w]	
Hepatitis B and C serology [x]		x															
PK assessments				Refer to Appendix 2 (Schedule of Pharmacokinetic Assessments)													
Triplicate ECG [y]		x		x [j]		x		x	x	x [z]				x			
Study drug administration [aa]				x	x	x	x	x	x	x							

Appendix 1
Schedule of Assessments (cont.)

	Screening (Days prior to Randomization)			Treatment Period, 28-Day Cycles									Melanoma Recurrence /NPM	End of Tx Visit [b,c]	Post Tx FU [d]	Early Study Term Visit [b,e] (Post-Treatment)	Post-Recurrence FU/*End of Study*
				Cycle 1				Cycle 2		Cycle 3–13	Every 13 Wk [a]	Every 26 Wk					
Day(s)	–90	–28	–14	1	8	15	22	1	15	1							
CT or MRI scan of chest, abdomen, and pelvis	x										x [bb]		x [bb]		x [bb]	x [cc]	
Brain MRI scan	x [dd]												x [dd]	x [cc]	x [dd]	x [cc]	
Concomitant medications [ee]				x	x	x	x	x	x	x				x			
Adverse events [ff]				x	x	x	x	x	x	x				x			
SAEs and non-serious AESI [ff]	x [gg]			x	x	x	x	x	x	x				x	x	x	x
PROs [hh]				x		x		x	x	x [hh]			x	x	x [hh]	x	
Plasma/serum sample (exploratory biomarker) [ii]				x		x		x		x			x	x	x		
Optional whole blood (RCR) [jj]				x													

Appendix 1
Schedule of Assessments (cont.)

	Screening (Days prior to Randomization)			Treatment Period, 28-Day Cycles									Melanoma Recurrence /NPM	End of Tx Visit [b,c]	Post Tx FU [d]	Early Study Term Visit [b,e] (Post-Treatment)	Post-Recurrence FU/*End of Study*
				Cycle 1				Cycle 2		Cycle 3–13	Every 13 Wk [a]	Every 26 Wk					
Day(s)	–90	–28	–14	1	8	15	22	1	15	1							
Pathologic review/molecular analysis for SCC/KA, new primary neoplasms, and recurrence [kk]				Tissue sample(s) to be sent when identified													
Follow-up for new primary malignancy and survival [ll]															x [mm]		x [mm]

AESI = (non-serious) adverse event of special interest; anti-HBc = hepatitis B core antibody; CT = computed tomography; cuSCC = cutaneous squamous cell carcinoma; eCRF = electronic Case Report Form; DFS = disease-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire; FF = fresh frozen; FFPE = formalin-fixed paraffin-embedded; FU = follow-up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEENT = head, eyes, ears, nose, and throat; KA = keratoacanthoma; LFT = liver function test; MRI = magnetic resonance imaging; NPM = new primary melanoma; PK = pharmacokinetic; PRO = patient-reported outcome; QTc = corrected QT; RCR = Roche Clinical Repository; SAE = serious adverse event; SCC = squamous cell carcinoma; Tx = treatment; Wk = week.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. The timing interval assessments (such as the head and neck examination and imaging studies) should be calculated from the Cycle 1, Day 1 visit, unless indicated below. The frequency of the dermatological examination will be calculated after the first examination, which should occur after 4 weeks of study drug administration.

Appendix 1
Schedule of Assessments (cont.)

[a] Study assessments required every 13 weeks (e.g., surveillance for melanoma recurrence) may be performed within a window of ±2 weeks.

[b] Assessments completed at melanoma recurrence or occurrence of a new primary melanoma do not need to be repeated at the end-of-treatment or early termination visit.

[c] Patients who complete study drug treatment or discontinue study drug treatment early will be asked to return to the clinic 28±3 days after the last dose of study drug for an end-of-treatment visit.

[d] All patients will be followed for recurrence of melanoma, occurrence of a new primary melanoma, and new primary malignancies *until end of study*. Regular physical examinations are to be done every 13±2 weeks *until end of study (see Section 3.2)* or until a melanoma recurrence or occurrence of a new primary melanoma, whichever occurs first. Imaging studies are to be done as follows: contrast-enhanced CT or MRI of the chest, abdomen, and pelvis every 13±2 weeks until Week 104 and every 26±4 weeks thereafter until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study*, whichever occurs earlier. In addition, all patients will undergo contrast-enhanced MRI of the brain (or CT if MRI is not generally available or is contraindicated) every 52±4 weeks until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study*, whichever occurs earlier. Note: Patients who have had a DFS event do not need additional scans or physical examinations for melanoma recurrence surveillance. However, these patients must still have a chest CT (or MRI) for SCC surveillance at 13±2 weeks and 26±2 weeks after last dose of study drug.

[e] Patients who discontinue post-treatment follow-up early will be asked to return to the clinic to complete study assessments within 28 days.

[f] Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

[g] An FFPE tumor block is required for the assessment of *BRAF*^{V600} mutation status by using the **cobas**® BRAF V600 Mutation Test. If a tumor block cannot be provided, at least five serially cut, unstained tumor tissue slides (5-μm thick sections) from one block may be used. A locally obtained **cobas**® BRAF V600 Mutation Test using current primary or involved lymph node tissue can be used for screening purposes even if performed outside of the 90-day screening window.

[h] For patients eligible for the study, the archival tissue sample will also be used for further molecular analyses; therefore, it is highly recommended that an FFPE tumor tissue block (alternatively, an additional 10–20 unstained slides will be acceptable) be provided at recurrence/occurrence of a new primary melanoma, and a FF tumor tissue block should be provided if lesions are accessible. FF tissue should be prioritized over FFPE (tissue block or 10–20 slides) for recurrence tissue.

[i] Includes temperature. Heart rate and systolic and diastolic blood pressure to be recorded while the patient is in a seated position after a 5-minute rest period.

[j] If performed within 7 days of the Cycle1, Day 1 visit for screening, the test does not need to be repeated at Cycle 1, Day 1.

[k] Includes measurement of height (at baseline only) and weight and HEENT, neck, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological system examinations. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF, as appropriate. An interval medical history should be obtained coincident with each follow-up physical examination that should document changes from baseline in new or concomitant diseases, medications, and allergies. Physical exams will occur on Cycle 1 (Day 15±3 days), Cycle 2 (Days 1 and 15, each ±3 days), Day 1 (±3 days) of every subsequent 4-week cycle, and at the end-of-treatment visit. Thereafter, physical examinations done by the investigator will be obtained every 13±2 weeks from the last dose of study drug until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study*, whichever occurs earlier. Patients who have had recurrence of melanoma or occurrence of new primary melanoma will not be

required to continue to have physical examinations. For all patients, as part of the physical examination, a thorough head and neck evaluation to monitor for non-cuSCC, consisting of at least a visual inspection of the oral mucosa and lymph node palpation, must be performed by the site investigator every 13 ± 2 weeks during the study drug administration period.

[l] Physical examinations will occur every 13 ± 2 weeks from last dose of study drug during post-treatment follow-up until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study*, whichever occurs earlier. Patients who have had recurrence of melanoma or occurrence of new primary melanoma will not be required to continue to have physical examinations. Once a patient completes the treatment period or discontinues study drug early, a thorough evaluation of the head and neck by the site investigator will be performed at the end-of-treatment visit as part of the physical examination. During post-treatment follow-up, a thorough head and neck evaluation to monitor for non-cuSCC will occur (as part of the physical examination for patients who continue to have physical examinations) at 13 ± 2 weeks and 26 ± 2 weeks from the last dose of study drug. For patients who no longer require physical examinations, the head and neck examination will occur independently at 13 ± 2 weeks and 26 ± 2 weeks from the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).

[m] Complete evaluation of the skin by a designated dermatologist or his or her designee who is experienced in the diagnosis and management of cuSCC/KA will be conducted at baseline, after 4 weeks ± 1 week of study treatment (at Cycle 1) and every 13 ± 2 weeks during the study drug treatment period. Once a patient completes the treatment period or discontinues study drug early, dermatologic examinations (including a complete evaluation of the skin) will occur at the end-of-treatment visit, at 13 ± 2 weeks, and at 26 ± 2 weeks from the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up). Any suspicious lesions identified during the screening period to the examination at 26 ± 2 week during post-treatment follow-up must be biopsied/excised and sent for pathologic examination. The available specimen block/sections should be sent to the Roche-designated central pathology laboratory for confirmation of diagnosis. One normal skin punch biopsy (3–4 mm punch) is to be submitted as clinically indicated (only one per patient is required, regardless of the number of lesions submitted).

[n] If, at any time, a head and neck cancer is suspected (e.g., on the basis of signs or symptoms), the patient will be referred to a head and neck surgeon/otorhinolaryngologist or his or her designee who is experienced in the diagnosis and management of SCC of the head and neck. The head and neck surgeon/otorhinolaryngologist or designee will perform a complete evaluation of the head and neck consisting of at least a visual inspection of the oral mucosa, palpation of the tonsils, base of tongue, and lymph nodes and flexible fiberoptic laryngoscopy in order to evaluate at least the sinonasal cavity, the nasopharynx, the base of tongue, larynx, and hypopharynx. For patients who have been referred to a head and neck surgeon/otorhinolaryngologist or designee who is experienced in the diagnosis and management of SCC of the head and neck, this evaluation will continue to be conducted every 26 ± 2 weeks during the study drug administration period. Once a patient completes the treatment period or discontinues study drug early, a complete evaluation of the head and neck by a head and neck surgeon or otorhinolaryngologist will be performed at 26 ± 2 weeks after the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up). Any suspicious lesions identified from the screening period to the examination at 26 ± 2 weeks after last dose of study drug must be biopsied/excised and sent for pathologic examination. The available specimen block/sections should be sent to the Roche-designated central pathology laboratory for confirmation of diagnosis.

[o] Visual and digital evaluation of the anus and anal canal is required as part of the physical examination at screening, at Cycle 6, Day 1 (± 2 weeks), and at the end-of-treatment visit (± 2 weeks). In addition, all female patients will undergo a pelvic examination, including visual inspection of the uterine cervix and Pap smear, at screening, at Cycle 6, Day 1 (± 2 weeks), and at end-of-treatment visit (± 2 weeks). Pelvic examinations, including Pap smear, that were conducted up to 3 months

prior to the start of the 90-day screening period and found to be normal, need not be repeated at screening.

[p] For patients with personal history of adenomatous colon polyps or colorectal cancer, family history of colon cancer in which a first- and/or second-degree relative has been diagnosed with colorectal cancer at or after the age of 60 years, or signs or symptoms that could be related to colon cancer as determined by the site investigator or designee, colonoscopy to the cecum, with adequate bowel preparation, will be performed by a gastroenterologist or his or her designee who is experienced in the colonoscopic diagnosis of colorectal polyps and colorectal cancer (within the 90-day screening period). For select patients (described above), the screening colonoscopy is not required if colonoscopy to the cecum with adequate bowel preparation and adequate resection of all visualized polyps was performed within 1 year of the start of the 90-day screening period, unless the site investigator deems it necessary. All patients must have colonoscopy within 3 months of discontinuation of study drug. All polyps found at the screening or subsequent colonoscopies will need to be adequately resected. Please note that a patient with a personal history of more than three (> 3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) > 2 cm in size will be excluded from this study; this also applies to the screening colonoscopy for the select patients described above (see Section 4.1.2).

[q] Stool sample will be collected at screening, Cycle 6, Day 1 (±2 weeks), and at the end-of-treatment visit (±2 weeks). If the stool occult sample is positive at screening, the patient must be cleared for study inclusion by a gastroenterologist or appropriately trained designee.

[r] Includes hemoglobin, hematocrit, platelet count, WBC count, WBC differential (ANC), lymphocyte, monocyte, eosinophil, and basophil counts, and other cell counts.

[s] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, calcium, total bilirubin, albumin, ALT, AST, alkaline phosphatase, phosphorus, magnesium, LDH, and uric acid.

[t] If a patient discontinues study drug early, a serum pregnancy test will be performed at 12 ± 2 weeks and 26 ± 2 weeks after the last dose of study drug (except in the case of withdrawal of consent or loss to follow-up).

[u] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test within 14 days prior to randomization. Female patients of childbearing potential are defined as sexually mature women without prior hysterectomy who have had any evidence of menses within the past 12 months.

[v] Serum pregnancy test to be conducted every three cycles (e.g., Cycles 3, 6, 9, and 12 or every 12 ± 2 weeks), starting from Cycle 1, Day 1, during study drug administration, and at 12 ± 2 weeks and 26 ± 2 weeks after the last dose of study drug.

[w] Pregnancy test does not need to be performed if last pregnancy test was within 12 ± 2 weeks or if it has been 26 weeks since the last dose of study drug.

[x] Hepatitis B (HBsAg and total anti-HBc) and HCV antibody.

[y] Triplicate digital ECG recordings will be obtained within approximately 2–5 minutes of each other. ECGs should be obtained from the same machine whenever possible. Patients should be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, and conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to the first daily administration of study drug and any scheduled vital sign measurements and blood draws.

[z] After Cycle 3, Day 1, monitor ECGs on Day 1 (± 3 days) of Cycles 6, 9, and 12 and at the end-of-treatment visit. If vemurafenib treatment has been temporarily interrupted due to QTc > 500 ms (but ≤ 60-ms increment compared with baseline) OR due to change from baseline of greater than 60 ms without QTc > 500 ms, then

upon resumption of vemurafenib, ECG (measured in triplicate) and electrolytes should be monitored at Day 1 (i.e., day when study drug is resumed) pre-dose, then every 2 weeks (±3 days) for at least two cycles, then Day 1 (±3 days) of the following cycle, and then Day 1 (±3 days) of every subsequent third cycle. This replaces the protocol-mandated ECG monitoring that is outlined in this appendix. ECG monitoring will be done at the end-of-treatment visit.

[aa] Study drug will be administered at a dose of 4 tablets twice per day orally for 52 weeks (thirteen 28-day cycles). The first dose is to be taken in the morning, and the second dose is to be taken approximately 12 hours later in the evening. On most study days, the study drug is to be self-administered at home. On study days that require either ECG monitoring and/or PK sample procurement, the first daily dose of study drug should be administered at the study site after completion of these assessments.

[bb] Contrast-enhanced CT or MRI scan of the chest, abdomen, and pelvis will be performed every 13±2 weeks until Week 104 and every 26±4 weeks thereafter until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study*, whichever occurs earlier. Unscheduled imaging studies must be performed if recurrent disease or an occurrence of a new primary melanoma is suspected on clinical grounds. Patients who have had a DFS event do not need additional scans for melanoma recurrence surveillance. However, these patients must still have a chest CT or MRI for SCC surveillance at 13±2 weeks and 26±2 weeks after last dose of study drug.

[cc] Does not need to be performed if within 13±2 weeks since the last assessment.

[dd] Contrast-enhanced MRI of the brain (or CT if MRI is not generally available or is contraindicated) will be performed at screening and every 52±4 weeks thereafter until recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study* , whichever occurs earlier. Unscheduled brain imaging studies must be performed if recurrent disease or an occurrence of a new primary melanoma is suspected on clinical grounds.

[ee] Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, and nutritional supplements) used by a patient from 7 days prior to the date of informed consent until the end-of-treatment visit.

[ff] After initiation of study drug, all adverse events regardless of relationship to study drug will be reported up to and including 28 days after the last dose of study drug. Thereafter, only SAEs, any death, and other adverse events of concern that are believed to be related to prior treatment with study drug should be reported.

[gg] 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).

[hh] Patient-reported outcomes will be elicited from all patients with use of the EORTC QLQ-C30 questionnaire, which should be self-administered at the investigative site prior to the completion of other study assessments and the administration of study treatment. In post-treatment follow-up, the EORTC QLQ-C30 questionnaire will be completed every 13±2 weeks until recurrence or occurrence of a new primary melanoma or until *end of study (see Section 3.2),* whichever occurs first.

[ii] Serum and plasma samples for exploratory biomarker assessments include one blood sample in a serum separator tube (6 mL) and one 6-mL blood sample that has been anti-coagulated in EDTA. Samples are collected at Cycle 1 (Day 1 pre-dose and Day 15±3 days), Cycle 2 (Day 1±3 days), Cycle 3 (Day 1±3 days), at the end-of-treatment visit, and every 52±2 weeks after last dose of study drug, at the recurrence of melanoma, occurrence of a new primary melanoma, or *until end of study*, whichever occurs earlier. In the event of melanoma recurrence or occurrence of a new primary melanoma during study treatment or if the patient discontinues study treatment because of other reasons, a sample should be taken upon drug discontinuation.

[jj] An optional whole blood sample (6 mL in EDTA) will be collected from patients consenting to RCR guidelines. The sample is collected at Cycle 1, Day 1 or at the first visit following the RCR consent if this occurs after Cycle 1, Day 1.

[kk] All new primary malignancies will be reported *until end of study*, whether or not a patient has exhibited recurrence of melanoma or an occurrence of a new primary melanoma while in the study. Melanoma tumor tissue will be collected at recurrence of melanoma, as (pathologically documented) FF tissue and FFPE tissue. For presumed or suspected SCC (cutaneous [including KA] and non-cutaneous), new primary neoplasms (including new primary melanoma) or other suspicious lesions: FFPE tissue.

[ll] Any suspicious lesions identified must be biopsied/excised and sent for pathologic examination. For SCC and other primary neoplasms, the available specimen block/sections should be sent to the Roche-designated central pathology laboratory for confirmation of diagnosis and further molecular characterization *until end of study*, whether or not a patient has exhibited recurrence of melanoma or occurrence of a new primary melanoma while in the study.

[mm] Overall survival follow-up (post-recurrence/occurrence of new primary melanoma) will occur via telephone calls and/or clinic visits every 13 ± 2 weeks *until end of study. For all patients including those without recurrence or a new primary melanoma a final overall survival follow-up via telephone call or clinic visit should occur at the end of study (see Section 3.2).*

Appendix 2
Schedule of Pharmacokinetic Assessments

	Cycle 1				Cycle 2		Cycles 3–13	End-of-Treatment Visit/Unscheduled Visit [a]
Day	1	8 [b]	15 [b]	22 [b]	1 [b]	15 [b]	1 [b]	Any time during study visit
Time	Prior to morning dose and between 1 and 4 hours after morning dose				Prior to morning dose		Prior to morning dose	

[a] Unscheduled pharmacokinetic assessments should also be obtained in the circumstances listed below:

As soon as possible after the diagnosis of melanoma recurrence or occurrence of a new primary melanoma while on study treatment (i.e., in conjunction with the tumor biopsy for biomarker assessments).

Note: In the event of melanoma recurrence or occurrence of a new primary melanoma during study treatment or if the patient discontinues study treatment because of other reasons, a pharmacokinetic sample should be taken upon drug discontinuation as well as at the study visit most proximate after study treatment discontinuation.

Coincident with the diagnosis of squamous cell carcinoma while on study treatment.

Coincident with any dose interruption and/or reduction for toxicity.

Note: In the event of dose reduction or dose interruption, an additional unscheduled pharmacokinetic sample should be taken immediately before the patient resumes treatment at the modified dose as well as at Day 1 of the next cycle of treatment. During Cycle 1, if drug is not administered on a visit day, only one pharmacokinetic sample should be collected on that day.

[b] The pharmacokinetic assessments should be performed within ± 3 days of the scheduled visit.

Appendix 3
New York Heart Association Guidelines

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or angina pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: Criteria Committee, New York Heart Association, Inc. Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels. 6th revised ed. Boston: Little, Brown and Co, 1994:114.

Appendix 4
European Organisation for Research and Treatment of Cancer 30-Item Quality of Life Questionnaire (Version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short wa k outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 4
European Organisation for Research and Treatment of Cancer 30-item Quality of Life Questionnaire (Version 3) (cont.)

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand

Full document available at:

http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp111.pdf

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

6 Biopsy

The following is a discussion of the different forms of biopsy appropriate for suspicious pigmented lesions.

6.1 Complete excisional biopsies

The ideal method for skin lesions suspected of being melanoma is complete excision with a 2mm margin.[1] The National Comprehensive Cancer Network advises that the margin of normal skin should be no larger than 3mm to avoid interfering with subsequent lymphatic mapping[2] and Roberts et al 2002 suggest a margin of 2 to 5mm.[3] The ellipse specimen should follow the lines of relaxed skin tension with the deep margin in subcutis. Focally suspicious areas can be indicated on a diagram or marked for sectioning by the pathologist e.g. with ink, suture, superficial or punch incision. Primary closure is the preferred method of closure following excisional biopsy and skin flaps or grafts should be avoided because these may compromise the definitive re-excision.

A retrospective analysis of 298 naevi which showed significantly different degrees of atypia in different zones of 36% of cases concluded that complete excisional sampling of atypical naevi is necessary.[4]

6.2 Partial biopsies

Partial biopsies of suspicious pigmented lesions have been shown to be less accurate (as measured by Breslow thickness) than subsequent wide local excision of suspicious melanocytic lesions or melanoma.[5] A retrospective review of 114 cases of lentigo maligna (with or without invasion) showed a higher risk of misdiagnosis with partial biopsy compared with excisional biopsy.[6] Farrahi et al and Karimipour et al found that 21% of 1783 melanoma patients undergoing various techniques of partial biopsy were upstaged on subsequent excisional samples (which showed significantly higher Breslow thickness).[7] They concluded that the smaller the percentage of lesion removed by biopsy, the greater the degree of inaccuracy was likely to occur. In a series of 46 partially biopsied pigmented lesions from actinically damaged skin, 40% of re-excisions revealed deeper invasion or diagnostic changes not seen on original biopsy, with 28% of these felt to be of prognostic or therapeutic significance. In 20% of cases, the initial biopsy did not identify invasion that was later seen on the excision sample.[8]

At times, complete excision is not practical for clinical, technical or other reasons, so partial biopsy may be necessary. This may be considered where the lesion is large or on a site where total excision may cause cosmetic or functional impairment, when there is a low index of clinical suspicion or significant comorbidities. All biopsies should include the most suspicious or invasive zones. The biopsy type and proportion of the lesion sampled should be indicated on the pathology request form. Careful planning of the biopsy site is essential and use of dermoscopy may be helpful in targeting the most suspicious area. It may be appropriate to indicate in the pathology report that a partial biopsy may not be fully representative of the lesion.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Partial biopsies are an important cause of litigation in the US because of inadequate material being available for analysis by the pathologist.[9] They should only be performed by appropriately trained clinicians aware of the possible limitations of the technique. Evaluation of the subsequent excision specimen may be impaired by reparative changes, and accurate determination of Breslow thickness, regression or lymphocytic infiltration may be compromised.

A **punch biopsy** provides dermis for assessment of tumour invasion but samples only a limited breadth of large lesions and is therefore prone to sampling error. Multiple punch biopsies may minimise this source of error.

A **broad superficial shave biopsy (or curettage)** can provide a larger area of epidermis for histology, but often fails to include sufficient dermis for full assessment of invasion. These biopsies are therefore only suitable for lesions that are likely to be confined to the epidermis (e.g. when attempting to differentiate in situ melanoma from solar lentigo or seborrheic keratosis). In order to maintain the integrity of the epidermis on the sample, at least papillary dermis must be present across the shave. Superficial shave biopsies heal with little or no scar and are therefore suitable for use on the face.

Deep shave biopsies (saucerisation) include varying amounts of reticular dermis and may transect the base of a melanoma, impairing the assessment of Breslow thickness more often than with excisional biopsy. Any form of shave biopsy may incompletely sample the periphery of the lesion and samples can be difficult to orientate in the laboratory. Deep shave biopsies heal with a scar.

Incisional biopsy removing as much of the lesion as is feasible with primary closure can be a very useful method of partial biopsy.

In a retrospective analysis, excisional biopsy demonstrated better diagnostic accuracy than punch or shave biopsies, with deep shave (at least to mid dermis) favoured over punch biopsy.[10] In a study of dysplastic naevi (some of which were later diagnosed as melanoma on histology), 21 of 22 shave biopsies and 29 of 41 punch biopsies were concordant with the subsequent excision.[11] It should be noted that the type of shave used in this study was of the 'saucerisation' type, a style of shave biopsy that is not commonly used in many centres. A retrospective review of 223 cases of melanoma showed that shave samples generally gave the thinnest samples compared with punch or excisional biopsies, and that 50% of these shave biopsies showed at least one positive margin.[12] In Karimipour et al 2005, shave biopsy was less accurate in determining Breslow thickness.[7]

In a multicentre RCT of 2164 melanoma patients, Martin et al found that prognosis was not affected by previous incisional biopsy of the lesion.[13] A comparison of 265 melanomas sampled by incisional biopsy with 496 control melanomas not subjected to incisional biopsy did not show effects on prognosis, or on risk of recurrence.[14]

It is important to consider the weaknesses of partial biopsies when interpreting the pathologist's report. If the result does not accord with the clinical impression or there is diagnostic uncertainty, a better sample should be obtained, preferably by performing a complete excision.

The theoretical risk of melanoma dissemination by biopsy prior to excision has generally been rejected.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

6.3 Alternative approaches

Frozen section and cytological analysis are inappropriate for suspicious pigmented lesions, but may be of value when assessing potential metastases from a melanoma, for example, in a lymph node.

When clinical suspicion of malignancy is low, observation may be appropriate, possibly backed up by dermoscopy, clinical photographs and an accurate description and measurement of the lesion. Referral to a specialist should be considered before biopsy for lesions in technically difficult anatomical locations (e.g. the eyelid) or where the operator is not confident in achieving an adequate sample or good cosmetic result.

Where clinical suspicion remains despite a negative pathology report following a partial biopsy, rebiopsy or excision should be performed. Even after complete excision, if the pathology result does not correlate with the clinical impression, discussion of the case with the pathologist is recommended. Review of the slides by a second pathologist may be appropriate in some circumstances.

Evidence summary	Level	Reference
Partial biopsies versus completeness of excision Complete excision with a 2mm margin is the most reliable biopsy method for skin lesions suspected of being melanoma	IV	1, 3
One-third of atypical naevi show significantly different degrees of atypia in different zones indicating that complete excisional sampling of atypical naevi is necessary	III–3	4
Partial biopsy has been shown to be less accurate (as measured by Breslow thickness) than the subsequent wide local excision of suspicious melanocytic lesions or melanoma	III–3	5
Partial biopsies are an important cause of litigation because of inadequate material being available for analysis by the pathologist	IV	9
A retrospective review of 114 cases of lentigo maligna (with or without invasion) showed a higher risk of misdiagnosis with partial biopsy compared with excisional biopsy. In another study, 21% of partial biopsies were upstaged on subsequent excisional samples (which showed significantly higher Breslow thickness), with greater inaccuracy related to smaller percentages of lesion removed by biopsy	III–3	6, 7
In a series of 46 partially biopsied pigmented lesions from actinically damaged skin, 40% of re-excisions revealed deeper invasion or diagnostic changes not seen on original biopsy, with 28% of these felt to be of prognostic or therapeutic significance. In 20% of cases, the initial biopsy did not identify invasion that was later seen on the excision sample	IIII–3	8

continued over...

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Evidence summary continued...	Level	Reference
Partial biopsies are an important cause of litigation because of inadequate material being available for analysis by the pathologist	IV	9
Types of biopsies (punch, shave, incisional) Excisional biopsy demonstrated better diagnostic accuracy than punch or shave biopsies. In a study of dysplastic naevi (some of which were later diagnosed as melanoma on histology), 21 of 22 shave biopsies and 29 of 41 punch biopsies were concordant with the subsequent excision. In a retrospective review, shave samples generally gave the thinnest samples compared with punch or excisional biopsies, and 50% of these shave biopsies showed at least one positive margin. In another study, shave biopsy was less accurate in determining Breslow thickness	III–3	
In a multicentre RCT, prognosis was not affected by previous incisional biopsy of the lesion	II	13
A comparison of melanomas sampled by incisional biopsy compared with melanomas not subjected to incisional biopsy did not show differences between prognosis, or on risk of recurrence	III–3	14

Recommendations

	Grade
1. The optimal biopsy approach is complete excision with a 2mm margin and upper subcutis	C
2. Partial biopsies may not be fully representative of the lesion and need to be interpreted in light of the clinical findings	C
3. Incisional, punch or shave biopsies may be appropriate in carefully selected clinical circumstances, for example, for large facial or acral lesions, or where the suspicion of melanoma is low	C

6.4 Good practice point

- It is advisable to review unexpected pathology results with the reporting pathologist

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

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Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

12 Management of regional lymph nodes in melanoma

All patients with invasive melanoma are at risk for metastasis to the regional lymph nodes. An important part of the follow-up protocol for these patients therefore involves careful examination of the lymph nodes at each follow-up visit. Lymph nodes containing metastatic melanoma often increase in size quickly, sometimes appearing overnight according to the patient. An involved node is usually non-tender and firm to hard in consistency.

The risk of metastasis to lymph nodes is directly related to the Breslow thickness of the primary melanoma.[1] Thus, metastases are rare for thin melanomas (< 0.75mm) and the risk for tumours 0.75–1.0mm thick is about 5%. Intermediate thickness melanomas (1–4mm) have a risk that starts at about 8% for 1mm tumours and this rises steadily to 30% with increasing depth. Melanomas thicker than 4.0mm have a risk of approximately 40% for nodal involvement, in addition to a high risk of systemic spread, but the involved regional nodes are usually not clinically apparent at the time of primary diagnosis.

12.1 Sentinel lymph node biopsy

Since the last publication of these guidelines, a significant body of evidence has accumulated regarding lymphatic mapping and sentinel lymph node biopsy (SLNB). A sentinel node is one that receives lymphatic drainage directly from the primary tumour site. Lymphatic mapping to determine the location of sentinel nodes involves the intradermal injection of a small dose of radioactive tracer at the primary tumour site. At the time of surgery, the surgeon injects patent blue dye adjacent to the primary tumour and identifies the sentinel node as 'hot and blue' through a small incision at the location indicated by the radiologist. The sentinel node is removed and sent for histological examination. Often there may be sentinel nodes in more than one lymph node field, particularly if the tumour is located along the central axis of the torso. Melanomas of the head and neck region regularly drain to more than one zone of the cervical node field.

Sentinel node biopsy can be technically demanding, particularly in the head and neck, and should not be undertaken without appropriate training in this technique.[2] Expert execution and interpretation of the pre-operative lymphoscintigraphy is crucial to the success of the procedure as the failure to correctly identify the sentinel node will be counterproductive to good management of the patient. Furthermore, the pathologist plays a big role in achieving accurate results from a SLNB. The reliability of sentinel node biopsy after prior wide excision is unknown but it may lead to the wrong lymph node being analysed. Patients who are being considered for sentinel node biopsy should be referred before wide local excision of the primary tumour site. If sentinel node biopsy is being considered it is important that lymphatic mapping be done prior to wide excision.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

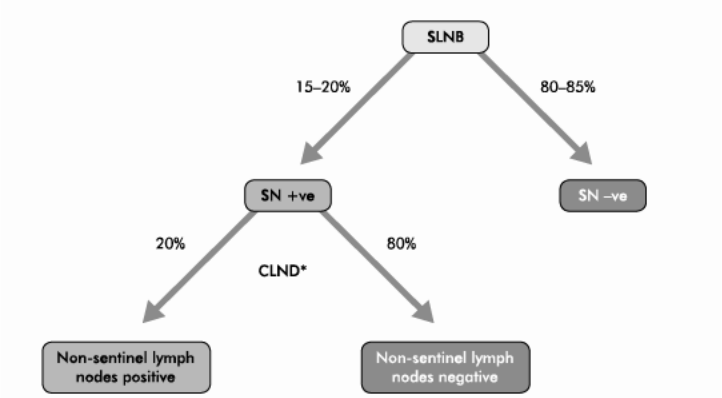
The status of the sentinel node reliably indicates the presence or absence of micrometastases in that node field and is the most accurate prognostic factor in primary melanoma added to the additional prognostic information from the primary lesion.[3]
An international multicentre randomised controlled trial[4] (MSLT-1) was designed to assess the outcome of patients with occult metastases detected by SLNB compared with those who received wide local excision alone. The first Multicenter Selective Lymphadenectomy Trial (MSLT-1) randomised 1347 patients with intermediate thickness (1.2–3.5mm) melanomas to the primary aim strata; 1269 of these patients of these patients were evaluable because they accepted the assigned treatment (either wide excision plus post operative observation, with delayed completion lymph node dissection for clinically detectable nodal recurrence; or wide excision plus SLNB, with immediate completion lymph node dissection for sentinel node metastases. An additional 647 patients with lesions thinner than 1.2mm (low risk of nodal metastases) and thicker than 3.5mm (high risk of distant metastases at initial diagnosis) were enrolled to evaluate surgical morbidity and accuracy of the procedure, but were considered unlikely to exhibit survival differences based on modelling from the John Wayne Cancer Institute's database.[5] In the primary aim group of patients with intermediate thickness melanomas (where the risk of a positive sentinel lymph node is 15–20%, Figure 3) the results of the third of five planned interim analyses were as follows; five-year melanoma-specific survival rates were similar in the two groups (87.1±1.3% and 86.6±1.6%, respectively) (hazard ratio, 0.92; 95% CI, 0.67–1.25; P = 0.58). The five year survival rate for sentinel node positive patients was 72.3±4.6% and 90.2±1.3% for node negative patients (hazard ratio for death, 2.48; 95% CI, 1.54–3.98; P<0.001). The mean estimated five-year disease-free survival rate was 78.3±1.6% in the biopsy group and 73.1±2.1% in the observation group (hazard ratio, 0.74; 95% CI, 0.59–0.93; P=0.009). The five-year survival was significantly higher in the group that underwent immediate lymph node dissection for a positive sentinel node compared to the group who underwent nodal observation and had delayed lymphadenectomy for clinically apparent nodal metastases (72.3±4.6% vs. 52.4±5.9%; hazard ratio for death, 0.51; 95% CI, 0.32–0.81; P=0.004). This statistic was not a primary outcome point in the original study design but it was a predetermined secondary outcome measure. The results of the interim analyses of this study and the interpretation of the data therein are still actively being debated.[6]

Preliminary information from the 4th interim analysis (median follow-up 59.5 months) confirms the results of the 3rd interim analysis and also shows a statistically significant lower rate of distant metastasis in the sentinel lymph node biopsy group (18.1% vs 21.2%) compared with wide local excision and observation.[5]

There is still no overall survival advantage shown at this time.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Figure 3 Distribution of lymph node metastases for melanomas 1.2–3.5mm thick



*CLND = completion lymph node dissection

Sentinel node biopsy should be discussed with patients who have a primary tumour 1.2–3.5mm thick. In addition, there are other patients with thinner tumours who are at particular risk of having a positive sentinel node. Therefore SLNB may be discussed with patients with melanomas 0.75–1.2mm thick based on the characteristics of the primary tumour, such as ulceration, Clark level (IV or V), or a high mitotic rate.[7] Where the true Breslow thickness cannot be determined, usually because the melanoma was diagnosed by shave biopsy, patients may also be offered SLNB. The risk of micrometastatic disease is inversely related to the patient's age and those younger than 35 years with a thin primary may benefit from sentinel node biopsy.[8] Patients with thick primaries (4mm or greater) are at substantial risk of developing disseminated metastatic disease. However, the status of the sentinel node in these patients is still the most important prognostic factor in this group of patients and biopsy may be recommended to assist in determining prognosis and to improve local disease control.[9]

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Evidence summary	Level	References
Sentinel lymph node status provides accurate prognostic information for disease-free and overall survival for melanomas stage T1b[10] or greater	I	1, 3
To date, the MSLT-1 study shows no overall survival benefit	II	4, 5
Patients undergoing SLNB have a significantly lower rate of distant metastasis compared with wide local excision and observation	II	5
The interim results of the MSLT-1 study shows a potential survival benefit to patients with 1.2–3.5mm thick melanomas with positive sentinel lymph nodes who undergo immediate completion lymphadenectomy compared to those in the control group who undergo clinical observation and develop nodal recurrence	III-2	4
Sentinel node biopsy can be technically demanding and requires specialised expertise and resources	III-1	2

Recommendations

	Grade
1. Patients with a melanoma greater than 1.0mm in thickness be given the opportunity to discuss sentinel lymph node biopsy to provide staging and prognostic information	C
2. SLNB be performed only, following a full discussion of the options with the patient, in a unit with access to appropriate surgical, nuclear medicine and pathology services	C

12.2 Therapeutic lymph node dissection

Therapeutic lymph node dissection is an operation involving the radical clearance of a lymphatic field and, in melanoma, is indicated for the presence of metastatic lymphadenopathy. Lymph node metastasis detected during clinical observation should be confirmed by guided fine needle biopsy of the suspicious node. Ultrasound imaging and guide FNB by a clinician experienced in the examination of lymph nodes may serve to increase the sensitivity of this procedure. A negative fine needle biopsy is not conclusive and should be repeated if the node remains clinically suspicious after a period of observation of one month. Only in centres where cytological diagnosis is unavailable, or if needle biopsy is unhelpful, is open biopsy recommended. If open biopsy is deemed necessary, the biopsy incision should be placed so that it can be easily excised in continuity with the lymph node field if radical lymphadenectomy is subsequently performed.

For patients with a positive SLN current practice is completion lymph node dissection.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

However it is not known how to best manage patients with micrometastases detected by SLNB. This question is currently being investigated by MSLT-II, in which patients with histopathological or molecular (RT-PCR) evidence of tumour in the sentinel node are randomly assigned to receive completion lymph node dissection or observation.[11] MSLT-II is ongoing and the results are not yet available.

A systematic review of randomised controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence showed no significant overall survival benefit for patients undergoing elective lymph node dissection.[12] Therefore, except in rare circumstances, elective lymph node dissection is not recommended for melanoma patients.

Radical lymph node dissections for melanoma are relatively difficult operations and should be undertaken only by surgeons appropriately trained for the operation. There is a substantial risk of recurrence in dissected node fields in patients with clinically positive lymph nodes and only a thorough formal dissection will substantially lower the risk of recurrence in a dissected node field. A dissection can only be deemed thorough if it includes levels I–III in the axilla and a complete clearance of the femoral triangle nodes in the groin.[7] Extended procedures that include removal of the pectoralis minor muscle in the axilla and superficial parotidectomy in the neck should be considered. When dealing with lymphatic metastases in the groin, consideration should be given to the status of the ipsilateral external iliac and obturator nodes in the pelvis. Extension of the inguinal dissection to include the nodes in the pelvis, an ilio-inguinal dissection, may be indicated in the following circumstances: evidence of involvement of the pelvic nodes on staging investigations; gross clinical involvement or evidence of involvement in three or more nodes in the inguinal region; clinically suspicious nodes high in the groin.[7,13] Therapeutic neck dissection in melanoma patients carries a high risk of recurrence in the nodal field. This is a difficult operation, fraught with complications, and specific training is essential to achieve the optimal outcome. Even when surgeons with specific training undertake this dissection, the incidence of recurrence in the neck is considerable (up to 28%). Postoperative radiation therapy could be considered if the pathology report indicates matted nodes, extracapsular spread, and large size and/or large number of involved nodes.[14,15] (Refer to Chapter 13 *Management of locoregionally recurrent melanoma*).

All patients with positive lymph nodes are at high risk for systemic dissemination. It is therefore important to arrange consultation with a multidisciplinary melanoma treatment centre if possible.[16] Refer to Chapter 18 *Multidisciplinary care of melanoma*. Even where minimal involvement of the lymph nodes is found on node dissection, a referral of these patients to a melanoma centre may allow them to enrol or participate in clinical trials of adjuvant therapies. Refer to Chapter 13 *Management of locoregionally recurrent melanoma* for a discussion of the evidence regarding this treatment modality for lymph node metastases.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Evidence summary	Level	References
Elective lymph node dissection is not recommended, regardless of the Breslow thickness of the primary tumour	I	7, 12
Completion lymphadenectomy can result in complications in about a third of patients – most of these are minor but the rate of clinically significant lymphoedema following axillary or groin dissection is 5–10%	IV	2
All patients with positive lymph nodes are at high risk for systemic dissemination. It is therefore important to arrange consultation with a multidisciplinary melanoma treatment centre if possible	IV	16

Recommendations

	Grade
3. Patients who have positive sentinel lymph node biopsy be offered completion lymphadenectomy, or be referred to a specialist centre for discussion of further treatment options	C
4. Therapeutic node dissection be offered to all patients with evidence of metastatic nodal disease after excluding stage IV disease using appropriate investigations	C

12.3 Good practice points

- A therapeutic node dissection includes a full levels (I to III) clearance in the axilla. A therapeutic neck dissection may include a superficial parotidectomy as clinically indicated
- Patients with inguinal node metastases be considered for clearance of the intra-pelvic iliac and obturator nodes when the staging investigation demonstrates evidence of involvement
- Elective clearance of the pelvic nodes be considered when there is gross macroscopic disease in the inguinal node field or there are three or more histologically positive nodes below the level of inguinal ligament
- Patients with lymph node metastases be offered discussion with a multidisciplinary team with a view to enrolment in clinical trials

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

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Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

13 Management of locoregionally recurrent melanoma

Locoregionally recurrent melanoma refers to recurrence of melanoma in the anatomical region from the primary site to the regional lymph nodes, after apparently complete excision of primary melanoma. Locoregionally recurrent melanoma has a spectrum of presentations, temporally and anatomically. Anatomically, locoregional recurrence can be defined as:

- local recurrence at the primary excision site, being either:
  - re-growth of incompletely excised primary melanoma, involving the excision site scar or graft (persistent melanoma); or
  - local metastasis at the primary site.
- in-transit metastasis or satellitosis, due to lymphatic and/or haematogenous metastasis
- regional lymph node metastasis
- occurring in isolation or in association with disseminated disease.

These distinctions are important, as the intent of treatment and the prognosis differ greatly. Where possible, patients should be treated in conjunction with a specialist centre.

13.1 Persistent melanoma

The distinction between persistent melanoma and local metastasis is made histologically (see Chapter 7 *Histopathological reporting of cutaneous melanoma*). Persistent melanoma is a rare finding and should be excised completely.[1] There is no evidence indicating the superiority of any particular size of excision margin; margins used for the excision of primary melanoma should be considered. Adjuvant radiation therapy should be considered for close or positive margins unsuitable for re-excision, if normal tissue tolerances can be respected.[2]

Evidence summary	Level	References
Persistent melanoma should be excised completely	IV	1
For persistent melanoma which has been excised with close or positive margins, adjuvant radiation therapy reduces the risk of further recurrence	IV	2

Recommendations

	Grade
1. Persistent melanoma be excised completely	C
2. Adjuvant radiation therapy be considered for close or positive margins unsuitable for re-excision	C

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

13.2 Local metastasis, in transit metastasis and satellitosis

Local metastasis, in transit metastasis and satellitosis are recurrences that generally occur in the lymphatic vessels more proximally towards the regional lymph nodes. Patients generally have a poor prognosis with frequent development of distant metastasis. The goal of treatment is maintenance of local control. There is a wide spectrum of clinical presentation and rate of disease progression.

Recurrent lesions may be managed by a variety of methods, including excision, cryotherapy, CO_2 laser, intralesional injection or application of drugs or immunomodulating agents, and radiation therapy.[3,4] There is no evidence that other local treatments are equivalent to excision where this is possible. Adjuvant radiation therapy should be considered for close or positive margins unsuitable for re-excision, if normal tissue tolerances can be respected.[2] There is no survival advantage for prophylactic regional drug therapy, although disease free survival is improved.[5] Slowly progressive lesions may be observed until they become symptomatic. There are few data comparing the efficacies of these modalities. These methods are of particular use when the disease progresses slowly.

Evidence summary	Level	References
Adjuvant regional drug therapy improves disease free interval but does not improve overall survival	II	5
For local metastasis, in transit melanoma and satellitosis, a range of local treatments have been reported as effective for local control, with no direct comparison to surgery	IV	3, 4

Recommendations

	Grade
3. Local metastasis, in transit metastases and satellitosis may be managed using a variety of local treatments	C
4. Prophylactic isolated limb perfusion (ILP) is not recommended	A

The management of patients with multiple, rapidly growing or rapidly progressive lesions depends on the anatomical location. Involved limbs should be treated with regional drug therapy. Isolated limb perfusion (ILP) using melphalan under hyperthermic conditions is the standard, but involves a high level of technical skill and experience to minimise complications.[6] Isolated limb infusion (ILI), which is a simpler method of regional drug delivery, appears to provide a response rate and duration of response similar to that of ILP.[7] Response rates approaching 90%, including complete response rates of 60–70%, are routinely achieved with these methods, with low complication rates. Response rates may be sustained for periods approaching a year in approximately 50% of responders. The use of ILP or ILI obviates or delays the need for palliative amputation in most cases. ILI is the more common method in Australia.

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Double ILP or ILI procedures are not associated with improved response rates or duration of response. However, further ILP or ILI following relapse is associated with response rates similar to those achieved with the initial ILP.

The use of drugs other than melphalan remains investigational. The addition of tumour necrosis factor α (TNFα) to melphalan does not significantly improve the response rate or duration of response compared with melphalan alone. However, there is some evidence that a second ILP using the combination of melphalan and TNFα may be of value following an initial ILP with a poor response.

Evidence summary	Level	References
Regional drug therapy using isolated limb perfusion (ILP) or isolated limb infusion (ILI) produces high overall, complete and durable responses Repeated ILP or ILI for recurrence in the same limb produce similar response rates to those achieved for the initial procedure ILP/ILI is technically challenging, with a documented incidence of serious complications	II	6, 7
ILI is a simpler alternative to ILP that may produce equivalent results	IV	7

Recommendations

	Grade
5. Recurrence on a limb with multiple or rapidly progressive lesions not suitable for local treatments is best managed with ILP using melphalan under hyperthermic conditions if technically possible	A
6. ILI may be substituted for ILP	C

The management of extensive or rapidly progressive, in transit metastases unsuitable for regional drug therapy (e.g. proximal limb, trunk, head/neck) is difficult and must be individualised and discussed by a multidisciplinary team. Options include combinations of systemic drug therapies and local therapies.[3,4]

Evidence summary	Level	References
For recurrent melanoma with multiple and/or rapidly growing lesions which cannot be managed by regional drug therapy, a range of local treatments have been reported as effective for local control	IV	3, 4

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Recommendation

	Grade
7. Recurrence involving multiple or rapidly progressive lesions that are unsuitable for regional drug therapy be managed on an individual basis by a multidisciplinary team proficient in a range of local treatments	C

13.3 Regional lymph nodes

Regional lymph nodes should be considered in the management of locoregionally recurrent melanoma according to the following situations:

- **clinically uninvolved lymph nodes with no previous dissection**: SLNB has been suggested, although evidence for its value in this situation is lacking[8]
- **clinically involved lymph nodes with no previous dissection**: the nodal basin should be dissected, to improve local control.[9] The use of adjuvant postoperative radiation therapy remains controversial and must be decided in relation to its potential toxicity and other therapies. Postoperative radiation therapy could be considered if the pathology report indicates matted nodes, extracapsular spread, and large size and/or large number of involved nodes.[2,10] Although most evidence relates to the initial management of lymph nodes, extrapolation to the recurrent situation seems reasonable. No particular radiation treatment schedule has been found superior to other schedules
- **clinical recurrence in a previously dissected nodal basin**: further dissection should be performed if possible, with consideration of postoperative radiation (if not previously given).[2,10]

Evidence summary	Level	References
For patients without previous lymph node dissection, there is insufficient evidence to determine whether the information provided by SNB following locoregional recurrence of melanoma improves outcome	IV	8
The optimal management of clinically involved lymph nodes in a previously untreated nodal basin is lymph node dissection, which is superior to radiation therapy alone	IV	2, 9
Postoperative radiation therapy to a nodal bed may be effective in reducing the local recurrence rate when there are adverse pathological features	IV	2
The optimal management of recurrence in a previously dissected lymph node region is surgical removal of melanoma, followed by postoperative radiation therapy if this has not been delivered previously	IV	2

Appendix 5
Excerpts from the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (cont.)

Recommendations

In the context of locoregionally recurrent melanoma:	Grade
8. SLNB be considered if the nodal basin has not been dissected and if there is no clinical evidence of nodal involvement	D
9. Lymph node dissection be performed for clinically involved nodes with no previous dissection, following confirmation of melanoma, preferably by fine needle biopsy	C
10. Postoperative adjuvant radiation therapy be considered for adverse pathological findings, though the value remains uncertain	C
11. Clinical recurrence in a previously dissected nodal basin be managed by excision if possible, followed by radiation therapy (unless given previously)	C

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Appendix 6
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
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 or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 7
Fitzpatrick Skin Phototypes

Skin type	Reaction to sun exposure[a]
I	Always burns, never tans
II	Always burns, minimal tan
III	Burns minimally, gradually tans
IV	Burns minimally, tans well
V	Very rarely burns, tans profusely
VI	Never burns, tans deeply

[a] After the first 1 hour of sun exposure on untanned skin on the first day of spring.

Appendix 8
Impact of Vemurafenib on Concomitant Medications

Impact of RO5185426 on Concomitant Medications		
Substrates		
CYP 1A2[1]	**CYP 2C9[1]**	**CYP3A4[2]**
amitriptyline	**NSAIDs:**	**Macrolide antibiotics:**
caffeine	diclofenac	clarithromycin
clomipramine	ibuprofen	erythromycin
clozapine	lornoxicam	telithromycin
cyclobenzaprine	meloxicam	Anti-arrhythmics:
estradiol	S-naproxen_Nor	quinidine_3OH
fluvoxamine	piroxicam	
haloperidol	suprofen	**Benzodiazepines:**
imipramine N-DeMe		alprazolam
mexilletine	**Oral Hypoglycemic:**	diazepam_3OH
naproxen	tolbutamide	midazolam
olanzapine	glipizide	triazolam
ondansetron	Angiotensin II	
phenacetin_	Blockers:	**Immune Modulators:**
acetaminophen	losartan	cyclosporine
propranolol	irbesartan	tacrolimus (FK506)
riluzole	Sulfonylureas:	HIV Antivirals:
ropivacaine	glyburide	indinavir
tacrine	glibenclamide	nelfinavir
theophylline	glipizide	ritonavir
tizanidine	glimepiride	saquinavir
verapamil	tolbutamide	Prokinetic:
(R)warfarin	amitriptyline	cisapride
zileuton	celecoxib	
zolmitriptan	fluoxetine	**Antihistamines:**
	fluvastatin	astemizole
	glyburide	chlorpheniramine
	nateglinide	terfenadine
	phenytoin-4-OH2	
	rosiglitazone	**Calcium Channel Blockers:**
	tamoxifen	amlodipine
	torsemide	diltiazem
	S-warfarin	felodipine
		lercanidipine
		nifedipine2
		nisoldipine
		nitrendipine
		verapamil

Appendix 8
Impact of Vemurafenib on Concomitant Medications (cont.)

CYP 1A2[1]	CYP 2C9[1]	CYP3A4[2]
		HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone **Miscellaneous:** alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-Ndemethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone salmeterol

Appendix 8
Impact of Vemurafenib on Concomitant Medications (cont.)

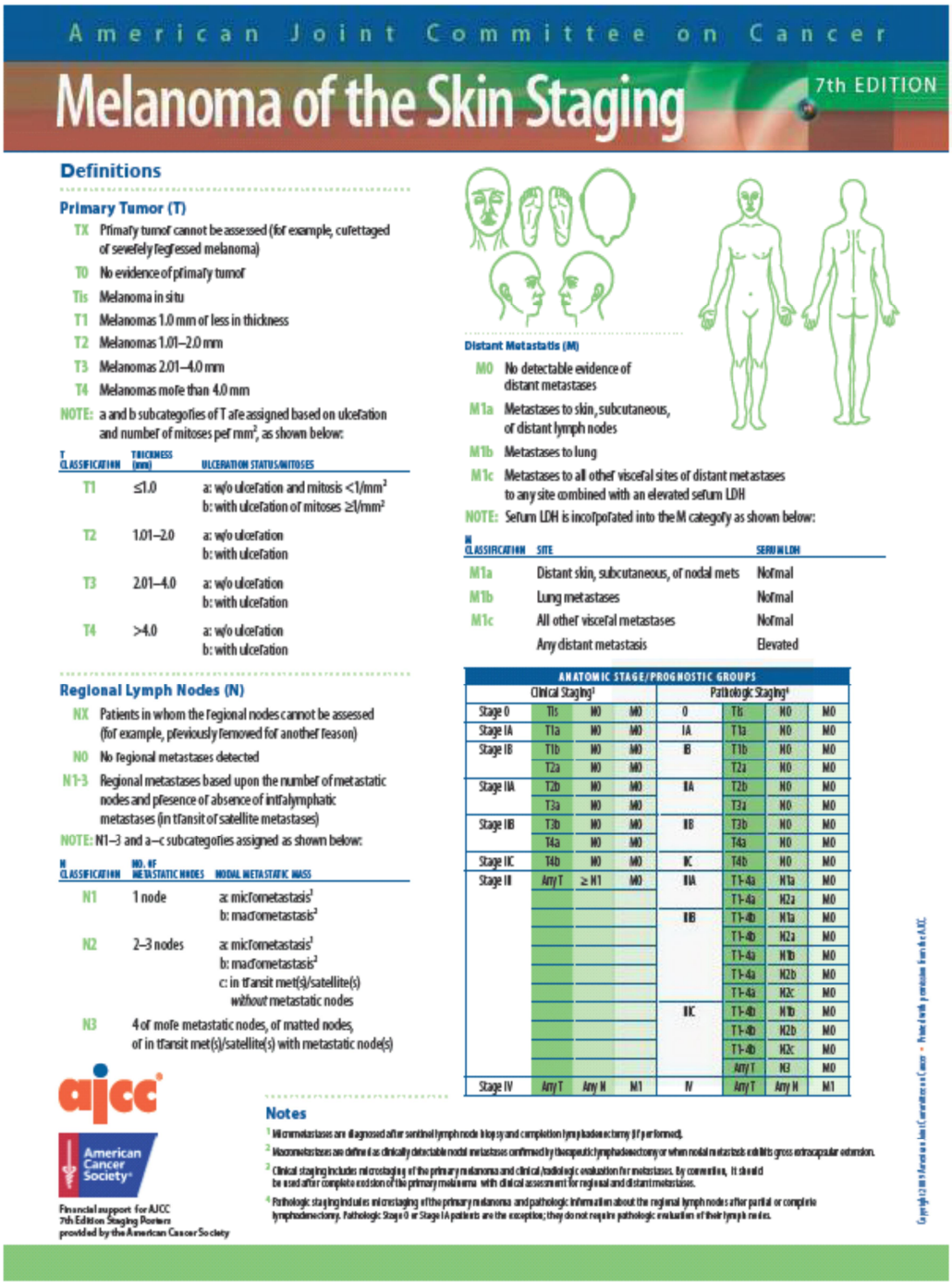
		sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

1 Exposure of these drugs may be increased following *vemurafenib* treatment.
2 Exposure of these drugs may be decreased following *vemurafenib* treatment.

Appendix 9
Medication Affecting 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	

Appendix 10
American Joint Committee on Cancer (Version 7): Melanoma of the Skin Staging



American Joint Committee on Cancer

Melanoma of the Skin Staging

7th EDITION

Definitions

Primary Tumor (T)

TX Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)

T0 No evidence of primary tumor

Tis Melanoma in situ

T1 Melanomas 1.0 mm or less in thickness

T2 Melanomas 1.01–2.0 mm

T3 Melanomas 2.01–4.0 mm

T4 Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and number of mitoses per mm², as shown below:

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS/MITOSES
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

NX Patients in whom the regional nodes cannot be assessed (for example, previously removed for another reason)

N0 No regional metastases detected

N1-3 Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

NOTE: N1–3 and a–c subcategories assigned as shown below:

N CLASSIFICATION	NO. OF METASTATIC NODES	NODAL METASTATIC MASS
N1	1 node	a: micrometastasis[1] b: macrometastasis[2]
N2	2–3 nodes	a: micrometastasis[1] b: macrometastasis[2] c: in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	

Distant Metastasis (M)

M0 No detectable evidence of distant metastases

M1a Metastases to skin, subcutaneous, or distant lymph nodes

M1b Metastases to lung

M1c Metastases to all other visceral sites of distant metastases to any site combined with an elevated serum LDH

NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	SERUM LDH
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]				Pathologic Staging[4]			
Stage 0	Tis	N0	M0		0	Tis	N0	M0
Stage IA	T1a	N0	M0		IA	T1a	N0	M0
Stage IB	T1b	N0	M0		IB	T1b	N0	M0
	T2a	N0	M0			T2a	N0	M0
Stage IIA	T2b	N0	M0		IIA	T2b	N0	M0
	T3a	N0	M0			T3a	N0	M0
Stage IIB	T3b	N0	M0		IIB	T3b	N0	M0
	T4a	N0	M0			T4a	N0	M0
Stage IIC	T4b	N0	M0		IIC	T4b	N0	M0
Stage III	Any T	≥ N1	M0		IIIA	T1-4a	N1a	M0
						T1-4a	N2a	M0
					IIIB	T1-4b	N1a	M0
						T1-4b	N2a	M0
						T1-4a	N1b	M0
						T1-4a	N2b	M0
						T1-4a	N2c	M0
					IIIC	T1-4b	N1b	M0
						T1-4b	N2b	M0
						T1-4b	N2c	M0
						Any T	N3	M0
Stage IV	Any T	Any N	M1		IV	Any T	Any N	M1

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Notes

[1] Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

[2] Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

[3] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.